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Cancer and Sexual Health

Humana Press

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Cancer and Sexual Health

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Preface

Due to the nature of my practice in my capacity as the Director of Male Sexual & Reproductive Medicine at Memorial Sloan-Kettering Cancer Center, it has become clear to me that to date there does not exist a reference work devoted to the link between cancer and human sexuality. Thus, it has been an ambition of mine for some time to develop this book. The purpose of this text is to act as a resource for those clinicians caring for cancer patients as well as act as a reference text for the sexual medicine clinician who may not see a large number of cancer patients. I hope that physicians, researchers, nurses, and clinician trainees will find this a valuable resource.

In the twenty-first century, while cancer is endemic, so too is the survival of the cancer patient. It is well recognized that the diagnosis of cancer represents a major stressor in a person's life. Add to this the common treatments for cancer and one can see the potential for a negative effect of cancer on a person's sexual health. Increasingly, patients are winning their battle with cancer and are surviving long periods of time. We see daily in practice patients with cancer of the testis, prostate, breast colon, and hematologic malignancies. So, the concept of survivorship has become increasingly important to cancer clinicians. Survivorship has become a medical specialty itself and refers to the focus not just on curing cancer, but also dealing with the consequences of the diagnosis and treatment of that cancer. It has been recognized that for many cancer survivors, sexual function represents a significant concern. I hope this book will help you in the management of the survivorship issues of your patients.

Such an opus is impossible to accomplish without the assistance of many different parties. First of all, I would like to thank the associate editors of this project who were integral to the development of the table of contents, the selection of the authors, and finally the review of the manuscripts. In the world of sexual medicine, all three are instantly recognizable names. Dr. Irwin Goldstein is a urologist and one of the founding fathers of modern sexual medicine. He has been a mentor to me since my training with him 15 years ago and is the current editor-in-chief of the Journal of Sexual Medicine. Dr. Raymond Rosen is an eminent clinician-scientist who has spent three decades treating patients with sexual problems, researching sexual problems, and educating future sexual medicine clinicians. He is the lead scientist at the New England Research Institute, one of the preeminent

epidemiologic research centers in the United States. Dr. Luca Incrocci is a radiation oncologist, an executive board member of the International Society for Sexual Medicine, and the world's foremost authority on the impact of radiation on sexual function. I would like to thank each and every one of the authors who have contributed to this book. For anyone who has written a book chapter, it is easy to understand how much work this entails. I believe we have congregated the world's leading experts in their respective areas.

Finally, I would like to extend my sincerest gratitude to the staff at Springer for the expert guidance and assistance in bringing this idea from the initial vision to the completed work. A debt of gratitude is due to Paul Dolgert for spearheading the initial effort which was expertly taken over by Richard Hruska for the completion of the project. Finally, to Kathryn Hiler for practicing the proverbial "herding of cats" in getting all of the manuscripts into production.

I hope this book will be a success, will help you in your daily practice, and will translate into helping our cancer patients. In the 12 months or so since this project started, we as editors already have ideas about chapters that are missing and topics not covered, which we will hopefully address in the next volume of this work.

New York, NY John P. Mulhall, MD

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Part I
Normal Sexual Function

Chapter 1
Functional Anatomy of the Male Sex Organs

Anthony J. Bella MD and Rany Shamloul MD, PhD

Keywords Anatomy • Prostate • Arterial supply • Cavernous nerves • Penis

Introduction

The male genital system consists of both external and internal sexual and reproductive organs, including the penis as well as the testis, epididymis, vas deferens, seminal vesicle and the prostate. In this chapter, an overview of the gross and microscopic anatomy of the male genitalia is provided.

Penis

The penis is essentially a tripartite structure, with bilateral corpora cavernosa, a midline ventral corpus spongiosum, and glans, all three of which are surrounded by loose subcutaneous tissue and skin which can be moved freely over the erect organ (Fig. 1.1). The corpora cavernosa facilitates an erection by complete relaxation of smooth muscle allowing arterial blood to flow into the corporal bodies. On the other hand, while the corpus spongiosum contains a considerable amount of erectile tissue, its main function is to provide adequate covering to the male penile urethra and contributes little to erectile function. The glans (head) of the penis is an extension of the corpus spongiosum. The point at which the glans is draped over the penile shaft is known as the coronal sulcus. The length of the penis varies widely, especially in the flaccid state. Stretched penile length, as measured from the pubic junction to the coronal sulcus or meatus, gives a reasonable approximation of erect length [1].

Skin and Fascia

Penile skin is continuous with that of the lower abdominal wall and continues over the glans penis; there it folds back on itself and attaches at the coronal sulcus. The folded portion is known as the prepuce. There are two fascial layers, the more superficial of which is the Dartos fascia, continuous with Scarpa's fascia of the abdomen. It continues caudally as the Dartos fascial layer of the scrotum and Colles' fascia in the perineum. The deeper fascial layer is Buck's fascia, which covers the corpora cavernosa and the corpus spongiosum in separate compartments, including coverage of the deep dorsal vein as well as the dorsal neurovascular bundles. The fundiform and suspensory ligaments attach to the pubic symphysis and Buck's fascia, and allow the erect penis to achieve a horizontal or upright angle.

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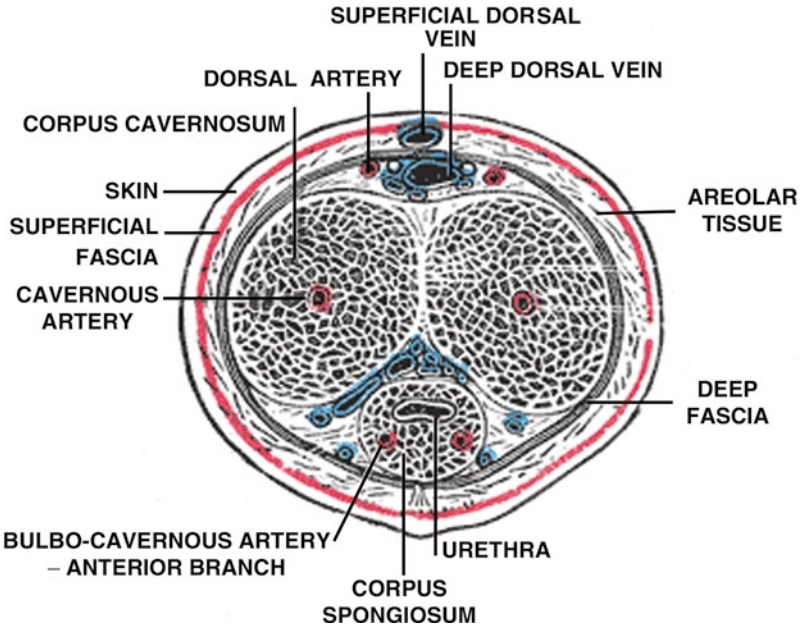

Fig. 1.1 Cross-sectional anatomy of the penis

Tunica Albigunea

The tunica albigunea is a strong bilayered fibrous sheath of heterogenous thickness that surrounds the corpora cavernosa. The main function of this thick covering is to both provide rigidity of the erectile bodies as well as functioning in the veno-occlusive trapping mechanism. It is composed of two primary layers, the outer of which is oriented longitudinally and the inner layer in a circular fashion. The inner layer contains strong supports (struts) that traverse the cavernosal space and serve to expand the support provided by the intracavernosal septum, which is akin to a midline strut. The tunica itself may be considered a "mesh" that is composed of elastic fibers that form an irregular, latticed network on which the collagen fibers rest. The composition and distribution of component fibers is a fundamental factor in rendering the function of the tunica; it is primarily composed of type I, but also type III, fibrillar collagen in organized arrays throughout which are interspersed elastin fibers [2]. Both fiber types are essential for normal function: the steel-like tensile strength of collagen is unyielding and resists uncontrolled deformity at high pressure, while elastin content allows for tunical expansion as these fibers are able to stretch to approximately 150% of "resting" length [3]. Elastin content is also an important determinant of stretched penile length.

Thickness ranges from approximately 0.8 mm at the 5 o'clock and 7 o'clock positions (just lateral to the corpus spongiosum) to 2.2 mm at the 1 o'clock and 11 o'clock positions. This coincides with the absence of the outer longitudinal layer at the ventral groove over the urethra; extrusion of penile prosthesis is most common at this location [4]. The corpus spongiosum lacks both the outer layer as well as the strong supports or struts.

In addition to providing a supportive framework to the paired corpora, the tunica albuginea is essential to venous trapping and pathophysiological changes such as those seen postradical prostatectomy or with Peyronie's disease may compromise this function and lead to venous leak. The emissary veins travel between the inner and outer layers of the tunica for short distances, and pierce the outer bundles in an oblique manner [5]. The outer longitudinal layer serves as a backboard, resulting in compression of the emissary veins during penile engorgement and limiting the amount of penile blood which is able to drain away from the corpora. The end-result is maintenance of an erect penis. Inadequate venous

occlusion may result in erectile dysfunction via the following mechanisms: (1) degenerative tunical changes secondary to Peyronie's disease, aging, diabetes, or traumatic denervation injury (postradical pelvic surgery) impairing subtunical and emissary vein compression, (2) alteration in the fibroelastic components of the cavernous smooth muscle, trabeculae or endothelium, (3) inadequate cavernous smooth muscle relaxation, (4) acquired venous shunts, or (5) congenital anomalous large venous channels [6].

Corpora Cavernosa and Spongiosum

The paired corpora cavernosa originate separately underneath the ischiopubic rami and then merge as they pass under the pubic arch. The septum between them is incomplete, allowing for neurovascular communication between sides. They are supported by several fibrous structures, including the surrounding tunica albuginea, the intracavernous struts radiating from the inner layer of tunica albuginea, and perineural/periarterial fibrous sheaths. The spongy inner portion of the corpora consists mainly of interconnected sinusoids separated by smooth muscle trabeculae, which are surrounded by collagen and elastic fibers. These sinusoids are larger centrally and smaller toward the periphery. The corpus spongiosum and its distal termination in the glans penis are similar in internal structure to the corpora cavernosa except that the sinusoids are larger and there is a lack of outer layer of tunica albuginea. The tunica albuginea is not present in the glans penis.

Similar to the tunica, cavernosal design reflects a functional need for rigidity, strength, and flexibility. It has been suggested that the intracavernous fibrous framework adds strength to the tunica albuginea. Within the tunica are the interconnected sinusoids separated by smooth muscle trabeculae and surrounded by collagen (predominant types I and IV), elastin, fibroblasts, and loose areolar tissue [7, 8]. Smooth muscle predominates, accounting for 45% of corporal volume [9]. Alterations of the cytoskeleton for either tissue-type components and/or relative quantities may be responsible for changes in penile morphology in flaccid and erect states. For example, loss of compliance of the penile sinusoids has been observed as a by-product of aging, and is associated with increased deposition of collagen; hypercholesterolemia-induced dysregulation of collagen may also cause loss of compliance [10].

The structure of the corpus spongiosum is similar to that of the corpora except that sinusoids are larger and the outer layer of the tunica is absent. Intraspongiosal pressures reach only one-half to one-third that of the cavernosa due to the less constraining tunical layer, resulting in lesser venous occlusion [10]. The glans itself has no tunical covering, however, it is still able to engorge due to the presence of continued arterial inflow and venous outflow during erection [11]. Partial compression of the deep dorsal and circumflex veins between Buck's fascia and the engorged corpora cavernosa also contribute to glanular tumescence. The spongiosal and penile veins are externally compressed by the ischiocavernosus and bulbocavernosus muscles during the rigid erection phase, further increasing engorgement and pressure in the glans and spongiosum.

In the flaccid state, cavernous (or corporal) smooth muscle is tonically contracted with a partial pressure of oxygen measuring approximately 35 mmHg [12]. Blood flow to the penis is approximately 5 mL per minute [8]. With sexual stimulation and the release of neurotransmitters (mainly nitric oxide – NO) from the cavernous nerve terminals, smooth muscle relaxation occurs and the end-result is an erect penis.

Modulation of the cavernous smooth muscle tone is a complex process regulated by a myriad of intracellular events and extracellular signals; therefore it is not surprising that ultrastructure reflects these physiologic functions. Cavernous smooth muscle cells are composed of thin, intermediate and thick filaments which are primarily composed of actin, desmin or vimentin, and myosin, respectively [2]. In humans, two types of electrical activity have been reported for the corpus cavernosum: spontaneous and activity-induced [13].

Further, DiSanto and associates have reported overall composition to be in-between aortic (tonic) and bladder smooth muscle (phasic) [14].

Smooth muscle contraction and relaxation is primarily regulated by sarcoplasmic-free calcium. Each of the filament types has a specific role, but the primary mechanism is the interaction between actin and myosin. Contractile tone is conferred by cross-bridges linking regulatory myosin light chain globular heads and actin; tone is maintained with minimal expenditure of energy [15]. Relaxation occurs with a decrease in cytosolic calcium.

Smooth muscle fibers damaged by vasculogenic or neurogenic causes of erectile dysfunction demonstrate similar ultrastructural changes, suggesting a variety of pathological mechanisms with common endpoints [16]. Patients undergoing implantation of a penile prosthesis for ED of varying etiologies have been shown to have a decreased number of smooth muscle cells and sinusoidal endothelial changes [16]. The decreased oxygen tension of arteriogenic ED may diminish trabecular smooth muscle content, leading to venous leakage. Diabetes may compromise contractility, reduce cavernous smooth muscle content, thicken the basal lamina, increase collagen, and cause the loss of endothelial cells [16, 17]. Cavernous nerve injury at the time of radical prostatectomy may also decrease the levels of cavernous smooth muscle while increasing collagen content, compromising the erectile process [18].

Associated Musculature

The paired ischiocavernosus muscles originate from the ischial tuberosity, cover the proximal corpora, and insert into the infero-medial surface of the corpora. Nerve supply of these muscles is from the perineal branch of the pudendal nerve. The ischiocavernosus muscles function primarily to allow the corpora cavernosa to obtain very high intracorporal pressures that would not be possible with arterial pressure alone. The bulbospongiosus muscle originates at the central perineal tendon, covers the urethral bulb and corpus spongiosum, and inserts into the midline. Nerve supply of this muscle is through a branch of the perineal nerve. The bulbospongiosus muscle has an important role in the ejaculation of semen.

Penile Vascular Anatomy (Fig. 1.2)

The internal pudendal artery, a branch of the internal iliac artery, is the main source of arterial blood supply to the penis. In many instances, however, accessory arteries arise from the external iliac, obturator, vesical, and/or femoral arteries, and may occasionally become the dominant or only arterial supply to the corpus cavernosum [19]. Damage to these accessory arteries during radical prostatectomy or cystectomy may result in vasculogenic erectile dysfunction (ED) after surgery [20, 21]. The internal pudendal artery becomes the common penile artery after giving off a branch to the perineum. The three branches of the penile artery are the dorsal, bulbourethral, and cavernous arteries. The cavernous artery is responsible for tumescence of the corpus cavernosum and the dorsal artery for engorgement of the glans penis during erection. The bulbourethral artery supplies the bulb and corpus spongiosum. The cavernous artery enters the corpus cavernosum at the hilum of the penis, where the two crura merge. Distally, the three branches join to form a vascular ring near the glans. Along its course, the cavernous artery gives off many helicine arteries, which supply the trabecular erectile tissue and the sinusoids. These helicine arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection. The helicine arteries enter into the blood sinusoids directly without traversing a capillary bed. The blood supply to the penile skin is dependent upon the right and left external pudendal arteries that arise from the femoral artery.

The venous drainage from the three corpora originates in small venules leading from the peripheral sinusoids immediately beneath the tunica albuginea. These venules travel in the trabeculae between the tunica and the peripheral sinusoids to

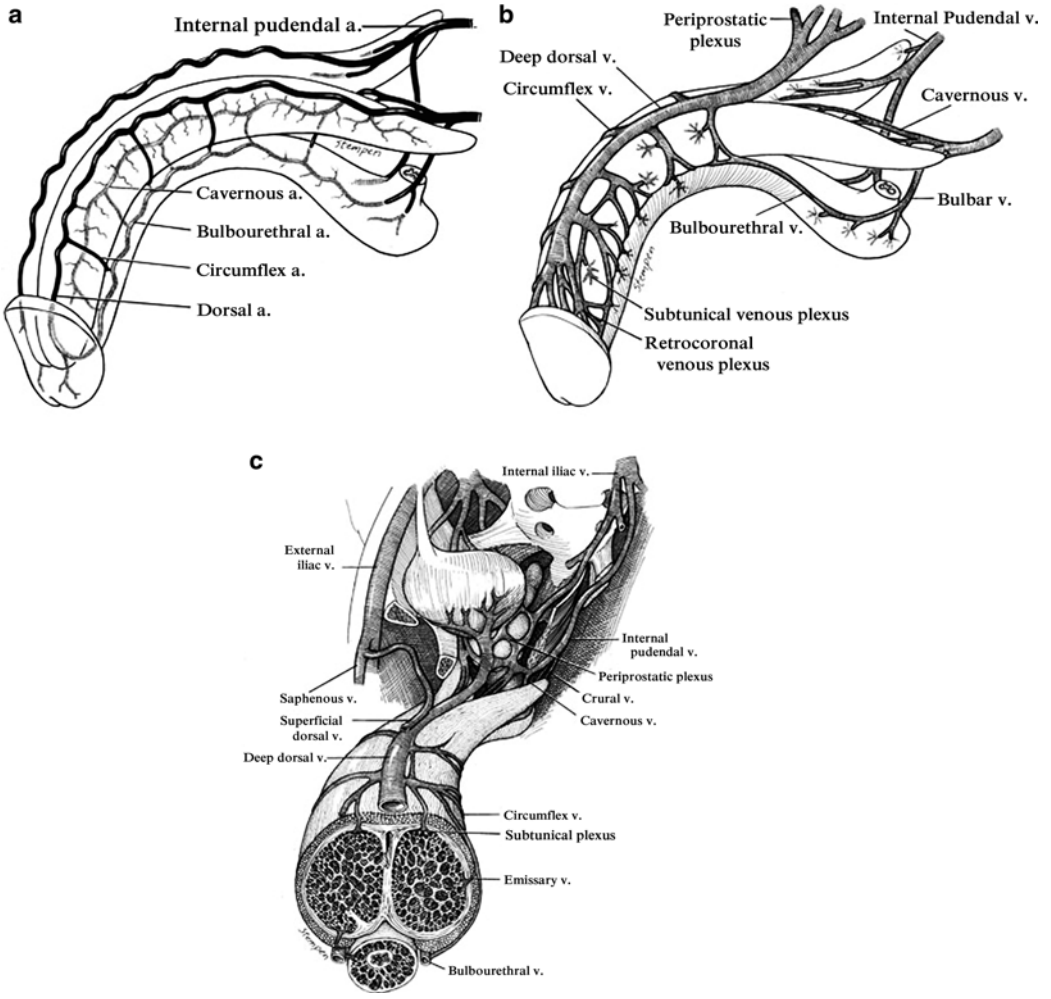

Fig. 1.2 (**a**) Arterial anatomy of the penis, (**b**) venous anatomy of the penis, and (**c**) dorsal venous plexus

form the subtunical venular plexus before exiting as the emissary veins. Outside the tunica albuginea, the venous drainage is as follows:

1. The skin and subcutaneous tissue drain through multiple superficial veins that run subcutaneously and unite near the root of the penis to form a single (or paired) superficial dorsal vein, which in turn drains into the saphenous veins. Occasionally, the superficial dorsal vein may also drain a portion of the corpora cavernosa.
2. In the pendulous penis, emissary veins from the corpus cavernosum and spongiosum drain dorsally to the deep dorsal, laterally to the circumflex, and ventrally to the periurethral veins. Beginning at the coronal sulcus, the prominent deep dorsal vein is the main venous drainage of the glans penis, corpus spongiosum, and distal two-thirds of the corpora cavernosa. Usually, a single vein, but sometimes more than one deep dorsal vein, runs upward behind the symphysis pubis to join the periprostatic venous plexus.
3. Emissary veins from the infrapubic penis drain the proximal corpora cavernosa and join to form cavernous and crural veins. These veins join the periurethral veins from the urethral bulb to form the internal pudendal veins.

Lymphatics

Lymphatics of the prepuce and penile shaft converge dorsally, and then drain into both right- and left-sided superficial inguinal lymph nodes via channels alongside superficial external pudendal vessels. Lymphatics of the glans and penile urethra pass deep to Buck's fascia and drain into both superficial and deep inguinal nodes.

Innervation

The penis is supplied by both somatic and autonomic nerves. The somatic dorsal nerves primarily provide sensory innervation for the penile skin and glans, and approximately follow the course of the dorsal penile arteries, eventually becoming the pudendal nerve and entering the spinal cord via S2–4 nerve roots. The pudendal nerve gives off a motor branch to the ischiocavernosus and bulbocavernosus muscles whose contraction help to increase the rigidity of erection. The pudendal nerve also gives a sensory branch that supplies the penis, perineum, and the rectum.

Sympathetic autonomic fibers derive from the hypogastric plexus and join parasympathetic autonomic fibers from S2–4 in the pelvic plexus. Cavernous nerves represent the penile branches of the pelvic plexus that ramify once piercing the corporal bodies, and thus contain both sympathetic and parasympathetic fibers.

Urethra (Fig. 1.3)

The male urethra is a canal that extends from the bladder neck to the external urethral meatus passing through the substance of the corpus spongiosum. It is about 20–22 cm in length. The urethra is essentially a potential canal that opens only during micturition and has a characteristic S-shaped course. The male urethra is further divided into the following parts:

1. Posterior urethra: This is composed of the prostatic urethra and the membranous urethra. The prostatic urethra is approximately 3 cm in length and considered to be the widest and most distensible part of the canal. It extends from the neck of the bladder passing through

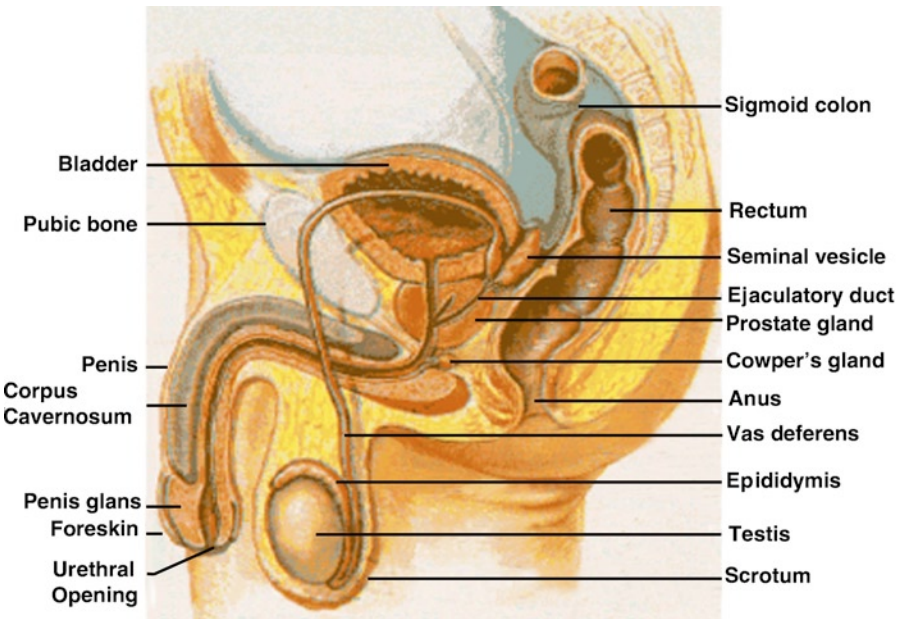

Fig. 1.3 Cross-sectional anatomy of the pelvis

the substance of the prostate to end at the prostatic neck by becoming the membranous urethra. Its posterior wall shows an elevation termed the "veromontanum" which is related to three important structures: the prostatic utricle, paired ejaculatory ducts, and the prostatic ducts. The membranous urethra is the thickest part of the urethra as it passes through the urogenital diaphragm and it is a muscular organ with both smooth and skeletal muscles. The skeletal muscle part of the membranous urethra forms the external (voluntary) sphincter.

2. Anterior urethra: This portion is about 15-cm long extending from the membranous urethra to the external urethral meatus at the tip of the glans penis. The anterior urethra is formed by the bulbous urethra and the penile or pendulous urethra. The bulbous urethra is the proximal part of the anterior urethra and is surrounded by the bulb of the penis and the bulbospongiosus muscle, while the penile urethra is the distal-free part of the anterior urethra and is the continuation of the proximal bulbar urethra at the lowest level of symphysis pubis. The penile urethra ends by passing through the glans penis where it forms a small dilatation named the "fossa navicularis" to terminate at the external meatus, the narrowest point of the entire canal.
3. Urethral sphincters
   (a) The internal sphincter controls the bladder neck and the prostatic urethra above the opening of the ejaculatory ducts. It consists of involuntary nonstriated muscles and is supplied by autonomic nerve supply.
   (b) The external sphincter, within the membranous urethra is formed of voluntary striated muscles and supplied by somatic nerve supply [11].

Testis

The male testes are ovoid organs suspended by the spermatic cord within the scrotum. The spermatic cord has three fascial layers, namely the external spermatic fascia, the cremasteric muscle and fascia, and the internal spermatic fascia. The spermatic cord contains vascular and nonvascular structures, the most important of which is the vas deferens. The scrotum itself is a sac formed of an outer thin skin layer (containing sebaceous glands and hair but no subcutaneous fat), the dartos muscle and the dartos fascia.

Each testis is about 4.5 cm long (average of 3.5–5.5 cm), about 3 cm wide (average of 2–3.5 cm) and 3 cm in its anteroposterior diameter. The volume of each testis ranges from 15 to 25 mL [22]. Generally, the testis has three main coverings, called the tunics. The outer layer is the tunica vaginalis, the intermediate layer is the thickened tunica albuginea, and the inner layer is the tunica vasculosa. By the time of birth both testes should be completely descended in the scrotum. Abnormal testicular positions are not uncommon and can affect one or both testes. This may include testis suspended high in the scrotum (at the scrotal neck) or having an inguinal canal location, or being ectopic (not in the normal descent pathway) or less commonly impalpable (abnormal or absent). The testicular orientation is usually vertical in the scrotum. A transverse lie of the testis is considered pathological and may predispose to recurrent attacks of testicular torsion especially in adolescent boys [23].

The inner aspect of the tunica albuginea gives off a number of thin septa that converge on the posterior aspect of the testis itself to form a mass of fibrous tissue known as the mediastinum testis. The mediastinum testis acts as a supporting structure to the testicular vessels and ducts that pass through it. The parenchyma of the testis exists within the aforementioned framework. It is light brown in color and is divided into several hundred lobules by fibrous septa. Each lobule contains a number of seminiferous tubules that harbor the germ cells, the supporting Sertoli cells and are further surrounded by the interstitium [24].

The testicular artery is main arterial blood supply to the testis. It is a branch from the abdominal aorta originating just below the root of the renal artery. The testicular artery crosses the ureter (supplying it) and then passes through the inguinal canal within the spermatic cord

where it ends by forming a convoluted network of vessels that supplies the testis through the mediastinum testis. Thus, the mediastinum testis is considered to be the most vascular part of the testis. The testicular artery also gives a branch to the upper part of the epididymis. Further blood supply to the testis comes from the vasal artery which originates from the inferior vesical artery, supplying mainly the vas deferens.

Testicular venous drainage can be divided into three main groups. The anterior group, called the testicular veins, is formed by the pampiniform plexus which is closely associated with the testicular artery. This pampiniform plexus constitute the main venous drainage of the testis. As blood passes high through this plexus, its branches decrease gradually until passing through the external inguinal ring where they become the single testicular vein. The left testicular vein drains into the left renal vein, while the right testicular vein drains into the inferior vena cava [25].

The middle group of the testicular venous drainage, made up of the vasal veins, drain the vas and the epididymis into the prostatic and the vesical venous plexuses. Finally, the posterior group, made up of the cremasteric veins, becomes separated from the spermatic cord at the external inguinal ring and drains into the inferior epigastric vein [25].

The intratesticular lymph ducts originate in the testicular interstitium and ascend inside the spermatic cord to drain finally into the paraortic lymph nodes at the lumbar region. Nerve supply to the testes primarily originates high in the spinal cord from the 10th and 11th thoracic segments. These nerves accompany the testicular artery through its passage in the inguinal canal, supplying the tunica albuginea of the testes with autonomic pain receptors while the testicular parenchyma itself is devoid of any pain receptors.

Epididymis

The human epididymis is a comma-shaped structure that overlies the superior and posterior surfaces of the testis. It is formed of the head (upper part), the body (intermediate), and the tail (lower part). The tail is attached firmly to the lower pole of the testis by a fibrous remnant of the gubernaculums known as the epididymal ligament. Microscopically, the epididymis is formed as follows: the seminiferous tubules in the testis form a network in the mediastinum testis named the rete testis. From this rete testis arise (12–20) efferent ductules (vasa efferentia) that pass from the testis to the epididymis to form the epididymal lobules in the epididymal head. Then, they unite to form the convoluted duct of the epididymis that is 6 m long enclosed within a connective tissue sheath in the body of the epididymis. Finally, this epididymal duct ends in the tail of the epididymis by joining the vas deferens. The arterial supply of the epididymis comes from a branch from the testicular artery (internal spermatic artery) that is a branch from the aorta; additional collaterals from the cremasteric (external spermatic artery) and vasal arteries are present. Venous drainage is from the vena marginalis of the epididymis, and may join the cremasteric veins and the pampiniform plexus of veins, forming a network of about 15 veins around the testicular artery. These veins fuse in the inguinal canal to form the testicular (internal spermatic vein) that drains into the left renal vein (on the left side) and the inferior vena cava (on the right side).

Vas Deferens

The human vas deferens is a muscular tube of about 45 cm long and 2.5 mm in diameter. It begins as a continuation of the lower end of the epididymal duct at the level of the epididymal tail and ends by uniting with the duct of the seminal vesicle to form the ejaculatory duct that opens on the veromontanum on the prostatic urethra [25]. The vas deferens runs a long course that can be divided into five main segments. The epididymal aspect starts at the epididymal tail and runs a winding course within the tunica vaginalis along the posterior aspect of the testis. Following that, the scrotal portion runs a straight

course within the spermatic cord. As the vas enters the inguinal region (the inguinal part) through the external inguinal ring, it is accompanied by the artery of the vas deferens. The pelvic part of the vas begins in the pelvic retroperitoneal space (related to the ureter and the urinary bladder) and then dilates forming the ampulla of the vas. The vas then narrows again, unites with the duct of the seminal vesicle to form the ejaculatory duct, which opens in the prostatic urethra. The arterial supply to the vas comes from the vasal artery off of the inferior vesical artery branch of the internal iliac artery. The vasal artery gives a dense network of the capillaries to the vas. The venous drainage and the lymphatic drainage of the vas follow that of the epididymis.

The Prostate

The prostate has the shape of an inverted cone with posterior, anterior, and two inferolateral surfaces. It measures about 3.5 cm transversely at its base and about 2.5 cm in its vertical dimension. It surrounds the prostatic part of the urethra, related anteriorly to the symphysis pubis and posteriorly to the rectum. The prostate is mostly formed (70%) of a glandular element and a small fibromuscular element (30%). The acini and the ducts of the glands are lined by a columnar epithelium. Prostatic ducts open into the prostatic urethra. The arterial supply of the prostate comes from the inferior vesical artery and the middle rectal artery. The venous drainage of the prostate is into the inferior vesical veins or the vertebral venous plexus [26].

Seminal Vesicles

These paired organs are formed of a highly convoluted glandular sac about 5 cm long and 1 cm wide. They lie lateral to the vas deferens and their ducts join it to form the ejaculatory ducts. The arterial supply and venous drainage are similar to that of the prostate.

Other glands related to the urethra include the Cowper's glands, which are a pair of glands on either side of the membranous urethra whose ducts open into the bulbar urethra. Their main function is to secrete drops of mucoid secretion called the pro-semen during the excitation stage of the male sexual response cycle. Littre's glands are multiple mucous glands on the submucosa of the penile urethra and open by ducts into the penile urethra. Tyson's glands are located just proximal to the coronal sulcus with their ducts opening on either side of the frenulum. These glands produce a sebaceous secretion known as the smegma, which helps the retraction of the prepuce over the glans penis in non-circumcised males.

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Chapter 2
Functional Anatomy of the Female Sex Organs

Van Anh T. Ginger and Claire C. Yang

Keywords Anatomy • Vagina • Clitoris • Uterus

Introduction

The emphasis of the study of the female sex organs has long been on understanding its reproductive role rather than sexual responsiveness. The majority of anatomic descriptions for these organs have been from the context of reproduction. Yet, there is a growing awareness that while sharing some of the same anatomical structures and hormonal milieu, sexual function and fertility/reproductive function are distinct, with unique physiological responses.

The following is a brief presentation of the anatomy and histology of the female sex organs, from the perspective of understanding the pathophysiology of sexual function.

General Structural Relationships

The external genitalia are referred to collectively as the vulva and consists of the mons pubis, clitoris and bulbs, labia majora, and labia minora (Fig. 2.1). The *mons pubis* is an area of fatty tissue overlying the pubic symphysis, covered by pubic hair. The body of the *clitoris* extends into the mons for several centimeters, before bifurcating into the crura, which run bilaterally under the inferior pubic rami. Between the crura lie the clitoral bulbs, draped over the *urethra*, with the bulk of their tissue lateral to the vaginal walls (Fig. 2.2). Only the glans clitoris is visible externally, approximately 1 cm superior to the urethral meatus. The *labia majora* are fatty, elongated, hair bearing folds of tissue forming the lateral boundaries of the vulva. The medial aspects of the labia majora fuse with the *labia minora*, which are thin folds of skin outlining the *introitus*, or entry to the vagina. The anterior aspects of the labia minora split and fuse with the ventral aspect (or frenulum) of the glans clitoris and also unite over the glans as a hood, known as the clitoral prepuce. The posterior aspects of the labia minora fuse in the midline at the lower aspect of the introitus. The urethra is located immediately superior to the introitus.

The internal genitalia are comprised of the vagina, the uterus (including cervix), uterine tubes, and ovaries (Fig. 2.3). The vagina is immediately posterior to the urethra and bladder and extends from the perineum superiorly and posteriorly toward the cervix, which protrudes into the vagina at approximately a 90° angle. The uterus typically is positioned posterior and superior to the bladder. Posterior to the vagina is the rectum. Loops of intestine are found superior and posterior to the uterus. The ovaries and uterine tubes extend laterally from the superior aspect of the uterus.

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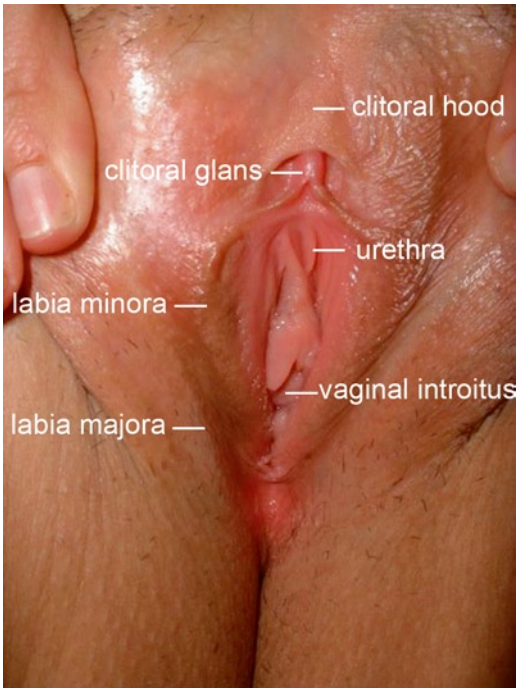

Fig. 2.1 Female external genitalia (premenopausal woman) (Image from http://commons.wikimedia.org/wiki/File:Womans_vulva.jpg. Under GNU Free Documentation License.)

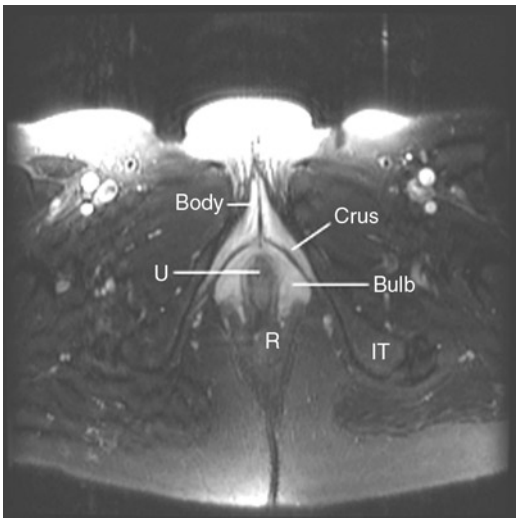

Fig. 2.2 Axial view of female genitalia, magnetic resonance image. The high intensity signal of the clitoris and the bulbs is a function of the high blood flow within these structures. (The high signal intensity of the mons and surrounding tissue is artifact.) *Body* body of clitoris; *Crus* clitoral crus; *U* urethra; *R* rectum; *IT* ischial tuberosity (image courtesy of Kenneth R. Maravilla, MD)

External Genital Anatomy

Gross anatomical and histological study of the clitoris, clitoral bulbs, labia minora, and urethra reveals them to contain specialized vascular tissues that are sexually responsive [1] and consist of two histologically distinct types of vascular tissue. The first type is the trabeculated erectile tissue seen in the clitoris and the bulbs. Gross examination of these structures demonstrate large, dilated vascular spaces that are filled with blood and are spongy in appearance (Fig. 2.4). On histological examination, the erectile tissues are trabecular, with smooth muscle underneath the epithelium of the vascular spaces. The erectile tissue of the clitoris and bulbs is very similar to that of the male corpora cavernosa and corpus spongiosum. In contrast to the clitoral and bulbar erectile tissue, the labia minora and glans clitoris are composed of nonerectile vascular tissue in which the blood vessels are dispersed within a fibrous matrix, with only a minimal amount of smooth muscle. Nonerectile, sexually responsive vascular tissue is also found surrounding the urethral lumen and within the walls of the vagina (see below).

Clitoris

The structure of the clitoris has been "rediscovered" many times over the years by anatomists due to the frequent omission or misrepresentation of the organ in historical and contemporary anatomical texts. The clitoris is comprised of two erectile bodies, the corpora cavernosa. The body is the convergence of two corpora, and the crura are the extensions of the corpora beneath the descending pubic rami. Each of the corpora cavernosa is surrounded by a thick fibro-elastic tunica albuginea (Fig. 2.5). Because the majority of the clitoris is hidden by the mons pubis, there is a lack of appreciation for the substantial nature of these erectile bodies in the vulva (Fig. 2.4). The clitoral body and the crura can be 10 cm or more in length with the body measuring 5–7 cm in length.

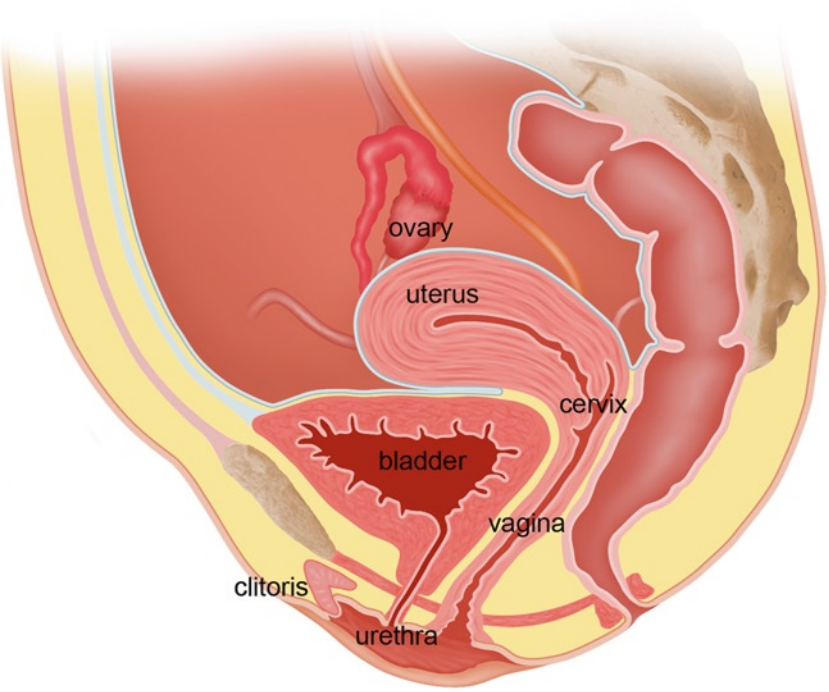

Fig. 2.3 Female internal genitalia, sagittal view (based on drawing by Robert Holmberg, Seattle, WA)

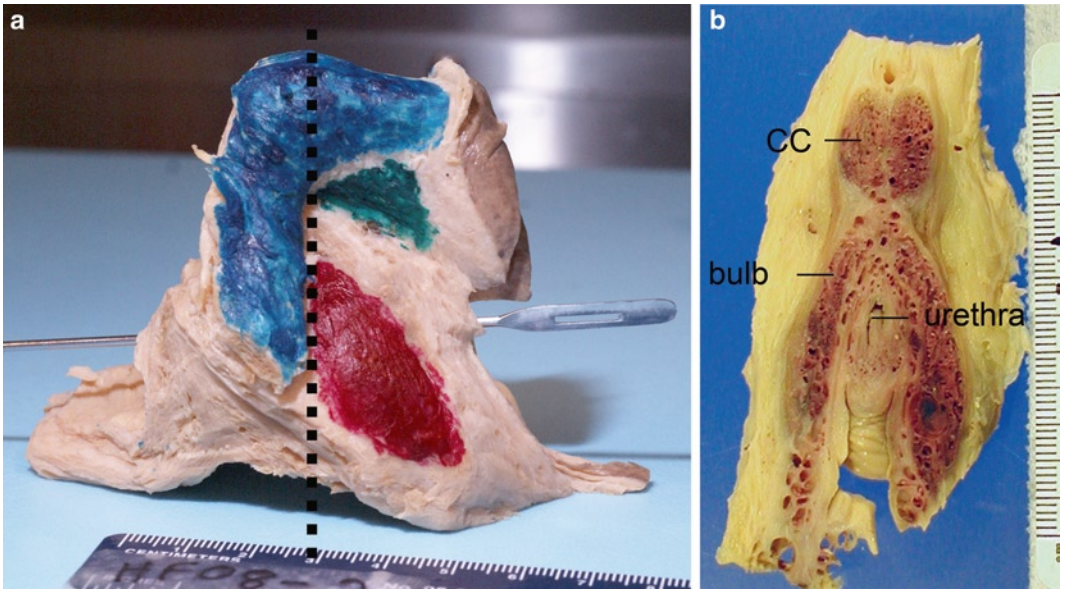

Fig. 2.4 Clitoris and bulb. (**a**) Gross sagittal view of external genitalia. Clitoris is inked *blue*, with body extending anteriorly into mons pubis and prepuce (glans not visible), and right crus amputated. Skin appears *dark brown*, and subcutaneous tissue is *tan*. Pars intermedia, a collection of vessels between the clitoral body and urethra, is stained *green*. Right clitoral bulb stained *red*. Metal probe placed through urethral lumen (not visible). *Vertical line* indicates the approximate level of the cross-section seen in adjacent image 1.4**b**. Centimeter ruler. (**b**) Axial view of genital cross-section. The darker colored tissue is erectile tissue with residual pooled blood. The large, dilated vascular spaces are apparent in the clitoral body and the bulbar tissue draped over the urethral lumen. The rugae of the anterior vaginal wall is seen beneath the urethral lumen. Width of clitoral body approximately 1.5 cm

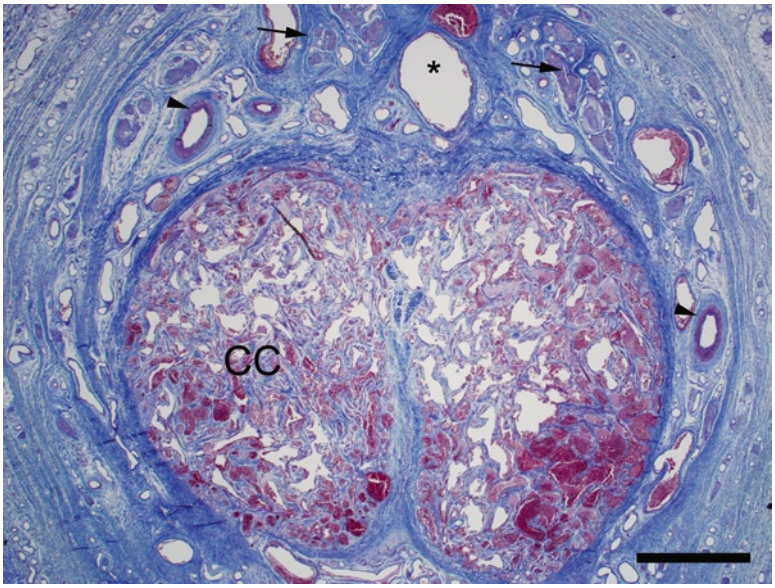

Fig. 2.5 Midshaft cross-section of clitoral body, Masson's trichrome stain. Collagen/connective tissue stained *dark blue*, smooth muscle (and residual pooled blood) stained *red*. The two corpora cavernosa converge to form the clitoral body. They are surrounded by a fibrous tunica albuginea and separated by a fibrous septum. Dilated vascular spaces comprise the erectile tissue of the corpora, some filled with residual corpuscles. Surrounding the tunica, particularly on its dorsal surface, is a collection of arteries, veins, nerves, and supporting tissue. *Arrowhead* artery; *arrow* nerve fascicles, *asterisk* vein. Bar = 1 mm

The glans clitoris rests as a fibrovascular cap at the tip of the clitoral body. Unlike its male counterpart, the glans clitoris lacks smooth muscle within its fibrovascular cap, thus differentiating it from the erectile tissue of the clitoris and bulbs. Despite its diminutive size, the glans clitoris is richly innervated and is an important mediator of sensory input for sexual arousal (Fig. 2.6). The clitoris appears to be a purely sensory organ [2].

On histological examination, the clitoral tissue is composed of large vascular spaces with mainly vascular epithelium and smooth muscle interspersed throughout. The trabecular nature of the erectile tissue allows for engorgement and expansion during sexual arousal.

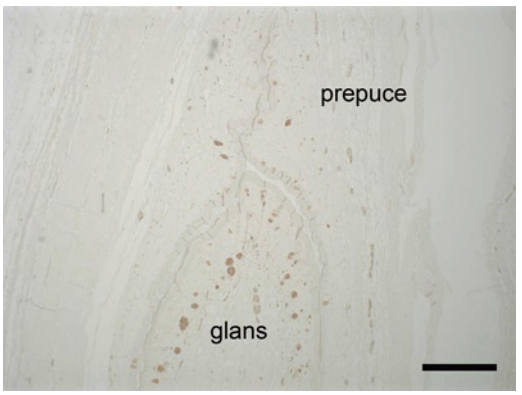

Fig. 2.6 Longitudinal section of clitoral glans and body, S100 antibody stain. Neural elements are stained *brown*. The bulbous head of the glans is surrounded by preputial tissue. Just beneath the epithelium of the glans is an abundance of neural elements, including nerve fibers and receptors. Bar = 1 mm

Bulbs

The clitoral bulbs drape over the urethra (similar to a saddle bag) with the two globular bulbs lying inferior to the clitoral body (Fig. 2.4). The bulbs are also referred to as the vestibular bulbs, but are more closely related to the clitoris than the vestibule [3]. The bulbs lie flanking the urethra

and vagina and sit recessed within the vestibule. They do not surround the introitus as suggested by some texts. There is no tunica albuginea enveloping the erectile tissue.

The size of the bulb varies between individuals and may be dependent on age and estrogenization. The bulbs are considered the equivalent of the male spongiosum, but the bulbs do not completely encircle the urethra. The histologic features of the bulb are similar to that of the clitoris. The erectile tissue of the clitoris has slightly less smooth muscle and interstitial fibro-elastic tissue, while the bulbs have more prominent fibro-elastic tissue and smooth muscle bundles lining the vascular spaces (Fig. 2.7).

During sexual arousal, the bulbs become engorged with blood. The bulbar trabecular tissue and the absence of a tunica allow for significant enlargement of the organ with increased blood flow during sexual arousal. The expansion of the bulbs and their subsequent encroachment on the introital opening may contribute to a sensation of genital engorgement.

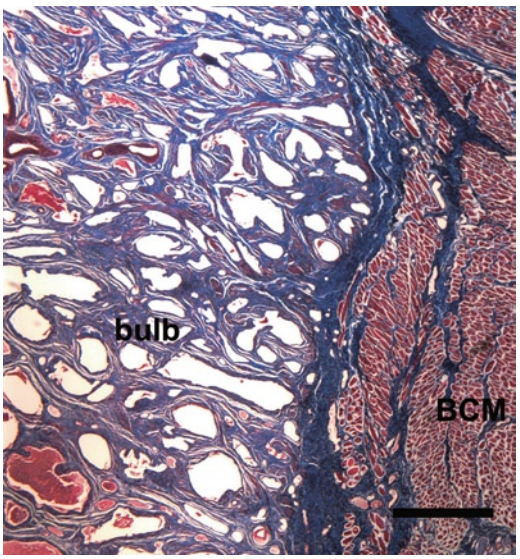

Fig. 2.7 Clitoral bulb, Masson's trichrome stain. Collagen/connective tissue stained *dark blue*, smooth muscle (and residual pooled blood) stained *red*. The erectile tissue of the bulb, like that of the clitoris, is comprised of trabecular vascular spaces designed to accommodate large volumes of blood during sexual arousal. In contrast to the clitoris, there is no surrounding tunica albuginea. Skeletal muscle of the bulbospongiosus muscle (BSM) is seen to the *right* side of the image. Bar = 1 mm

Labia Majora

The labia majora are two elongated folds of skin that extend between the mons pubis and the perineal body (Fig. 2.1). They enclose the labia minora, glans clitoris, and the vaginal introitus. They are hair bearing, pigmented skin folds. The subcutaneous tissue of the labia majora consists mostly of fat. They also contain the terminations of the round ligaments, some smooth muscle bundles, sparse nerves, and blood and lymphatic vessels. The labia majora change with sexual arousal, from what appears to be passive vasocongestion, rather than active increase in blood flow as occurs in the other parts of the vulva.

Labia Minora

The labia minora are folds of tissue between the introitus and labia majora (Fig. 2.1), and unlike the labia majora, they contain very little adipose. This skin is generally smooth, hairless, and pigmented. There is great variation in the size and shape of the labia minora between individuals. There can be some degree of atrophy with decreased estrogenization. Trauma due to childbirth and other types of irritation of the labia minora can result in asymmetric hypertrophy.

Numerous vascular structures of varying sizes are surrounded by collagenous connective tissue, not smooth muscle (Fig. 2.8). The tissue immediately deep to the epithelium is nontrabecular (nonerectile) vascular tissue. This is in distinction to the trabecular vascular tissue of the clitoris and bulbs, designed to accommodate large volumes of blood during arousal. Elastin is abundantly present, presumably to allow for labial engorgement and enlargement during sexual arousal, since there is very little smooth muscle and no trabecular erectile tissue within the labia minora. Vascular structures in the labia minora are more numerous than in the labia majora.

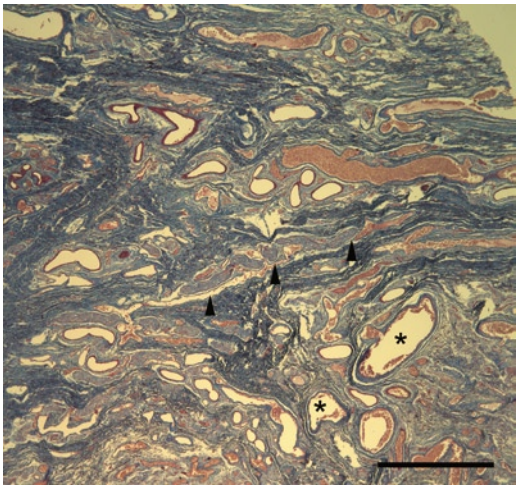

Fig. 2.8 Labium minus, elastic Masson's trichrome stain. The substance of the labium minus is filled primarily with collagen (*dark blue* stain), interspersed with elastin fibers (*black wavy lines*). Dilated vascular spaces are evident, many filled with *red* corpuscles (two examples designated by *asterisks*). Large nerve trunks traverse through this specimen, one identified by *arrowheads*. Bar = 1 mm

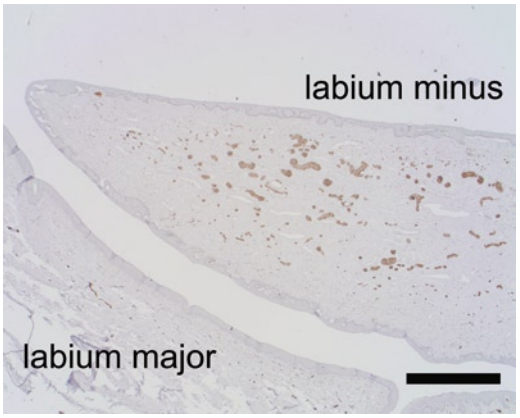

Fig. 2.9 Labium minus and labium major cross-section, S100 antibody stain. The rich innervation of the labium minus is evident with the staining of neural elements. The labium major specimen is fractured due to processing. Bar = 1 mm

Neural fibers and receptors are abundantly apparent within the labia (Fig. 2.9). There is a central core of neural elements which is present along the length of each labium. This neural core appears to travel alongside the major vascular structures within the labium minus and is the neurovascular substrate through which labial

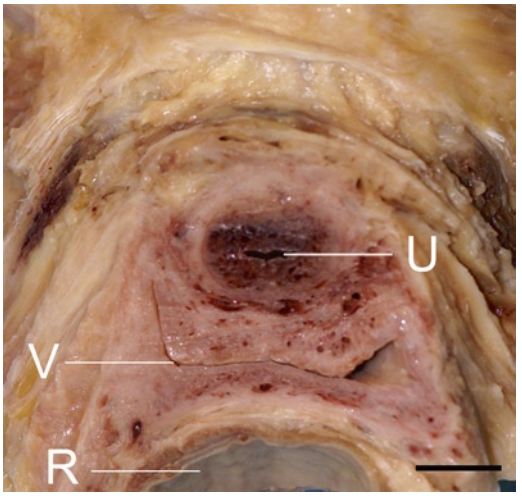

Fig. 2.10 Urethra, vagina, rectum gross specimen, axial cross-section approximately 3 cm proximal to urethral meatus. The dark tissue surrounding the urethral lumen is nonerectile vascular tissue. The collapsed vagina is seen between the urethra and rectum. Vessels are apparent in the substance of the vaginal walls, also considered nonerectile vascular tissue. *U* urethral lumen; *V* vagina; *R* rectum. Bar = 1 cm

engorgement occurs in response to sexual arousal. This is in contrast to the labia majora, where nerve fibers and receptors are sparse.

Given the generous vascular and innervation patterns within the labia minora, as well as evidence that the tissue is sexually responsive [4], there is good reason to believe that alteration of the labia minora can change sexual responsiveness. Exenterative procedures, such as vulvectomy, reduction labiaplasty, and certain forms of female circumcision, can have a deleterious effect on the sexual response by ablating the substrate through which sexual sensations enter the central nervous system.

Urethra

The urethra is a midline structure and sits deep within the introitus. It is a rugated muscular tube that is lined by stratified squamous epithelium, which becomes transitional epithelium as it approaches the bladder. The distal urethra is flanked by the erectile tissue of the clitoral bulbs. The urethral tissue bears a nonerectile vascular pattern (Fig. 2.10) and engorges with sexual

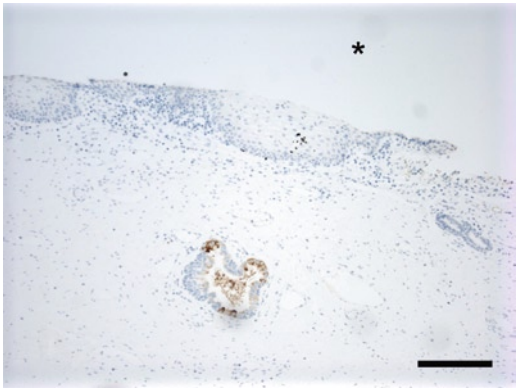

Fig. 2.11 Periurethral gland, PSA stain. The urethral tissue surrounding the lumen includes occasional glands that stain positively (*brown*) for prostate-specific antigen (PSA). The glandular elements, however, are not coalesced into any macroscopic organ. *Asterisk* designates urethral lumen. Bar = 0.1 mm

arousal. It is surrounded by the erectile tissue of the clitoral bulb, but the urethra itself contains no erectile tissue.

There are paraurethral glands along the length of the lumen. Some of these glands stain positively for prostate specific antigen (PSA) [5], leading some to state that this area is homologous to the male prostate. However, the glands are isolated (Fig. 2.11) and do not have any recognizable endocrine or exocrine function in women (the exocrine function of PSA is to liquefy semen). The region of the anterior wall of the vagina overlying the midurethra has been identified as the Grafenberg spot (or "G-spot"), an area that in some women is particularly sensitive to tactile stimulation. Numerous anatomical studies of the area have not identified gross or histological findings to distinguish it from other parts of the urethra or vaginal wall [6].

Blood Supply of the External Genitalia

The main source of blood supply for the pelvis is the internal iliac, or hypogastric, artery. From this, the internal pudendal artery gives off multiple variable branches, including the dorsal artery of the clitoris, the perineal artery, posterior labial artery, artery to the bulb, as well as the deep artery of the clitoris, which is centrally located in the erectile tissue of the corpora cavernosa. Small branches also supply the vaginal wall [7]. The venous drainage of the clitoris and bulb is via the deep dorsal vein, which then drains into the vesical venous plexus within the pelvis.

A secondary source of blood supply to the external genitalia arises from the femoral artery. A branch of the femoral artery, the external pudendal artery, divides into a series of anterior labial branches to supply the labia majora and labia minora. The external pudendal artery enters laterally from the thigh and tracks towards the vulva to join with the posterior labial arteries from the internal pudendal artery. The venous drainage of the labial skin is via the external pudendal vein, which drains into the greater saphenous vein. There is variation in tissue vascularity with age, with less vascular structures found in older women compared to younger women.

Innervation of the External Genitalia

The innervation of the external genitalia involves both somatic and autonomic fibers (Fig. 2.12). The pudendal nerve, arising primarily from spinal segments S2–4, is the main source of somatic innervation and its terminal branches to the genitalia are the dorsal nerve of the clitoris (DNC) and perineal nerve. A third branch of the pudendal nerve, the inferior rectal nerve, provides innervation to the perirectal skin, the anal sphincter, and parts of the musculature of the posterior pelvic floor. The DNC is exclusively a sensory nerve, innervating the clitoris (crura, body, and glans). The perineal nerve provides sensory innervation to parts of the labia majora, the labia minora, introitus, distal urethra, and perineal skin, as well as motor innervation to the external urethral sphincter, and much of the pelvic floor skeletal musculature.

Multiple studies have examined the pathway of the DNC, and there is still some controversy regarding its exact course. Anatomic dissections in our lab have shown the DNC to run in parallel

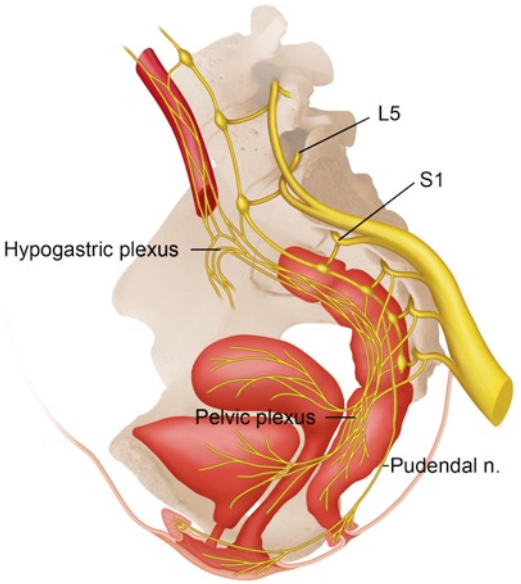

Fig. 2.12 General pattern of genital innervation. The somatic innervation of the female sex organs is mediated primarily through the pudendal nerve (S2–4). The sympathetic innervation is derived from T10 to T12, and the parasympathetic innervation is derived from S2 to S4. Not shown are autonomic fibers from the pelvic plexus to the erectile tissue of the clitoris and bulbs (based on drawing by Robert Holmberg, Seattle, WA)

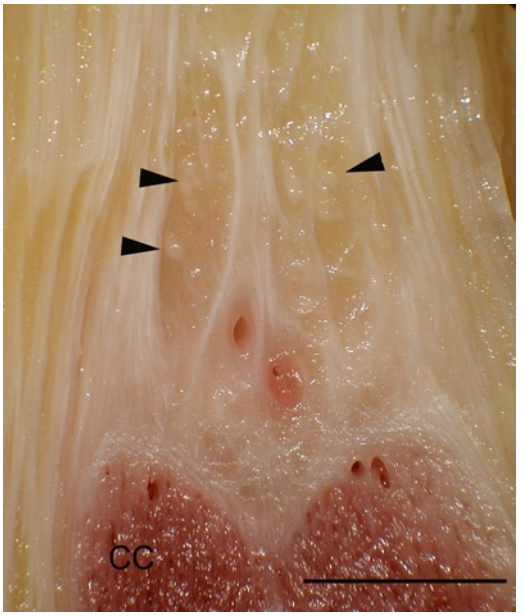

Fig. 2.13 Suspensory ligament and clitoris, gross view. The suspensory ligament is an acellular ligament that attaches the body of the clitoris to the symphysis pubis. White strands of the ligament are seen, surrounded by adipose. The ligament attaches to the dorsal aspect of the clitoral body. Within the strands of the suspensory ligament, nerve fascicles of the DNC travel toward the glans (cut ends of the nerves designated by *arrowheads*). The fascicles occur bilaterally, just lateral to the midline. *CC* corpus cavernosum. Bar = 5 mm

to the crura under the inferior pubic symphysis prior to ascending at the pubic ramus and proceeding within the suspensory ligament towards the glans clitoris (unpublished data) (Fig. 2.13).

Other areas of the vulva are innervated via nonpudendal fibers. Parts of the labia majora are innervated by the anterior labial branches of the ilioinguinal nerve.

The cavernous nerves carry the autonomic innervation to the erectile tissue of the clitoris and bulbs. While the DNC is visible to the naked eye, the fibers of the cavernous nerves are too small to identify without magnification. These sympathetic and parasympathetic fibers arising from the caudad thoracic spinal segments and the sacral spinal segments innervate the vessels and smooth muscle of the erectile and nonerectile vascular tissue of the vulva. (A more detailed description of the spinal origins of the autonomic fibers is described in section "Innervation of the Internal Genitalia.")

Internal Genital Anatomy

Vagina

The vagina is a flattened fibromuscular tube whose anterior and posterior walls are collapsed onto each other, extending from the introitus to the fornices that surround the cervix (Fig. 2.10). A longitudinal ridge is present along the mucosal surface of both the anterior and posterior walls; from these ridges, secondary elevations called rugae extend laterally. The vaginal wall consists of three layers: (1) the stratified squamous nonkeratinized epithelium and an underlying lamina propria of connective tissue; (2) the muscular layer, composed of smooth muscle fibers disposed both longitudinally and circularly; and (3) the adventitia, a dense connective tissue that blends with the surrounding fascia.

The lamina propria and connective tissue layers contain a rich supply of vascular channels. During sexual stimulation, the marked increase in fluid production in the vagina is believed to be caused by transudation across the vaginal wall. The transudate provides the lubrication needed for nonpainful and nontraumatic vaginal intercourse. There are no glands in the vaginal wall.

The stratified squamous epithelium of the adult vagina is several layers thick. The basal layer is a single layer of cylindrical cells with oval nuclei. Above this area are several layers of polyhedral cells that appear to be connected together much like those of the stratum spinosum of the epidermis. Above these are several more layers of cells that are flatter in appearance and accumulate glycogen in their cytoplasm. The most superficial cells are desquamated into the vaginal lumen where their intracellular glycogen is converted into lactic acid, probably by normal vaginal bacteria flora. The resulting acidity is believed to be important in protecting the female reproductive system from infection by most pathogenic bacteria.

Estrogen stimulates the production of glycogen and maintains the thickness of the entire epithelium. Before puberty and after menopause, when estrogen levels are relatively low, the epithelium is thin and the pH is higher than in the reproductive years (neutral before puberty and 6.0 or higher after the menopause). There is also much less transudate formed with sexual arousal following menopause.

The vaginal introitus is surrounded by the striated skeletal musculature of the pelvic floor, including the levator ani (ilioccoccygeus, pubococcygeus, puborectalis), the bulbospongiosus muscles, and the superficial and deep transverse perineal muscles. There is no discrete vaginal "sphincter," although the pelvic floor muscles in aggregate functionally contract the introital opening.

Uterus

The uterus is a muscular structure suspended in the pelvis by an arrangement of ligaments and supported inferiorly by the pelvic floor (Fig. 2.3). Its anatomy and histology is designed to accommodate the developing ovum, and it varies in size, shape, location, and structure as a result of hormonal fluctuations, pregnancy, age, and other circumstances. The reproductive physiology associated with this organ is beyond the scope of this chapter; the basic anatomy and histology, in the context of sexual function, will be described here.

Uterine Corpus (or Body)

The uterine corpus is a thick, pear-shaped organ, somewhat flattened anteroposteriorly. The wall of the body of the uterus is composed of three layers: (1) the endometrium, a glandular mucous membrane; (2) the myometrium or smooth muscle layer; and (3) the serosa.

The function of the endometrium is to provide a suitable environment for the implantation and subsequent growth of the developing embryo. As such, it is a luxuriant mucosa with a large population of glycogen-secreting glands and a rich vascular network. However, if there is no developing embryo implanted during a menstrual cycle, most of the endometrium is sloughed off (causing the menstrual flow) and is regenerated again in the next menstrual cycle. This cyclic shedding and regeneration of the endometrium is under the control of the ovarian hormones, estrogen and progesterone.

The myometrium consists of bundles of smooth muscle fibers separated by strands of connective tissue. Four layers of smooth muscle have been distinguished, but their boundaries are poorly defined owing to overlap between adjacent layers. Estrogen is essential for the maintenance of normal size and function in myometrial smooth muscle cells.

The serosa is the peritoneal covering of the uterus, attached to the uterus at the fundus and body. Four paired sets of ligaments are attached to the uterus (broad, round, cardinal, uterosacral) as well as peritoneal reflections (vesicouterine, rectovaginal, sacrogenital) that also support the uterus within the pelvis.

Cervix

The cervix is located at the inferior aspect of the uterus and is generally 2–3 cm in length. It consists primarily of dense collagenous connective tissue. Only about 15% of its substance is smooth muscle. In the uterine isthmus (the transition of the corpus to the cervix), the uterine lumen narrows down to form the internal os. Below this point, the lumen widens slightly to form the cervical canal (or endocervical canal). The external os at the lower end of the cervix provides communication between the lumen of the cervix and the vagina.

Inside the cervix, the endocervical mucosa is arranged in a series of folds and ridges. A longitudinal ridge runs down the anterior wall and another down the posterior wall; from each of these, small folds run laterally. The ectocervix is the part of the cervix that projects into the vagina and is covered by stratified squamous, nonkeratinizing epithelium.

Although it is considered primarily a reproductive organ, there is clinical evidence that the uterus and cervix do contribute to the sexual response.[8, 9] However, their relative contributions to sexual satisfaction may not be significant, according to studies that demonstrate improved sexual functioning following hysterectomy for benign disease.[10, 11] The exact mechanisms are unknown to explain sexual function changes following uterine surgery, whether it is caused by the alteration of local nerve [8] and blood supply, or by changing anatomical relationships.

Ovaries and Uterine Tubes

The ovaries are the germinal and endocrine glands of the female, contributing to the hormonal milieu in which the sexual response occurs. It is not known if the ovaries have any other function with regard to the sexual response and are typically not thought to undergo structural changes with sexual arousal. The uterine tubes are also not considered to be sexually responsive. They will not be discussed in this chapter.

Blood Supply of the Internal Genitalia

The pelvic organs are all supplied by a single arterial trunk, the internal iliac (hypogastric) artery. It forms with the bifurcation of the common iliac artery at the junction of the sacrum and the ilium. Descending in the lateral pelvis below the peritoneal reflection, the internal iliac artery gives off a series of visceral branches including the rectal, uterine, and vesical arteries. These course medially to enter the endopelvic space, at the base of the broad ligament. Before reaching the uterus, the uterine artery gives branches to the vagina and cervix. Within the broad ligament, a series of arterial branches is given to the body of the uterus until the uterine artery anastomoses with the ovarian artery at the uterotubal junction.

The uterine vein is usually plexiform, coursing laterally in the base of the broad ligament following the uterine artery before reaching the lateral pelvic wall. Here the plexus of veins forms a series of tributaries entering the internal iliac vein, which in turn empties into the inferior vena cava.

Innervation of the Internal Genitalia (see Fig. 2.12)

The uterus and vagina are innervated by autonomic and visceral afferent (sensory) fibers, which run along the uterine arteries. Sensory fibers from the uterine body descend in the parametrium (the lateral extension of the uterine subserosal connective tissue into the broad ligament) to join other fibers from the cervix to form a large plexus in the paracervical region called the uterovaginal plexus. These fibers then comingle with visceral afferents from other pelvic viscera, before entering the inferior hypogastric plexus. Ascending the sacral promontory, the fibers join the superior hypogastric plexus and enter the sympathetic chain via lumbar splanchnic nerves. From the sympathetic ganglia, white rami communicans conduct fibers

to the dorsal roots of spinal nerves T10–12. The uterovaginal plexus also includes parasympathetic motor fibers from sacral roots that enter the pelvis directly, as well as sympathetic motor fibers that enter from the sympathetic chain. The vaginal introitus is supplied by sensory fibers of the pudendal nerve. Contrary to many texts, the lower two thirds of the vagina is not somatically innervated; only the introitus and the first 1–2 cm of the distal vagina appear to have somatic sensation.

A comparative immunohistochemical study of the pelvic autonomic nerves to the uterus revealed that standard technique of radical hysterectomy results in transsection of the uterosacral ligaments, disrupting the major part of the hypogastric nerve. However, following the nerve-sparing technique of hysterectomy, only the medial branches of the hypogastric nerve appeared disrupted [9]. Division of the cardinal ligaments in the standard procedure identified the inferior hypogastric plexus running into the most posterior border of the surgical margin. The anterior part of the plexus was disrupted. Dissection of the nerves after the nerve-sparing procedure showed that the anterior part of the plexus was not involved in the surgical dissection. Dissection of the vesicouterine ligament disrupted only small nerves on the medial border of the inferior hypogastric plexus in both techniques. Whether this translates to improved postoperative sexual functioning in women with a nerve-sparing hysterectomy has not been definitively determined.

Understanding the causes of sexual dysfunction is dependent on a clear understanding of the pertinent genital anatomy. Recent research in female genital anatomy has clarified the nature of these structures, particularly in regard to their role in the sexual response. The vascular tissue of the genitalia, particularly of the vulva, is the anatomic substrate by which pelvic engorgement can occur during arousal. These tissues are erectile and nonerectile, and both types are sexually responsive. Other genital structures are not known to have direct motor responses during the sexual response, but may contribute to the sensory input required to generate and propagate the sexual reflexes. Malignancies involving the genital structures, or the treatment of malignancies, can affect the sexual response by direct injury or ablation, or indirectly by disruption of the vascular, neural, or hormonal supply to the genitalia.

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Chapter 3
Physiology of Libido

James G. Pfaus

Keywords Libido • Arousal • Nitric oxide • Medial preoptic area • Paraventricular nucleus

Introduction

Libido has always been associated with sexual motivation. The Latin root refers specifically to sexual lust, a term that conjures images of highly motivated behavior. Libido is observed in the strength of desire and responding toward a sexual incentive, and therefore can be regarded as a conscious reflection of sexual motivation, which we define here as the energizing force that generates our level of sexual interest at any given time. It drives our sexual fantasies, compels us to seek out and evaluate sexual incentives, regulates our levels of sexual arousal and desire, and enables us to masturbate, copulate, or engage in other forms of sex play. Although sexual motivation is often viewed as an internal process built upon neuroendocrine mechanisms, such as alterations in brain neurochemical function set forth by steroid hormone actions, it is also modulated by experiences and expectations, learned patterns of behavior and underlying neural activity related to sexual arousal, desire, reward, and inhibition. In turn, these aspects of sexual function feed back on mechanisms of motivation, either to increase (as in the case of arousal, desire, or reward, Fig. 3.1a) or decrease (as in the case of reward or inhibition, Fig. 3.1b) the expression of sexual interest or libido. Delineating the neural mechanisms that underlie these aspects of sexual function has been the focus of recent research in animals and humans.

Sexual Arousal

Physiological sexual arousal in all animals can be defined as increased autonomic activation that prepares the body for sexual activity. This includes parasympathetic blood flow to genital and erectile tissues and sympathetic blood flow from the heart to striated and smooth muscles that participate in sexual responses (e.g., increased breathing rate, heart rate, pupil dilation, etc.). Sexual arousal also includes a central component that increases the psychological preparedness to respond to sexual incentives.

Increases in general sympathetic outflow produce increases in libido. This can occur following the use of psychomotor stimulant drugs [1], or ingestion of herbal "aphrodisiacs" that contain psychoactive alkaloids or other substances that stimulate the autonomic nervous system [2]. However, these putative increases in libido are most likely to occur in sexually-specific situations, indicating an interaction between autonomic activation and the central processing of sexual incentives in the immediate environment. High sympathetic activation is an important antecedent of premature ejaculation [3], which is often characterized by "high" libido in

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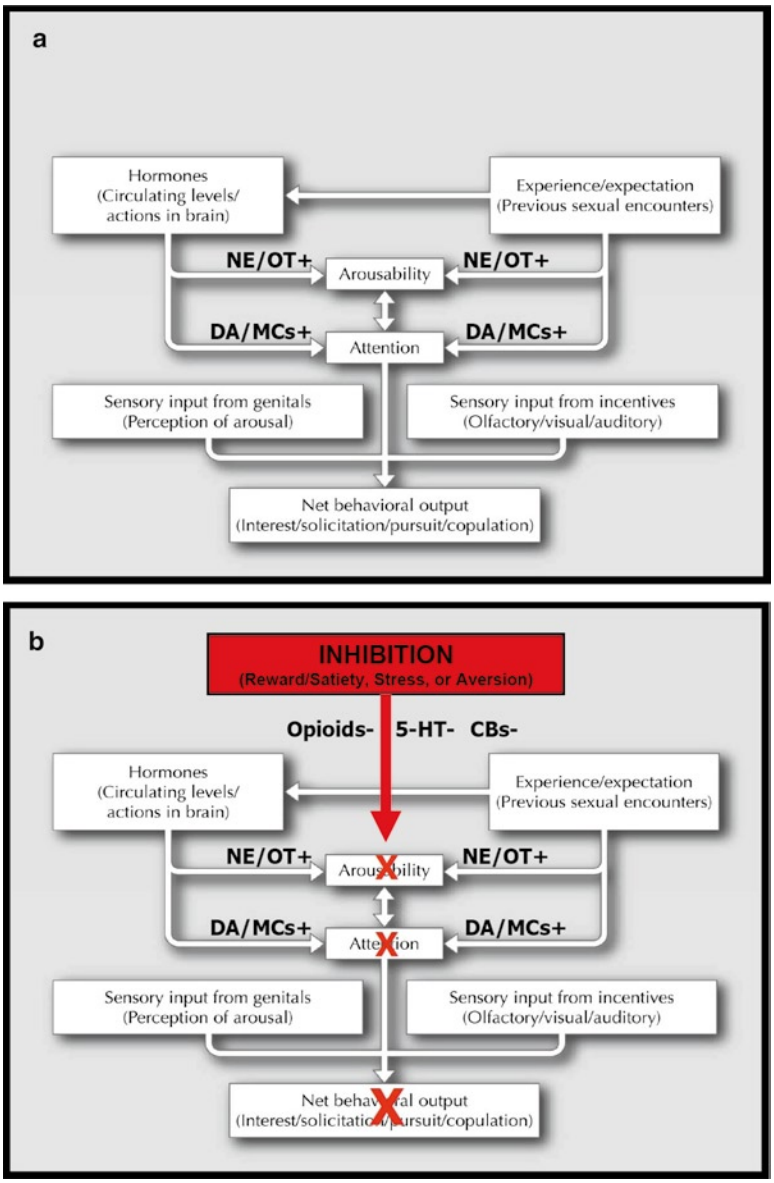

Fig. 3.1 Hypothetical relationship between experience, hormonal activation, arousability, attention, and stimulus processing from genital sensations and external incentives on libido. Note that excitatory and inhibitory feedback can occur anywhere in this flow chart to strengthen or reduce responding. Such feedback provides moment-to-moment modulation of libido. (**a**) Excitatory systems involve the activation of sexual arousability by norepinephrine (NE) and oxytocin (OT), and attention toward sexual stimuli by dopamine (DA) and melanocortins (MC). Sexual arousability involves both central and peripheral mechanisms involved in the control of autonomic outflow (directing genital blood flow, parasympathetic and sympathetic arousal, and orgasm). Attentional mechanisms involve both hypothalamic and limbic structures that focus attention toward particular sexual incentives. (**b**) Inhibitory systems involve the general activation of opioids, serotonin (5-HT), and endocannabinoids (CBs) that shut down excitatory systems during normal periods of refractoriness, or when under stress. Opioids released at orgasm provide a sense of pleasure and ecstasy. Serotonin activates mechanisms of satiety. Endocannabinoids activate sedation. Opioids serve a paradoxical dual function that inhibits hypothalamic and limbic centers involved in sexual arousability and attention during periods of intense sexual reward (e.g., orgasm), but also to sensitize mesolimbic dopamine systems such that subsequent activation by sexual incentives induces a greater focusing of attention. Thus, blunting opioid systems when they are overactivated by stressors can facilitate copulation, but blunting them under normal circumstances can blunt sexual reward and subsequent sexual desire. Blunting overactive serotonergic or endocannabinoid systems can release sexual arousal and desire from inhibition

anticipation of sexual activity. In women, situations such as acute exercise or exposure to stimuli that arouse a sympathetic response can produce increases in physiological sexual arousal. However, although vaginal pulse amplitude in response to visual erotica can be increased following exercise [4], or ephedrine [5], this does not translate into an increase in subjective sexual arousal. Thus, general stimulation of sympathetic outflow appears to make individuals more aroused in general, and may increase libido if the situation contains appropriate sexual cues.

Penile erection: Erection is stimulated in hypogonadal men or castrated male rats by androgens [6]. Treatments that enhance penile erection in nonhypogonadal men with erectile dysfunction (e.g., PDE-5 inhibitors such as sildenafil, tadalafil, and vardenafil, dopamine receptor agonists such as apomorphine, melanocortin agonists such as PT-141, prostaglandin E_1, oxytocin, α_2 receptor agonists such as yohimbine, idazoxan, and imiloxan, and vasodilators that act through nitric oxide substrates, such as nitroglycerine, sodium nitroprusside, and linsidomine) also enhance penile erection in gonadally-intact male rats [6, 7]. It is presumed that these compounds exert their erectogenic actions in the autonomic nervous system, although some of the drugs, e.g., apomorphine, oxytocin, and the α_2 receptor agonists, could exert actions centrally. In fact, apomorphine can induce erectile responses in male rats following infusions to the medial preoptic area (mPOA) of the anterior hypothalamus [8].

Psychogenic erections can be stimulated in men by exposure to visual sexual stimuli. The ease with which men achieve or maintain erection in response to erotic cues can be taken as an index of libido, and latency to, and duration of, full erection can be measured. Studies of the melanocortin agonist, bremelanotide (formerly PT-141) found that it induced erections in healthy men, and enhanced erection in response to visual sexual stimuli in men with erectile dysfunction [9]. "Noncontact" erections in rats can be provoked by exposure to sexually receptive females or vaginal estrous secretions [10]. Such erections are potentiated by androgens, by drugs that stimulate nitric oxide release in the paraventricular hypothalamus or dopamine release in the mPOA [11]. Conversely, dopamine receptor antagonists, such as haloperidol, reduce both physiological and subjective sexual arousal in men [1], and inhibit erections in male rats [12].

Brain activation during the presentation of visual sexual stimuli has been studied using either positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). These studies have found common regions of activation in men and women, including the anterior cingulate and medial prefrontal cortex, ventral striatum/nucleus accumbens, claustrum, hypothalamus, and amygdala [13–18], although the two latter structures are activated more in men than women viewing the same sexual stimuli [17, 18]. Activation of inferior extrastriate cortex, inferolateral prefrontal cortex, hypothalamus, and midbrain was correlated with subjective sexual arousal in men following an erotic film [15, 17, 18], whereas activation of parietal cortex in men by erotic pictures was correlated with subjective sexual arousal [16]. However, men with hypoactive sexual desire disorder display an abnormal activation of medial orbitofrontal cortex, a region previously implicated in the inhibitory control of motivated behavior, relative to control subjects [19]. In male and female rats, nearly identical regions of the brain are activated by copulatory stimulation, including ejaculation and vaginocervical stimulation. A subset of those regions (nucleus accumbens, hypothalamus, amygdala) activated by exposure of male rats to sexually arousing estrous odors or neutral odors paired with sexual reward [20].

Vaginal/clitoral arousal: Relative to our understanding of the mechanisms underlying penile erection, far less is known about the activation of physiologic or psychogenic sexual arousal in females. The nitric oxide-cyclic GMP pathway appears to be critical for vaginal blood flow, as it is for penile blood flow. Treatment with androgens facilitates vaginal nitric oxide synthase activity, along with vaginal smooth muscle relaxation [21]. However, studies testing the efficacy of PDE5 inhibitors to increase vaginal blood flow or pulse amplitude on their own, or to augment genital responses during the presentation of visual sexual stimuli, have generated conflicting

results, from no appreciable effects, to increases in subjective arousal, to increases in genital arousal without corresponding increases in subjective arousal [22]. Recently, a significant positive effect of sildenafil was shown on both subjective arousal and perception of genital arousal in women with arousal disorder and lower vaginal pulse amplitude [23]. Part of the problem conducting studies of female arousal concerns the high degree of variability in physiological and subjective responses. This may reflect several variables, including differences in placement of a vaginal plethysmograph, exposure to different types of sexual stimuli, and the phase of the ovulatory cycle in which women are tested.

Sexual Desire

No agreed-upon definition of sexual desire exists except that inferred from the definition of Hypoactive Sexual Desire Disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [24], in which "desire for and fantasy about sexual activity are chronically or recurrently deficient or absent." By converse logic, sexual desire would be the presence of desire for, and fantasy about, sexual activity. Desire can be viewed as distinct from arousal in animals and humans, with desire constituting a psychological interest in sex and behaviors that reflect such interest. Despite the fact that desire and arousal are separate processes, desire may be informed or confirmed by the presence of autonomic or central arousal. In fact, many women and men regard sexual desire and arousal as parts of one another, despite being given distinct definitions [25, 26]. Thus, desire as it is expressed physically in conscious, goal-directed behavior, most closely resembles the "lust" of libido.

Desire can be inferred in animals by their willingness to work for sexual reinforcers, or in behavior that reflects the anticipation of sexual activity [27]. Several lines of evidence link the desire for sex to the activation of brain dopamine systems. Microdialysis studies have shown that dopamine release in the mPOA and nucleus accumbens, increases in male rats in response to both conditioned and unconditioned incentive cues that predict sexual reward [28], and dopamine receptor antagonists injected peripherally or centrally to these regions disrupts anticipatory conditioned excitement [29]. Lesions of the basolateral amygdala (a region that sends glutamate afferents to the nucleus accumbens) decrease operant responding for secondary sexual reinforcers. This decrease can be reversed by infusions of amphetamine to the nucleus accumbens [30]. Conditioned partner preferences in rats occur when a neutral stimulus (e.g., almond odor) is paired with sexual reward. We have shown that presentation of the conditioned stimulus alone induces anticipatory psychomotor stimulation and activates brain regions in male and female rats associated with incentive motivation and attention (e.g., nucleus accumbens, ventral tegmentum), sexual behavior (mPOA, basolateral and medial amygdala), and reproductive processes (supraoptic and paraventricular nucleus of the hypothalamus). Such activation does not occur in control animals that receive either no association of the odor with reward, or that receive random association of the odor with reward and nonreward [31]. Indeed, we have found selective activation of both oxytocin- and GnRH-containing neurons by the odor in males and females, respectively, indicating that systems for sex and reproduction are being activated selectively. Finally, the melanocortin agonist bremelanotide increases rates of solicitation in female rats primed with estrogen and progesterone, or estrogen alone [32]. In preliminary studies, we found that the dopamine receptor agonist, apomorphine, also increases rates of solicitation in females primed with estrogen alone. To the extent that solicitation in female rats and anticipatory psychomotor stimulation in male rats are analogies of "sexual desire," the activation of these two neurochemical systems in the brain may form an important part of the pathway that mediates libido [33]. Interestingly, estradiol increases both dopamine and melanocortin synthesis in hypothalamic and limbic structures, and

androgens activate nitric oxide pathways that facilitate dopamine release. The increase in female-initiated sexual activity around the time of ovulation [34], and the increase in anticipatory sexual activity in males, may be primed by the activation of these two systems by steroid hormones.

Sexual Reward

An emerging idea from animal studies is that desire is linked to an expectation of reward, and that such expectation fluctuates in time given the actual level of reward experienced. Sexual reward is inferred in animals by the strength of operant or instrumental responding toward a particular sexual reinforcer, and in the strength of copulatory responding (i.e., from behaviors that typically denote desire). Contextual factors, such as settings, are also important components of positive sexual experiences for both men and women. Recent work using the conditioned place preference (CPP) paradigm has been particularly useful in delineating the behaviors and neurochemical systems necessary for sexual reward in rats [35, 36]. For male rats, ejaculation is critical in the formation of CPP, whereas for female rats the ability to control the initiation and rate of copulation (pacing) is critical. If one distinctive side of a CPP apparatus is paired with a rewarding sexual experience, and the other distinctive side is paired with a less rewarding sexual experience (e.g., copulation but not ejaculation in males, nonpaced copulation in females), both male and female rats will spend significantly more time in the side associated with reward, indicating a preference for contextual cues associated with reward. Systemic administration of the opioid receptor antagonist, naloxone, during rewarded training trials blocks the induction of sexual CPP in both males and females. Likewise, naloxone blocks the formation of conditioned partner preferences in rats [37, 38] and produces a state of sexual nonreward that makes female rats lose interest in solicitation and male rats lose interest in chasing females. This suggests that the release of endogenous opioids is a critical factor in the sexual reward induced by ejaculation in males and pacing in females, and that it activates (or sensitizes) desire. Interestingly, treatment with dopamine receptor antagonists do not block the induction of sexual CPP or conditioned partner preference, indicating that dopamine activation is not a necessary component of sexual reward [38–40], although it is required for animals to display conditioned appetitive responses and may be necessary for smaller, more appetitive types of reward when animals attempt to gain access to sex partners and solicit sex. Systemic administration of opioid agonists disrupt the initiation of sexual behavior in both male and female rats [41], and opioid agonists infused directly into the mPOA have similar inhibitory effects in male rats. Dopamine release decreases abruptly in the nucleus accumbens and mPOA when male rats ejaculate and the incentive salience of females is diminished during the absolute refractory period. The decrease in dopamine release in the nucleus accumbens may be due to an activation of serotonin release in the lateral hypothalamus by ejaculation [42]. Lesion studies suggest that the nucleus accumbens plays an excitatory role in sexual arousal whereas the lateral hypothalamus plays an inhibitory role in sexual arousal, but an excitatory role in the regulation of ejaculation [43].

Activation of oxytocin and vasopressin pathways by sexual reward may be a critical component of future social bonding. Monogamous Prairie voles bond with their first sex partner for life and share parental duties [44]. Polygamous Montaine voles do not, nor do rats. Monogamous bonding in female Prairie voles can be disrupted by injections of an oxytocin antagonist, whereas bonding in male Prairie voles is disrupted by injections of a vasopressin antagonist [45]. Male Prairie voles have a greater density of the vasopressin type 1a receptor in the ventral pallidum compared to male Montaine voles, and viral gene transfection of the V1a receptor to the ventral pallidum of male Montaine voles renders them behaviorally monogamous [46]. As noted above, male and female rats can be conditioned to display a partner preference based on odors or

other cues associated with sexual reward [47, 48], and we have recently found that such cues activate oxytocin and vasopressin neurons, in addition to dopamine release. Thus, a consequence of early sexual reward is bonding to cues that predict the reward, cues that become highly arousing and desired. In humans, this process may play an important role in the formation of preferences for cues that we find attractive at a distance.

Brain imaging studies have also been conducted in men and women during manual genital stimulation to orgasm [49, 50]. In men stimulated to ejaculation, PET revealed an increased activation of the cerebellum and midbrain regions, including the ventral tegmental area, zona incerta, and subparafascicular nucleus, along with the intralaminar thalamus, lateral putamen and claustrum. No increased activation was observed in hypothalamic regions, and decreased activation was observed in the amygdala and surrounding entorhinal cortex. Most of these regions are activated by ejaculation in male rats, although the general activation patterns offered by PET do not have the fine-grained spatial resolution of the neuronal markers typically used in rat brain sections (e.g., induction of nuclear Fos protein). It is possible that small hypothalamic regions may still have been activated but undetected. In women with complete spinal cord injury, but that still experienced orgasm from masturbation, fMRI revealed an activation of hypothalamic structures, including the paraventricular nucleus, the medial amygdala, anterior cingulate, frontal, parietal, and insular cortices, and cerebellum, by orgasm. Because of the spinal damage, it was concluded that the stimulation of orgasm traveled through the Vagus nerve to activate the brain.

Sexual Inhibition

Sexual inhibition can be induced by stressful life events or following high sexual rewards (i.e., during a refractory period in which reproductive capacity needs to be regenerated prior to a resumption of copulation) [51]. In either case, the activation of inhibitory pathways for sexual arousal and desire generates a state of reduced libido (Fig. 3.1b).

Activation of opioid, serotonin, and endocannabinoid release during sexual reward is associated with an inhibition of ongoing sexual behavior. This has been studied in male rats following sexual exhaustion. Male rats allowed to copulate with multiple ejaculations to sexual exhaustion do not respond to female solicitations for a period of 24–72 h. This inhibition can be reversed by the 5-HT-1A agonist 8-OH-DPAT (an autoreceptor agonist that inhibits serotonin release), the α_2 receptor agonist yohimbine, and the opioid receptor antagonist naloxone [52]. Thus, blockade of opioid or serotonin transmission, or activation of parasympathetic pathways involved in erection, can overcome the state of inhibition induced by sexual exhaustion. Activation of opioid transmission by stress may also play a role in sexual inhibition. Male rats find novel environments stressful. In fact, males that are not desensitized to the environment in which they have their first sexual experiences often do not copulate. Preexposure to the environment, or treatment with naloxone, increases the proportion of males that copulate on their first trial [53]. Interestingly, sexually naïve males sensitized to amphetamine do not show inhibition during their first exposure to females in a novel environment, despite the drug exposure happening weeks before [54]. Although sexually experienced males show signs of fear (e.g., freezing) in novel environments, they do not show subsequent sexual inhibition if a receptive female is placed into the environment. Together, these data suggest that sensitized dopamine systems, produced either by sexual experience or amphetamine preexposure, or blockade of opioid transmission, can overcome the stress-induced inhibition of sexual responding in males.

Conclusions

Libido reflects our level of sexual interest at any given time. It is determined that the interaction of neural systems underlie sexual arousal, desire,

reward, and inhibition, processes that are highly influenced by steroid hormone actions. This is especially true for brain dopamine systems that modulate attention toward external sexual incentives and help generate appropriate motor responses. The neuroanatomical and neurochemical mechanisms that influence this process, and are influenced by it, are only beginning to be understood. Likewise, studies into the nature of sexual reward, its translation into pleasure, bonding, and sexual inhibition, and the mechanisms that underlie them, have only begun. We have understood libido for centuries at a behavioral level. Studying its biological basis will help us identify mechanisms of sexual function and dysfunction, and perhaps allow us to better understand how function and dysfunction, desire and inhibition, are integrated in the experience of all individuals.

The stress that cancer imposes on an individual, both in terms of the threat to life and any physical disfigurement or inactivation induced by surgical removal of cancerous tissue, has profound effects on libido. High degrees of stress activates sympathetic arousal (the "fight or flight response"), which diminishes the ability of individuals to become sexually aroused, and which focuses attention on stress-related stimuli at the expense of rewarding (e.g., sexual) stimulation. Individuals who become preoccupied by the threat of recurring disease, or by a physical "deformity" resulting from tissue removal, often experience a blunting of sexual desire. Removal of tissue important for sexual function, including radical prostatectomy or removal of clitoral, penile, or pelvic smooth muscle, disrupts sexual function and blunts the sexual reward and pleasure achieved during sexual intercourse. The activation of inhibitory brain systems by stress, shame, or an expectation of sexual nonreward, needs delicate treatment by clinicians. Any sparing of sexual function and pleasure can be explored by individuals and couples with their doctors and therapists, and individuals still interested in sex should be encouraged and reminded that they are still sexual beings with the ability to experience real sexual pleasure and intimacy.

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Chapter 4
Physiology of Orgasm

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Keywords Orgasm • Cortex • Cerebellum • Pelvic musculature • Contraction • Oxytocin

Introduction

The human orgasm, although tantalizingly short, is perhaps the greatest bodily pleasure that most men and women can experience without recourse to drugs. It is a complex of subjective mental with physical body changes. Its pleasure can never be recalled exactly which is perhaps one of the reasons for desiring its repetition. It dissolves body boundaries and thus unites lovers in a unique manner. In men, because it normally routinely accompanies ejaculation, it has simply been regarded as the drive reward for attempting procreation, and in evolutionary terms, as a spur to distribute their genes as widely as possible. In women, however, because it is far less easily induced, especially by coital penile thrusting alone, its putative biological purpose(s) have been subjected to extensive discussion. This has resulted in the unresolved dichotomy of whether it is an evolutionary adaptation or just a by-product. Unfortunately, the arguments from the various protagonists have become more philosophical rather than physiologically based, have produced more heat than light, and will not be repeated.

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A number of reviews have been published on the female orgasm [5–13], but fewer on that of the male [6, 10, 11, 13–15].

The present article summarizes most of the known evidence-based facts about human orgasmic activity with a sprinkle of the salt of speculation where such facts are still wanting.

Definitions of Orgasm

It is strangely difficult to define an orgasm accurately despite the fact that most adults have experienced the activity [8]. A review on orgasm published in 1981 [7] tabled some 13 definitions from the literature, while 20 years later Mah and Binik [10] undertook the same exercise and now listed twenty six, despite this they preferred not to produce one of their own. One difficulty discussed by Levin [8] is that each specialty (physiology, endocrinology, brain imagery, and psychology) that examines the activity has its own requirements for a definition. Another problem arises in ascertaining exactly when an orgasm starts; is it when the subject first mentally perceives it starting (subjective initiation) or is it when the first physical manifestations of it appear (objective initiation) as these two may not occur at the same time. Some physical manifestations have been used to identify the occurrence of orgasm in females (see Section below on objective signs of orgasm in women).

Because we do not have the exact picture of the neural brain activity underlying an orgasm, most definitions relay on describing the observable or reported physical changes. Despite this, a

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reasonably comprehensive operational definition for women is "An orgasm in the human female is a variable, transient peak sensation of intense pleasure creating an altered state of consciousness usually accompanied by involuntary rhythmic contractions of the pelvic striated circumvaginal musculature, often with concomitant uterine and anal contractions and myotonia, that resolves the sexually-induced vasocongestion (sometimes only partially), usually with an induction of well-being and contentment" [12]. In the case of males, "An orgasm in the human male is a transient peak sensation of intense pleasure creating an altered state of consciousness usually accompanied by involuntary rhythmic contractions of the pelvic striated musculature normally forcefully ejecting semen, often with concomitant anal contractions and myotonia ending usually with feelings of languor, well-being and contentment."

Common Features of Orgasm in Males and Females

Despite the fact that orgasm has a strong subjective component, there are some common response patterns in men and women, which are described briefly below.

Mental Experience

Trying to describe an orgasm in words, either for men or women, is a difficult task especially if there is a loss of conscious focus, yet these needs to be undertaken if we wish to compare mental and physical experiences between the sexes. One ingenious study [16] obtained written descriptions of orgasms from 29 male and 29 female subjects and then removed or altered any feature that could identify the sex from which the description came. These were then given to a panel of expert judges who had to decide what sex the descriptions were from. They were not able to select them into such groups suggesting strongly that what males and females experience during orgasm is probably very similar if not identical. More recently, Mah and Binik [17] developed and evaluated an orgasm rating scale (ORS) for assessing sensory, cognitive, and affective aspects of the experience in both men and women. The only substantive gender difference observed in their ORS evaluation was that men gave a higher rating to "shooting sensations," which was interpreted as related to the ejaculation of the semen, a feature of orgasm obviously not well developed for most women.

Cardiovascular Phenomenon

At the initiation of orgasm, both males and females have their highest blood pressure, heart rate, and respiratory rates of their sexual encounter ([6], p 278).

Pelvic Musculature Contractions

Powerful and highly pleasurable pulsatile contractions of the striated musculature of the pelvis (especially the bulbocavernosus and ischiocavernosus) take place at the initiation and during orgasm in men and in most women. In the case of men, the contractions create the spurting, projectile ejection of the semen that is preloaded into the urethra by the contractions of the smooth muscle of the vas deferens and capsules of the prostate and seminal vesicles. Usually, up to six or seven forceful contractions are needed to expel all the semen containing sperm, but a significant number of further contractions can still occur without any fluid expulsion [18], presumably a built-in safety factor to ensure that all the sperm are ejected.

The role of these pelvic muscular contractions in the female is more problematic. Some authors regard orgasm as a "sensory-motor reflex loop" and that orgasm occurs as a muscular response, "without the contractions there has been no orgasm" [19]. Others do not agree, reporting women who have orgasms but do not perceive any such contractions. Whether this is because they are very weak contractions or that the women are poor at sensing such changes in

their bodies is not known as there have been no laboratory studies undertaken on such women. A number of functions have been suggested, which are listed below and brief criticisms of the proposals are given in the brackets after each item:

1. To eject paraurethral glandular secretions from the urethra (not all women have these).
2. To empty the vasocongested genital tissues (a single orgasm usually does not accomplish this, [20]).
3. To end sexual arousal (women are serially multiorgasmic).
4. To stimulate male arousal to capture his semen (not all women have the contractions).
5. To create pleasurable feelings (voluntary contraction of the muscles does not create pleasure).

Some authors, however, think that they are vestigial or an accidental by-product – the probable result of the common fetal origins of the striated pelvic muscles essential for male ejaculation, but not for female's. They are an example of a "biological spandrel" [21]; as they cause no harm, there is no reason to actively dispense with them and so they remain in the female.

Bohlen et al. [22] recorded the pelvic contractions in 11 nulliparous women during their orgasms. They did not find any relation between the number or strength of the contractions and the subjective pleasure of the orgasm.

Rectal Sphincter Contractions

Rectal sphincter contractions can occur during orgasm in some but not all women ([6], p 129) and in males during ejaculation and orgasm ([6], p 174).

Activation or Deactivation of Areas in the Brain

In the last few years, a number of studies have been undertaken using brain imaging with either PET (Positron Emission Tomography) or fMRI (functional Magnetic Resonance Imaging) techniques during sexual arousal to examine what areas of the brain are activated or deactivated using regional Cerebral Blood Flow (rCBF), and a few of these studies have also examined orgasm. While they have opened up a completely new way to compare what happens in the brains of men and women during arousal, it could be said that in some ways they have created more problems than they have solved. This is because the various groups have used different methods of stimulation, different controls for basal values, different techniques of handling the data obtained, and different interpretations of the final results. There is no consensus or clear picture of brain functioning during sexual arousal and orgasm. One thing that the studies have accomplished, however, is the rejection of the concept of an orgasm center in the brain. All the studies show that a number of areas of the brain are activated and others deactivated at arousal and orgasm, indicating the concept of a common multiple site coactivation or a neural network as a model for brain orgasm [15]. What we don't understand is how the activated and deactivated components combine to create an orgasm; unfortunately while knowing the parts involved is obviously essential, we cannot reverse engineer an orgasm from them.

According to Georgiadis et al. [23], common areas of brain activation at orgasm in men and women are found in the anterior lobe of the cerebeller vermis and deep cerebellar nuclei and profound deactivations are found in the left ventromedial and orbitofrontal cortex. The only prominent difference during orgasm between the genders was a male-based activation of the periaqueductal gray matter, while in the case of women a larger activation of the right insula was observed compared to men, a difference, however, mainly caused by the deactivation in men.

Facial Grimacing

A characteristic face usually occurs in both men and women during orgasm. The mouth is held open (possibly due to spastic contractions of the surrounding muscles), the eyes are shut, and the facial muscles create a grimace that leads to any observer thinking that the person is suffering from

significant pain rather than exquisite pleasure! The "grimace and contortion of a woman's face graphically express the increment of myotonic tension throughout her entire body" ([6], p 128).

Hyperventilation

Hyperventilation occurs during high levels of sexual arousal and it runs through orgasm. Peak respiratory rates as high as 40 per minute have been recorded ([6], p 277) compared with the basal levels of 12–14 per minute. The open-mouthed hyperventilation can be linked to facial grimacing (see above) and to vocalizations (see below). It has been suggested that the hyperventilation by lowering the CO_2 in the plasma could create giddiness and light headedness often associated with high levels of arousal and orgasm [24, 25].

Vocalizations

During orgasm, most males and females vocalize involuntary, usually nonverbally, and these vocalizations often accompany each pelvic contraction (see above Section on "Pelvic Musculature"). These vocalizations, especially of the female who are said to produce more sounds than males during coitus, convey to the sexual partner the fact that they are experiencing an orgasm of ecstasy and extreme pleasure. They are much appreciated by males who are often taking the lead in sexually arousing the female and like the feedback of their successful lovemaking [26]. The vocalizations, moreover, act as a sexual stimulus, especially to the male, enhancing his arousal.

Release of Prolactin and Oxytocin

Prolactin is released in both sexes at orgasm significantly increasing the concentration of the polypeptide in the plasma for approximately 60 min after the orgasm. It was initially proposed that this was a hormonal mechanism that terminated sexual arousal, but later studies showed that this was not the case in either males or females [27, 28].

While it is known that oxytocin is also released at orgasm in both men and women, the actual physiological functions of the nonapeptide have been poorly investigated. Proposals from animal studies that it is involved in sperm transport, namely facilitating ejaculation in males, uterine contractions in females, and in possible pair-bonding, are still unsettled [27].

Differences Between Female and Male Orgasms

While there are common features between female and male orgasms as listed above, there are also a few differences [29]. In brief, these are:

1. Unlike males, females generally do not have a PERT after their orgasms being multiorgasmic (but see Section below of female orgasms with urethral emission).
2. The pleasure of subsequent female orgasms after the first can be better, this is not the case for male orgasms.
3. The orgasm of females can be interrupted by external environmental stimuli or by cessation of the inducing sexual stimuli, but once the feeling of "ejaculatory inevitability" is experienced by a male, the ejaculation and concomitant orgasm is inevitable.
4. One type of recorded anal contraction at orgasm in males has not been observed in females (a divided rhythmic pattern), but the number of recordings for both sexes is very small [22].

There are also some claimed differences in brain activation at orgasm [15].

Female Orgasm

Sexual arousal of the female to induce orgasm is usually accomplished by stimulation of the genitalia (clitoris, labia minora, vagina especially

the anterior wall) and the surrounding area (perineum, anus, inner thighs) facilitated by nipple/breast stimulation [30, 31]. In some sensitive women, orgasm can be induced by mental imagery alone [32], while other unusual activations in aroused women have occurred from brushing their eyebrows or pressure on their teeth ([5], p 590). Laboratory studies with spinalized women have indicated that vibration of the cervix can lead to orgasm via a vagal pathway bypassing the spinal cord [33]; whether this path is in operation in able-bodied women has not yet been established. Consciousness is not required because orgasm can occur even during sleep. It is often assumed that for the female orgasm to occur, the willingness of the female to accept the sexual stimulation is an essential factor. However, unsolicited or nonconsensual stimulation can lead to unwanted sexual arousal and even orgasm [34].

According to the account of Masters and Johnson ([6], p 135), the female orgasm starts psychologically with a very brief transient sensation of "stoppage" or "suspension," which is followed by an intense thrust of clitoral awareness that radiates into the pelvis. A suffusion of pelvic warmth occurs which spreads into the rest of the body. The physiological start of the orgasm (p 128) occurs with intense pleasurable pulsing sensations perceived concomitant with contractions of the uterus, pelvic musculature, vagina, and anus. Involuntary vocalizations often accompany contractions of the latter three [26]. When these contractions have died away, most women are left with a feeling of calm, lassitude, and satisfaction and often with a dissipation of their sexual tensions. The dissipation of the vasocongestion in the vagina, however, is often only partially complete [20]. This may be part of the explanation why, unlike men, women can undertake another orgasm immediately after the previous and some can continue with them with appropriate stimulation for a considerable number. It is said that nothing is as good the second time, but this does not apply to women's orgasms as for many the later ones can be more pleasurable.

The duration of orgasm has been measured in the laboratory. Based on 26 healthy young subjects indicating the start and end of their felt orgasms, Levin and Wagner [35] recorded their duration as 19.9 ± 12 s (Mean ± Standard Deviation). The measured durations were not significantly correlated with their subjective grading. When the subjects tried to estimate the duration of their orgasm immediately after, the estimates were nearly half of their measured ones, indicating that orgasm creates an alteration of a subject's personal time sense. Clearly, simply asking women about their orgasm duration does not give a valid "objective" duration.

In relation to the intensity of orgasm, this has been correlated with: (1) the increase in heart rate at orgasm, the greater the increase the more intense and pleasurable was the orgasm [36] confirmed by Alzate et al. [37]; (2) the more women were in love/emotionally close to their partner, the more they were satisfied with the quality of their partnered-orgasms [38].

Uterine Contractions

Masters and Johnson ([6], p 116) reported that specific uterine contraction patterns do not develop unless orgasm is occurring and that when this occurs the degree of contraction parallels the intensity of the orgasm. The types of patterns, however, were not described and no data was presented to support these conclusions. Unfortunately, remarkably few records of uterine contractions at orgasm have been published and the importance of these contractions to the development of the subjective feeling of pleasure from the orgasm is poorly characterized. Indeed, the exact mechanism of the induction of the uterine contractions has yet to be identified, whether from oxytocin release at orgasm or from adrenergic innervation or from both.

Meston [39] claimed that hysterectomy, while not having a direct effect on sexual function, did in a number of women decrease their orgasmic pleasure which they related to their loss of the orgasmic uterine contractions.

Typologies of Female Orgasm

There is still controversy over a possible typology for the female orgasm. According to Masters and Johnson ([6], p 67), orgasms, however and whatever anatomical site they are generated from, are physiologically identical, "clitoral and vaginal orgasms were not separate biologic entities." Other investigators, however [40–42], found that women reported that stimulation of different sites created different sensory and orgasmic feelings, especially in relation to those generated by clitoral stimulation compared to those generated by anterior vaginal wall stimulation. Stimulating the clitoris gave "warm, ticklish, electrical, sharp" feelings, while stimulating the vagina was "throbbing, deep, soothing and comfortable" [42].

Limited physiological evidence is available to suggest that the balance between uterine smooth muscle and pelvic striated muscles contractions is different when orgasms are created either by stimulation of the vaginal anterior wall or by clitoral stimulation [30]. Singer [43], a philosopher, proposed from the limited descriptions in the literature available to him at the time three types of female orgasm which he named (1) vulval, (2) uterine, and (3) blended, a mixture of (1) and (2). The evidence for this typology was weak relying on descriptions of orgasms by a female novelist and experimental descriptions of a single couple during coitus (see [30] for details and criticisms).

An orgasm typology based on the characteristics of the pelvic muscular contractions measured at orgasm was suggested by Bohlen et al. [22], but as they only studied 11 women, two of whom had irregular contractions, the attempt was premature and has received no confirmation.

Female Orgasms with Urethral Emission

In a number of women, urethral emissions occur at orgasm and, in popular parlance, this is often called "female ejaculation." The fluid ejected is claimed not to be urine, but is thought to be a secretion from the urethral paraurethral or periurethral glands. The great variability in these glands has recently been confirmed with MRI imaging [44]. The volume ejected has been described as ranging from less than a milliliter to a remarkable, but unconfirmed, 90–900 mL [45]. There is no genital structure that can secrete or store the latter volumes, such extreme volumes have been called "gushing" and is proposed to be different to the urethral emissions [46].

Women are said to have more intense orgasms with ejaculation than those without [47]. The suggestion has been made that as the type of female orgasm accompanying this is similar to those in ejaculating males, females having this orgasm type will likely experience a post ejaculatory refractory time (PERT, see section below) when they are unable to have another orgasm for sometime after (see [48] for references).

Objective Signs of Orgasm in Women

Orgasm is a complex of subjective and physical events. The latter can either be observed or measured and they have been used to identify whether an orgasm has taken place or not [9]. The changes induced by orgasm are listed in Table 4.1.

Table 4.1 Specific objective markers of female orgasm

Those indicating impending orgasm (prospective)
Color changes of the labia minora (pink to deep red) (Masters and Johnson [6])
Those occurring during the orgasm (current)
Vaginal contractions (induced by rhythmic pelvic striated muscle contractions) (Masters and Johnson [6])
Uterine contractions (Masters and Johnson [6])
Anal sphincter contractions (Masters and Johnson [6], Van Netten et al. [77])
Release of prolactin (Levin [27] for reference)
Those occurring after orgasm (retrospective)
Areolar decongestion (rapid, causes corrugation of areolae) (Masters and Johnson [6])
Raised and maintained prolactin levels in the plasma (Levin [27] for reference)
Immediate transitory increase in vaginal pulse amplitude (VPA) (Meston et al. [12], p 793)
Rectal pressure changes (8–13 Hz band): marker for clitoral-induced orgasms (Van Netten et al. [77])

Specific Brain Activity During Female Orgasm

There are still very few studies of brain activity during the female orgasm that by Georgiadis et al. [49] are the most comprehensive. They used PET to measure rCBF during orgasm induced by clitoral stimulation and compared it with an imitation orgasm faked by the subjects. Orgasm was mainly associated with reduction of rCBf in the amygdala and profound reductions in the neocortex, especially in the left lateral orbitofrontal cortex, inferior temporal nuclei, and anterior temporal pole. The deactivation was thought by the authors to be an indicator of behavioral disinhibition during orgasm. The deep cerebellar nuclei, however, showed increased rCBF presumed to be involved in the orgasm-specific muscle contractions. An unusual finding was the lack of effect of arousal and orgasm on increasing the rCBF in the hypothalamus, an area noted for storing and releasing oxytocin and vasopressin at orgasm. Bianchi-Demicheli and Ortigue [15] have critically reviewed the neural control of the female orgasm including the role of the brain-spinal cord integration.

The Male Orgasm

Masters and Johnson [6] characterized the male orgasm/ejaculation process into two stages. The first (Stage 1) represented the contractions of the smooth muscle of the accessory organs starting at the vasa efferentia of the testes, passing along the epididymis, and then to the vas deferens and seminal vesicles and prostate. Seminal fluids are added to the ejaculate from the testes, epididymis, seminal vesicles, and prostate. The internal sphincter of the bladder contracts to prevent retrograde entry of the ejaculate into the bladder. The sensation of "ejaculatory inevitability" (feeling the ejaculate coming) arises just as Stage 1 is initiated; at this stage, it is not possible to prevent ejaculation occurring.

The second stage (Stage 2) occurs with the relaxation of the external bladder sphincter that allows the semen to enter the distended bulb and urethra of the penis. The semen is propelled into the urethra by the contractions of the smooth muscles of the ducts and the capsules surrounding the accessory organs, but the forceful ejection of the semen from the penile urethra is by the pulsing contractions of the pelvic musculature, mainly the bulbocavernosus. The first few are powerful and highly pleasurable, and subsequent ones are less so gradually weakening until they die away. Ejaculations without the striated pelvic muscle contractions are not as pleasurable as the semen seeps away. After ejaculation, a period occurs when the male cannot have either a repeated erection or an ejaculation [48], this is called the Post Ejaculatory Refractory Time (PERT); it is shorter in young men (minutes) and increases in duration on aging (hours).

As in the female, consciousness is not required for orgasm as it can occur during sleep (wet dreams or nocturnal emissions) and ejaculation and orgasms can be induced involuntary by another even if their stimulation is nonconsensual [34].

The Male Orgasm with Ejaculation of semen

Under normal conditions, the male orgasm is usually concomitant with ejaculation, but as the two have separate mechanisms [24], it is possible to have an orgasm without an ejaculation and an ejaculation without an orgasm.

The Male Orgasm Without Ejaculation of Semen

It is possible for a male to have an orgasm without the emission of semen. There are a number of conditions when this can take place. Males suffering from hypogonadism with its concomitant poor levels of androgens do not manufacture significant amounts of semen and thus orgasm occurs with a "dry ejaculation." Similarly, males

who have repeated ejaculations accompanied with semen discharge in the end exhaust their seminal fluids and thus have orgasms without any semen being ejaculated. It is also possible for the semen to be moved retrogradely into the bladder so that no semen appears during the ejaculation. The urine, on urination after such a scenario, can appear cloudy/milky because of the diluted semen. Treatment with a number of drugs (e.g., alpha blockers) can also prevent the ejaculation of semen, but leaves the orgasm intact [18].

The Post Ejaculatory Refractory Time (PERT)

One very highly significant difference between the male and female orgasm is that, in the male after its occurrence with ejaculation, there is a period called PERT when neither a second orgasm nor erection can occur. However, if the sexual stimulus is novel or of greater intensity, then a shorter PERT occurs. The physiological mechanisms underlying this refractory time are poorly understood [48]. Women do not appear to experience this feature after orgasm except for the possibility of those "ejaculating" at orgasm [48].

Orgasms Induced by Prostatic Massage

Massaging the prostate via the rectum digitally or by a physical device can create an orgasm without any stimulation of the penis. It is not an activity, however, liked by every male and it is said that it takes time and practice to achieve the orgasmic status by this type of stimulation. There have been no published reports on laboratory studies of prostate-induced orgasms in comparison with penile-induced orgasms. All the descriptions available are anecdotal. It is claimed that such orgasms are "deeper, more widespread and intense and last longer than those from penile stimulation" [50]. Other descriptions suggest that penile orgasms have between four and eight contractions, while those from the prostate around 12. Perry [51] characterized them as "emission type reflexive orgasms" with occasional oozing of semen from the penis and reported that they can be repeated several times in a subject. Levin [8] speculated that this type of activity indicated that only contractions of the smooth muscle of the genital ducts and capsules were involved without any of the pelvic striated muscles as a seeping semen orgasm of weak intensity occurs in males whose striated muscles are paralyzed [52].

Orgasms from prostate stimulation were ignored in the studies of Masters and Johnson [6], in the popular account of orgasm by Margolis [11], and even in the extensive review of the science of orgasm by Komisaruk et al. [13]. Until critical scientific investigations of these prostate-induced orgasms are undertaken in the laboratory, our knowledge of the activity will remain anecdotal and speculative.

Specific Brain Activity During Male Orgasms

There have been few studies on orgasm and ejaculation in males. Holstege et al. [53] were the first to use PET to measure changes in rCBF in the brain during arousal and orgasm/ejaculation with the female partners of the males undertaking simulation of the penis. Primary intense activation was seen at the mesodiencephalic transition zones which includes structures such as the midline, ventroposterior and intralaminar thalamic nuclei, the suprafascicular nucleus, the zona incerta, the lateral segmental central field, and the ventral tegmental area. Strong increases were observed in the cerebellum, while decreases were found in the amygdala and adjacent entorhinal cortex. Neocortical activity was only found in a few areas exclusively on the right side. It is interesting to note that the activated mesodiencephalic zone contains a dopaminergic group

of neurons that is connected to a large range of behaviors that are rewarding.

Typology of Male Orgasms

Most authors assume that there is no typology of the male orgasm and that they are all the same. However, there is anecdotal evidence that orgasms created by prostate massage are reported to be somewhat different from those obtained by penile stimulation (see Section above on orgasms induced by prostatic massage). Zilbergeld [54], a clinical psychologist and onetime practicing sex therapist, claimed that he had orgasms different to the pattern described by Masters and Johnson [6] and that a number of other men told him that they also experienced different patterns. This is an unexplored area of male sexuality.

Special Considerations

Can We Tell When Someone is Faking an Orgasm?

Faking an orgasm by the male when the penis is outside the vagina is clearly difficult as in most cases orgasm and the ejaculation of semen normally occurs together. Faking a male orgasm with the penis inside the vagina is easier as the semen is not seen. In a pilot study, heart rate responses in a male could be used to distinguish between real orgasms with an ejaculation and faked orgasms without ejaculation [55]. In the case of females, not so very long ago the answer to the heading question would have been "no we cannot!" However, there are now measurements that can identify the differences between females having an orgasm and faking one. Georgiadis et al. [49] found that by examining the frequency characteristics of recordings of the contractions of the rectum, they could easily distinguish between a real orgasm and a faked one.

Orgasm and Enhancing its Intensity of Pleasure

The experience of orgasm in both men and women is of course extremely pleasurable, but it is of great variety. The initial early orgasms that occur during sexual development are usually far less pleasurable than later ones in adulthood. Anecdotal reports of individual's first orgasms in either males or females indicate that they are of poor quality and not very exciting or satisfying, and individuals appear to have to "learn" and accept the orgasmic pleasure [7]. Fisher [42] examined many physiological aspects of responsiveness in women, but could not find one that had any bearing on orgasm consistency. Anyone who has experienced orgasms, even as an adult, knows that some are much more intense and pleasurable or satisfying than others. The factors that influence the intensity of pleasure of an orgasm are, unfortunately, poorly known. Novelty of the sexual stimulation is one [5]. Duration between orgasms is another significant factor especially in males; after a long period without sexual arousal, the subsequent orgasm is usually intense. It was suggested that the cause of this increase in pleasure was that a larger volume of semen was ejaculated ([6], p. 216). Levin [56], however, reported on a number of studies indicating that this relationship between a larger volume and increased pleasure does not hold. The duration of arousal is also of some benefit; short rapid arousal usually leads to a quick and less intense orgasm as opposed to that brought about by a slow build up employing teasing, intermittent stimulation.

Many attempts have been made to try to enhance the intensity of orgasms, but most of the claims to having achieved this are usually anecdotal reports unsupported by any scientific evidence. However, androgens are thought to be of importance in both men and women; low levels usually predicate poor quality orgasms.

Exercising the pelvic striated musculature, namely the bulbocavernosus (bc) and ischiocavernosus (isc), by contracting them some 60 times 3 times a day for about 6 weeks is claimed to enhance the pleasure of orgasm both for men and

for women. Unfortunately, the demands of the regime make it rarely maintained (see [57] for references). According to Berman et al. [58], voluntarily contracting the bc and isc muscles in the female contributes and intensifies sexual arousal and orgasm.

Some recreational (illicit or street) drugs are claimed to influence the intensity of orgasm. Unfortunately, many, if not most, of the studies do not distinguish between the effects during the early use of the drug and the effects after its chronic use, which often leads to a deterioration of all aspects of the sexual response in both men and women.

The volatile vasodilator amyl nitrite (street name "poppers") was much employed especially by homosexual males to enhance orgasm through inhalation when orgasm begins; its action is possibly mediated through its transient dropping of the blood pressure, compromising higher brain functions which may be inhibitory to pleasure. Anecdotal reports on the injection of heroin claim it to give a sensation (the "rush") likened to that of an orgasm, but in a study of heroin addicts [59] feelings of sexual orgasm on injection were rated relatively low down a 20 point feelings scale (ninth for males and 15th for females). This may be because chronic use of heroin is known to impair all phases of the sexual response. However, brain areas that are activated during orgasm also appear to be activated during the heroin rush [53]. A study with 20 male and 15 female "ecstasy" users (MDMA 3,4-methylenedioxymethamphetamine) reported that the drug delayed their orgasms but made it more intense in 85% of the males and 53% of the female [60].

Frequent use of cannabis (marijuana) does not appear to be associated with sexual problems in females, but in males it is linked with delay or prevention of orgasms in some men and with premature orgasm in others [61]. Johnson et al. [62] also noticed that cannabis users were more likely to experience inhibition of orgasm, while Halikas et al. [63] found users showing an increase in the duration of coitus, but a decrease in the number of orgasms. The use of induced asphyxia to enhance the pleasure of orgasm (asphyxiophilia) is an extremely dangerous, possible life-threatening behavior practiced mainly by males [64].

Female Orgasm and Reproduction

The putative role of the female orgasm in reproduction has been a contentious issue for many years with opposing schools of thought. One group argues that orgasm has no scientifically proven function as a reproductive mechanism, while the other supports the concept that the uterine contractions induced by orgasm facilitate rapid sperm transport from the vagina to the uterus by their "upsucking" action. Unfortunately, the latter proposal ignores the fact that during high levels of sexual arousal the uterus and its cervix is pulled up well away from the vaginal pool of semen by the mechanisms of vaginal tenting [6,65]. Furthermore, freshly ejaculated sperm are trapped in the seminal gel that needs enzymic breakdown; they are incapable of fertilizing the ovum until they have been reprogrammed by a complicated process called "capacitation." This process involves sperm interaction with various activating agents in the glandular seminal fluids [66], which are only brought together at ejaculation [65]. All this takes a considerable time and so rapid transport of sperm is the last feature needed; such transport of uncapacitated sperm would serve no functional purpose and they would be wasted as they cannot fertilize an ovum. In fact, there is now evidence that sexual arousal in the female creates genital tract conditions that delay sperm transport, thus allowing decoagulation and the precapacitation/capacitation changes to take place. Strangely, but not unexpectedly given the previous facts, the fastest sperm transport is in the nonsexually aroused woman (see [65] for references).

Female Orgasm After the Menopause

A worldwide survey has indicated that sexual desire and activity are widespread among the middle-aged and persist even into old age [67]. Sexual dysfunctions, however, do increase with age in females with the advent of the menopause when estrogen secretion is greatly reduced, but especially in males with the reduction in testosterone [68].

In their laboratory investigations of human sexual responses, Masters and Johnson ([6], p 223) compared those in the postmenopausal women with younger premenopausal subjects. They found that the former took longer in achieving full tumescence of the clitoris, had either a decrease in the normal expansion of their breast volume or it was absent, and showed a delay or even an absence of vaginal lubrication and a decrease in their vaginal expansion (tenting). At orgasm, the postmenopausal women had fewer vaginal contractions and rarely showed any rectal/anal sphincter contractions. The latter were regarded as an indicator of the intensity and pleasure felt by subjects during their orgasm. Because postmenopausal women had few such contractions, it was inferred that there was "a generalized reduction in the intensity of orgasm expression as part of the aging process" ([6], p 229). Unfortunately, this wording is ambiguous and it could mean there was a real decrease in the felt intensity of the orgasm or that, at specific sites, the physical signs of the orgasm intensity were reduced [69]. Basson [70] reported from her clinical experiences that androgen-deficient postmenopausal women had difficulty in achieving orgasm, and when they occurred, they were far less intense. More recently, even young healthy premenopausal women reported that the quality of their orgasms was significantly reduced by the pharmacological induction of experimental hypogonadism created by injections of depot leuprolide acetate for 5 months [68].

Some postmenopausal women experience pain during and after the uterine contractions induced during orgasm ([6], p 119 and 238). The pain is possibly caused by the effects of estrogen lack created during the postmenopause. The contractions of the uterus are mediated by both adrenergic and oxyntergic activation. In the premenopausal woman, these are balanced by the inhibitory, smooth muscle relaxing effects of the vipergic innervation of the uterus mediated by the neurotransmitter VIP (Vasoactive Intestinal Peptide), but in postmenopausal women VIP is without action in the low estrogen condition so that the procontractile innervation is left unopposed and presumably can cause uterine spasm and its attendant pain of hypoxia [69].

Male Orgasm with Aging

In males after 50, there is a gradual decrease in the testicular secretion of androgens which becomes more severe in some individuals than others. This decrease leads to sequelae of physical and metabolic changes now designated as the "andropause." It is claimed that the orgasms in aged men are less easily obtained and are less intense [71], but there is little published objective evidence [13]. Most discussion relies heavily on the laboratory data obtained by Masters and Johnson [6]. They reported on ejaculation/orgasm in 39 males aged 51–89 years. In these men, marked "reduced ejaculatory prowess" was evident as they could not expel the semen as far as younger men and the number of their pelvic muscular contractions was greatly reduced to one or two at the most, leading to a reduction in their "sensual experience" possibly impairing the "psychosexual pleasure of the ejaculatory process," viz, their orgasms.

Postorgasmic Illness Syndrome

This is a rare syndrome [72] first described in two patients by Waldinger and Schweitzer [73]. After an ejaculation/orgasm, the patients suffered from extreme fatigue, a flu-like condition with rhinitis, itching eyes, irritability, and decreased mood within 20–30 min. These symptoms gradually faded away over 3–7 days. The etiology of the condition is unknown and there is no specific treatment for it.

Do Orgasms have Health Benefits Other than Pleasure?

It is fitting to end on the positive health aspects of having orgasms apart from the pleasure and contentment they can impart. In a review of the beneficial roles of sexual activity, Levin [28] noted that orgasms have been used to reduce the

pain of dysmenorrhoea and other painful conditions; in males, it increases the number of immune cells (leucocytes) and a reduced number of ejaculations in the early part of life in males was associated with an increased risk of prostate cancer. Males who had frequent orgasms (more than 2 a week) had a lower mortality risk than those who did not [74]. Orgasm reduces stress [75] and has also been used by women as a soporific aid to facilitate falling asleep [76].

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Addendum

Since the chapter was written a number of papers have been published that add additional findings to topics dealt with in the review chapter.

Female Orgasm and Reproduction

In relation to the putative role of the female orgasm and its release of oxytocin in facilitating the transport of sperm through the female reproductive tract the recent review by Levin (2011) examined in critical detail the experimental studies undertaken to support the concept. The conclusion was that there was no experimental study able to unequivocally confirm the proposed mechanism and that the bulk of the evidence indicated that the female orgasm has little or no effective role in the transport of spermatozoa in natural human coitus

Levin RJ. Can the controversy about the putative role of the human female orgasm in sperm transport be settled with our current physiological knowledge of coitus? J Sex Med. 2011, doi.10.111/j.1743-6109.2012002162.x.

Postorgasmic Illness Syndrome

Further study of the postorgasmic illness syndrome (POIS) have been conducted by Waldinger, Meinardi, Zwinderman & Schweitzer (2011) to investigate whether the condition could have an immunogenic etiology. Some 33 men diagnosed with POIS were examined using a skin prick test with autologous diluted seminal fluid, of these 29 (88%) showed a positive test. This results suggested that POIS could be due to a Type 1 and Type 1V allergy to the male's own semen. In a further study 2 patients diagnosed with POIS agreed to a desensitisation programme using their own semen. This involved injecting initially very diluted seminal fluid subcutaneously (of gradually increased concentration) ending over 15 months in one case and 31 months in another. During the programme there was gradual amelioration in the symptoms of POIS of 60% in the former case and 90% in the latter. The effectiveness of the treatment suggested that the mechanism(s) underlying POIS may be an autoimmunogenetic/allergic condition.

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Chapter 5
Physiology of Female Genital Sexual Arousal

Irwin Goldstein and Jonathan Silberstein

Keywords Arousal • Engorgement • Lubrication • Neurotransmitters • Androgens • Hormones

Introduction

The waiting room of a busy oncology practitioner's office will include women patients who may also have sexual health concerns [1–7]. In many cases, the sexual health problems of these oncologic patients will be highly associated with their female oncologic health care problems and/or the treatments for their oncologic condition [8–12]. In the vast majority of cases, however, while great attention is provided to the oncologic concern, there is only limited attention given to their sexual health problems.

Women's sexual problems may be associated with significant personal distress including a diminution of self-worth and self-esteem, a reduction in life satisfaction, and a decline in the quality of her relationship with her partner [13–22]. In some women, a satisfying sex life may be important throughout their lives [23–26]. Partner's sexual health may also be impaired and this may further adversely affect the relationship. To provide the best overall women's oncologic health care, it is important that providers of such female oncologic health care be familiar with the basic aspects of appropriate women's sexual health.

"Sexual health" refers to a state of physical, emotional, mental, and social well-being related to sexuality. Women who have oncologic disorders have the right to a positive and respectful approach to sexuality and to sexual relationships, to have pleasurable and safe sexual experiences, free of coercion, discrimination, and violence. For sexual health to be attained and maintained, the sexual rights of all women must be respected, protected, and fulfilled. Women who have oncologic disorders have the right to sexual equity: the freedom from all forms of discrimination regardless of sex, gender, sexual orientation, age, race, social class, religion, or physical, and emotional disability. Women who have oncologic disorders also have the right to sexual pleasure; sexual pleasure is a source of physical, psychological, intellectual, and spiritual well-being [27].

Multiple challenges are commonly faced while engaging female patients presenting with primary oncologic disorders who also have sexual health concerns. It is simply difficult to find the time and the opportunity to discuss with such patients strategies to effectively manage their sexual health concerns. Oncologic health care clinicians often have received limited training in the diagnosis and treatment of women with sexual health concerns during medical school training, residency training, and/or subspecialty training [28–31].

Furthermore, sexual medicine issues are usually complex and are, in general, secondary to psychologic, physiologic, and relationship issues

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that are interrelated in unique and individual ways, molded with distinct couple dynamics. Psychologic factors include previous sexual trauma and abuse, depression, psychoses, anxiety, distraction, sexual neuroses, sexual inhibitions or idiosyncrasies, and/or interpersonal relationship issues [32–42]. Biologic factors may involve such pertinent factors as aging, bladder cancer, breast cancer, coronary artery disease, diabetes mellitus, endometriosis, female genital mutilation, hyperlipidemia, hypothyroidism, hysterectomy, infertility issues, interstitial cystitis, menopause, metabolic syndrome, obesity, organ prolapse, overactive bladder, pelvic floor dysfunction, persistent genital arousal disorder, pregnancy and childbirth, rectal cancer, renal failure, sexual pain disorders, sexually transmitted infections, sleep apnea, urinary tract infections, urinary incontinence, uterine fibroids, and vulvar dermatologic disorders [43–91]. Women's sexual health problems may also stem from the male partner, that is, should the male partner experience premature ejaculation, erectile dysfunction, inability to have an orgasm, Peyronie's disease, or prostate cancer, his sexual dysfunction can adversely affect his female partner's sexual health [92–99].

Health care clinicians need to be holistic in managing women with sexual dysfunction and be aware that both psychologic and biologic issues cause sexual health problems. The objective of this chapter, however, is to provide relevant, evidence-based, basic science and clinical information to oncology practitioners to better understand physiologic, biologic-based female sexual arousal. Female sexual arousal responses are multifaceted events consisting of central and genital components that occur following sexual stimulation. In particular, women interpret genital response as pulsing, throbbing, swelling, vasocongestion, engorgement, and lubrication (wetness) [100–104]. Genital sexual arousal is mediated by a host of neurotransmitters and vasoactive agents.

Various biochemical factors modulate the female genital sexual arousal response. Adrenergic and nonadrenergic noncholinergic neurotransmitters (such as nitric oxide) play a critical role in regulating genital physiological responses by mediating the tone of vascular and nonvascular smooth muscle. Vasoactive peptides (such as vasoactive intestinal polypeptide) and neuropeptides (such as neuropeptide Y) also modify genital sexual arousal by regulating epithelial cell function and vascular and nonvascular smooth muscle cell contractility [105–111].

Various hormonal factors modulate the female genital sexual arousal response. Sex steroid hormones are critical in the maintenance of genital tissue structure and function. Lowered levels of estrogens and androgens that happen in menopause induced by many oncologic treatments are associated with genital tissue alterations in structure that adversely affect the response to physiological modulators. Lowered levels of estrogens and androgens are also associated with reduced genital blood flow and lubrication in response to pelvic nerve stimulation [112–115].

The goal of this chapter is to provide a multidisciplinary approach to better understanding the physiological and molecular basis of female genital sexual arousal. There are many psychologic and physiologic interactions. At the discretion of the oncology practitioner, it is advised that women with sexual arousal concerns that appear biologically focused undergo psychologic management concomitant to the biologic-based care [12].

It is important that oncologists who are particularly interested in women's sexual health or want to improve their clinical management skills may wish to become members of the International Society for the Study of Women's Sexual Health (ISSWSH), an international, multidisciplinary, academic, clinical, and scientific organization. The purposes of ISSWSH are to provide opportunities for communication among scholars, researchers, and practitioners about women's sexual health; to support the highest standards of ethics and professionalism in research, education, and clinical practice relative to women's sexual health; and to provide the public with accurate information about women's sexual health. Interested healthcare professionals should visit the organization's Web site, http://www.isswsh.org. Other sexual medicine societies such as the International Society for Sexual Medicine. There are five regions of The International Society for Sexual Medicine, the

Sexual Medicine Society of North America, the European Society for Sexual Medicine, the Asia Pacific Society for Sexual Medicine, the Latin America Society for Sexual Medicine, and the Africa Gulf Society for Sexual Medicine.

Physiology

The female peripheral genital arousal response is observed by genital tissue engorgement and swelling, increased vaginal wall compliance, and production of lubricating fluids (mucus and fluid transudate) from several peripheral genital tissues including cervix, periurethral glands, and vagina. This is a multidimensional process under both central and peripheral regulatory factors that is also influenced by numerous complex psychosocial factors.

Central Factors in Female Sexual Arousal

Central factors regulating female sexual arousal may be considered to have regulation from the excitatory and inhibitory systems involving critical central nervous system structures involved in sexual arousal. The current state of knowledge is that sexual arousal may be considered to involve, in part, central sexual activation of various dopamine pathways in the medial preoptic area and nucleus accumbens that focus attention to sexual-based motivation stimuli and sexual-based motor patterns. The current state of knowledge is that inhibition of sexual arousal may be considered to involve, in part, central sexual activation of various inhibitory neurochemicals that feedback to multiple levels of the excitatory dopamine pathway [116–124].

Sexual arousal inhibition involves such neurochemicals as serotonin, endocannabinoids, and opiates. Conceptually, factors that inhibit the synthesis, release, or receptor binding of brain inhibitor neurochemicals will increase sexual excitation. The most prominent and well-studied brain inhibitor neurochemical is serotonin that is strongly linked to sexual inhibition. Factors that stimulate serotonin activity decrease sexual arousal, while factors that inhibit serotonin action increase sexual arousal. Other brain neurochemicals that are inhibitors of sexual arousal include endocannabinoids and opiates. Endocannabinoid and opiate activation, similar to serotonin release, act to decrease sexual arousal and diminish orgasmic capacity. Antagonists to these neurochemicals will increase sexual activity [116–124].

Sexual excitation involves such neurochemicals as oxytocin, noradrenaline, dopamine, and melanocortins. Conceptually, factors that activate the synthesis, release, or receptor binding of brain excitatory neurochemicals will increase sexual excitation. Oxytocin is a well-investigated sexual facilitator neurochemical that when delivered centrally acts to stimulate sexual behavior, especially orgasm. Another brain neurochemical that facilitates sexual arousal is noradrenaline, an alpha-1 adrenergic agonist, that in appropriate levels centrally, unrelated to levels consistent with panic or apprehension, is associated with increased sexual behavior. An alpha 2 receptor blocker, such as yohimbine, prevents presynaptic endogenous noradrenaline inhibitory feedback, and thus results in increased noradrenalin levels. Agents such as yohimbine facilitate sexual arousal. The most well-known sexual neurochemical facilitator consists of those pharmaceuticals that are dopamine agonists. Such agents are typically used for Parkinson's disease where they have been recognized for years to be associated with increases in sexual arousal. On the other hand, agents that are dopamine receptor antagonists have been shown to block sexual facilitation and result in lowered sexual arousal. Finally, other facilitator neurochemicals are melanocortin agonists which have been reported to stimulate sexual arousal in women with sexual dysfunction following intranasal and subcutaneous administration [116–124].

Centrally acting sex steroid hormones also participate in sexual arousal. Centrally acting sex steroids, such as testosterone, 17 beta estradiol, and progesterone, act at the molecular level to

direct the synthesis of multiple proteins such as enzymes and receptors for the various facilitory neurochemical systems including oxytocin, noradrenaline dopamine, and melanocortins. Centrally acting sex steroid hormones bind to specific androgen, estrogen, and progestin hormone receptor complexes in the cytoplasm that form transcriptional agents in the nucleus and lead to the synthesis of different neurotransmitter proteins and transmitter receptor proteins. The overall effect of the centrally acting sex steroid hormones is to provide the protein biochemical machinery to enable a state in which sexual stimulation is likely to result in sexual desire, arousal, and orgasm [116–124].

Peripheral Factors in Female Sexual Arousal

In female genital sexual arousal, the peripheral local hemodynamic processes, including genital vasocongestion and vaginal lubrication, are regulated by the tone of the vascular smooth muscle of the erectile tissue and by the tone of blood vessels within the genital tissues. For example, the tone of the nonvascular smooth muscle within the vaginal muscularis and the tone of the skeletal muscle that supports the vagina help regulate vaginal compliance. During sexual arousal there is increased blood flow to the vagina, clitoris, and external genitalia, as well as increased vaginal compliance.

Sex Steroid Hormones and Female Genital Sexual Arousal

At a fundamental basic science level, central and peripheral genital tissues, in general, utilize sex steroid hormones androgens - (testosterone and dihydrotestosterone) and estrogens (estradiol)/ progestins (progesterone) for structure and function. It thus seems reasonable, in textbook encompassing both oncology and sexual health, to have a chapter review contemporary data relating physiology of sex steroid hormones and pathophysiology of abnormal sex hormones [112–116].

Sex steroids both regulate the structure and function of genital organs such as the clitoris, external genitalia, and vagina, and modify the sexual arousal response including engorgement, swelling, and vaginal compliance. Sex steroid hormones, such as estradiol, testosterone, dihydrotestosterone, and progesterone, control cellular processes within genital tissues. Each cellular action affects particular physiological events such as growth and function of epithelial cells, smooth muscle cells, blood vessels, and nerves [112–116].

Sex steroids have been shown to regulate synthesis, secretion, and reuptake of critical neurotransmitters. Sex steroids have been shown to modify vascular and nonvascular smooth muscle contractility. Sex steroids have been shown to control mucification, keratinization, and permeability of the vaginal epithelium, and androgens and estrogens have been shown to produce growth factors and vasoactive and trophic substances. Further, sex steroids may regulate the synthesis and deposition of the connective tissue matrix within the vagina [112–116].

Estradiol has specific roles in regulating the development, growth, and maintenance of genital and nongenital organs and tissues. Estrogens are to modulate development, growth, and function of the mammary glands, bone, and skin. The decline in circulating estradiol levels associated with menopause is thought to be responsible for many sexual complaints. Clinical studies suggest that estradiol modulates genital hemodynamics. Estrogen deprivation leads to decreased pelvic blood flow, resulting in diminished vaginal lubrication, clitoral fibrosis, thinning of the vaginal wall, and decreased vaginal submucosal vasculature. In addition, estrogen deficiency leads to involution and atrophy of the genital organs, adversely affecting cervical, endocervical, and glandular mucin production. In contrast, estrogen replacement in postmenopausal women increases pelvic blood flow, re-establishing vaginal integrity and lubrication [70, 112–116, 125–129].

Testosterone and dihydrotestosterone have specific roles in regulating the development, growth, and maintenance of genital and nongenital organs. Androgens also represent the immediate precursors for the biosynthesis of estrogens. In women, androgens influence bone, adipose tissue, kidney, skeletal muscle, blood, ovaries, uterus, vagina, clitoris, and mammary gland. Androgens also regulate secondary sex characteristics. Androgens affect sexual desire, bone density, adipose tissue distribution, mood, energy, and well-being. Consequently, an imbalance in androgen biosynthesis or metabolism in women may have undesirable effects on general health and on sexual and reproductive functions [112–116, 130–134].

In this chapter, a review is made of physiology of sex steroids.

Androgens: Physiology and Pathophysiology

Dehydroepiandrosterone (DHEA) is an adrenal precursor sex steroid hormone that is converted to other androgens, such as delta 5 androstenediol, delta 4 androstenedione, and testosterone via the enzymes 3 beta and 17 beta hydroxysteroid dehydrogenase, and ultimately to estradiol via aromatase or to dihydrotestosterone via 5 alpha reductase. Any positive effects of DHEA on sexual function, including on sexual arousal, must take into account all the actions of DHEA, that is DHEA alone and as a precursor of multiple androgens (such as delta 5 androstenediol and delta 4 androstenedione and estrogens), especially testosterone and estradiol. DHEA receptors have been found on endothelial cells implying that DHEA is involved in the process of vascular smooth muscle relaxation. The physiologic process of vascular smooth muscle relaxation is intimately involved with peripheral sexual arousal [135–137].

Delta 5 androstenediol acts on its own receptors on the vaginal mucosa and is involved in the mucin content of vaginal lubrication. It is possible that low values of delta 5 androstenediol are associated with sexual arousal disorders [138].

Testosterone has been linked to central regulation of female sexual behavior. Animal studies reveal that androgen receptor message ribonucleic acid-containing neurons are widely distributed in the central brain regions such as the hypothalamus and telencephalon, thought to play a key role mediating the hormonal control of sexual behavior. These regions provide strong input to the medial preoptic and ventromedial nuclei, areas associated with sexual behavior. High densities of the enzyme aromatase are observed colocalized with high densities of androgen receptor mRNA-containing neurons in numerous regions of the brain integral to central control of sexual behavior. Testosterone, in conjunction with estrogen, appears to be associated with sexual behavior [139–142].

Androgens are critical in maintaining peripheral genital tissue structure and function. Androstenedione and testosterone levels have been shown linked to vaginal physiologic function. Androgen receptors have been reported in the vagina and vestibule; these may play a critical role in vaginal, vulvar, and vestibular health. Multiple preclinical studies in ovariectomized animals (rabbits and rats) have been performed. These investigations have shown that androgen treatment enhances vaginal tissue nitric oxide synthase expression and activity, facilitates vaginal smooth muscle relaxation, increases vaginal blood flow, enhances vaginal mucification, and maintains the health and integrity of the vaginal muscularis layer. Androgens contribute to other sexual and nonsexual physiologic functions, such as bone and skeletal muscle metabolism, cognition, energy, and feelings of well-being [112–116, 130–134].

In premenopausal women with regular menstrual cycles throughout their reproductive years, there is a rise in testosterone and androstenedione in the late follicular phase of the menstrual cycle and in the luteal phase. In women 50% of testosterone synthesis occurs in the ovaries and the adrenal glands, and the remaining 50% is from testosterone precursors such as androstenedione

and DHEA processed in the peripheral tissues [112–116, 130–134].

Aging adversely affects serum testosterone levels in a slow and progressive decline, in sharp contrast to estrogen and progesterone levels that fall abruptly with menopause. In the late reproductive years the midcycle rise in free testosterone, a hallmark of the menstrual cycle in young ovulating women, begins to diminish. Another factor is the level of adrenal precursors that serve as a prehormone for about half of ovarian testosterone production; serum dehydroepiandrosterone sulfate (DHEA-S) and DHEA also fall with increasing age. Thus, after menopause androgen insufficiency occurs, in part, due to reduced synthetic function in both the adrenal and the ovaries. Furthermore, sex hormone-binding globulin increases in postmenopausal women, especially those treated with oral estrogen therapy. The net effect of diminished androgen synthesis and increased sex hormone binding globulin is a reduced amount of free unbound testosterone. Clinical symptoms of low free testosterone include impaired sexual functioning such as decreased interest, poor lubrication, muscle wasting, osteoporosis, loss of energy, changes in mood and depression [112–116, 130–134, 136, 144–146].

A series of investigations have found correlations with diminished levels of androgens and female sexual dysfunctions, including sexual arousal disorder. Correlations between total testosterone, free testosterone, and DHEA-S were found in one study with a number of sexual domains using the Female Sexual Function Index. A significant correlation between androgens, sexual desire, and sexual arousal was demonstrated in a study of women in peri-menopause. A significant correlation between sexual desire and total testosterone, as well as with free testosterone, bioavailable testosterone, and dihydrotestosterone was also found in another study. Finally in a small group of healthy premenopausal women with and without symptoms of sexual disorders, those who had sexual disorders had a significant decrease in the concentrations of delta 5 androgenic steroids, predominant in the adrenal gland [148–152].

A multinational expert panel assessed the role of androgen insufficiency, from aging or any pathophysiology, in women with sexual health concerns including sexual arousal disorders. Androgen insufficiency was defined as a pattern of characteristic clinical symptoms in the presence of decreased bioavailable or free testosterone. There many symptoms of low testosterone even with adequate estrogen treatment. These include diminished sense of well-being, dysphoric mood; persistent unexplained fatigue; changes in sexual function, including decreased libido, sexual receptivity, and pleasure; and vasomotor instability was the symptom of decreased vaginal lubrication, even with adequate estrogen treatment. The inclusion of inadequate lubrication in the constellation of androgen insufficiency symptoms makes this especially of import to women with sexual arousal disorders [153].

Androgens: Clinical Data

Several clinical studies have examined the relationships between serum testosterone levels and sexual activity. In two studies in premenopausal women, transdermal testosterone therapy significantly improved many sexual functions and behaviors including sexual motivation, fantasy, frequency of sexual activity, pleasure, orgasm, and satisfaction. In postmenopausal women, transdermal testosterone patches significantly increased free testosterone, bioavailable testosterone, and dihydrotestosterone levels from the lower limit of the normal range to higher values within the normal range. The frequency of sexual activity and pleasure was significantly greater than placebo in one study and in another, significant increases were noted in total satisfying sexual activity, arousal, orgasm, pleasure, and body image following testosterone transdermal patch versus placebo in postmenopausal women. Women assigned to testosterone also reported significant decreased concern or distress about sexual functioning. The symptom improvements in sexual function were considered clinically relevant. The measure of improvement in sexual arousal is noted [154–156].

Any woman with sexual arousal concerns treated with testosterone therapy needs to be thoroughly counseled regarding risks and benefits and the need for routine follow-up and blood test surveillance testing. Safety issues for testosterone administration include acne and hirsutism. Other side effects such as balding, voice deepening, cliteromegaly, and polycythemia were not noted in clinical trials. There was no evidence that exogenous testosterone increases the risk of endometrial cancer or endometriosis. No significant adverse effects were noted from baseline on measures of blood lipids, including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglycerides [148–156].

Concerning the relation of androgens to aging, a prospective longitudinal study of serum testosterone, DHEA-S, and sex hormone-binding globulin levels through the menopause transition, as well as a study of androgen levels in women of all ages using mass spectrometry, both demonstrated a marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during the aging years. DHEA sulfate and total and unbound testosterone values decrease with age in women. Zumoff et al. reported that the testosterone concentration of women age 20–29 years was twice the value of women age 40–49 years. Guay et al. examined androgen values in women "without sexual dysfunction." Androgen concentrations were highest in the women age 20–29 years, decreased at approximately age 30. The calculated free testosterone in women "without sexual dysfunction" was 0.6–0.8 ng/dl for women age 20–29 years and 0.4–0.6 ng/dl for women between the ages of 30 and 39 and 40 and 49 years [146, 149].

Estrogens/Progestins: Physiology and Pathophysiology

In premenopausal women throughout the reproductive years, the primary source of estradiol is cyclical synthesis by the ovaries under the control of the pituitary via follicle stimulating hormone and inhibin. There is a rise in estradiol in the late follicular phase of the menstrual cycle and in the luteal phase. The luteal phase is characterized by a rise in progesterone, primarily synthesized in the corpus luteum of the ovary. As long as the premenopausal woman continues to regularly ovulate, estrogen and progesterone levels are maintained until the time of menopause. When ovulation ceases at menopause, estradiol and progesterone levels fall abruptly. Outside of the ovary, estrogen synthesis occurs via adrenal and ovarian androgen precursors. In addition, estrogen continues to be synthesized in the periphery (skin, adipose tissue, bone, muscle, etc.) in postmenopausal women through conversion of androstenedione to estrone and testosterone to estradiol, but the amount of estradiol synthesized depends, in part, on the enzymatic activity of aromatase [70, 112–116, 125–129].

Premenopausal women with sexual dysfunction, including female genital sexual arousal disorder who do not have regular, normal menstrual cycles and are otherwise amenorrheic, or dysmenorrheic or menorrhagic, should have the underlying pathophysiology managed. Other medical issues during the premenopausal years that interfere with cyclical estrogen and progesterone production include rapid weight loss and anorexia nervosa. It has been well documented that estrogen and progesterone levels in such conditions may fall and women with such conditions may exhibit sexual dysfunction with sexual arousal complaints [70, 112–116, 125–129].

Sex steroids act via cytosolic receptors in a genomic process that utilize transcription to induce protein synthesis directed to specific central nervous system or peripheral genital tissue structure and function. Estradiol also acts in a nongenomic fashion with direct interactions with numerous central neurotransmitter systems including catacholaminergic, serotoninergic, cholinergic, and gamma-aminobutyric acidergic systems. For example, the high concentrations of estradiol in the hypothalamus and the preoptic area suggest that estradiol in these critical brain regions is involved in sexual behaviors [157–159].

There is less known about the relationship of progesterone with sexual function. Progesterone has genomic activity via progesterone receptors that modulates gene expression and thus regulates neuronal networks that control sexual behavior. Of note, estradiol increases the expression of progesterone receptor that in turn functions as a critical coordinator of the sexual response [160–164].

Estrogens/Progestins: Clinical Data

Should there be the need for exogenous estrogen and progesterone treatment, there are many choices of estrogen and progesterone for women including bioidentical and synthetic forms of estradiol and progesterone as well as multiple delivery systems for administration including oral, transdermal, transvaginal, or parenteral. The choice of synthetic or nonsynthetic estrogen and progesterone utilized may have important implications on the woman's sex steroid hormonal milieu, especially the sex hormone binding globulin and androgen values. Thus, the choice of estrogen and/or progesterone may adversely influence sexual function – this is especially pertinent for synthetic progestin agents [165].

As an example, premenopausal women who are otherwise healthy, have no sexual health issues, and have normal menstrual cycles may opt for a reversible pharmacologic birth control, electing to use exogenous potent synthetic estrogen, such as ethinyl estradiol, in combination with various synthetic progestogens. These oral contraceptives diminish FSH and LH levels and reduce metabolic activity of the ovary including suppression of ovulation. Circulating levels of androgens, recognized sex steroids that are major modulators of sexual function in women, are decreased by oral contraceptives by two separate mechanisms: (1) direct inhibition of androgen production in the ovaries and (2) marked increase in the hepatic synthesis of sex hormone binding globulin. The combination of these two mechanisms may lead to very low circulating levels of free and bioavailable testosterone [166–168].

Clinical Female Genital Sexual Arousal Disorder Syndrome Associated with Low Estradiol

The important principle is that estrogens are required for genital, especially vaginal tissue structure and function. Estrogens act on estrogen receptors that exist in high levels in the genital tissues including epithelial/endothelial cells and smooth muscle cells of the vagina, vulva, vestibule, labia, and urethra. Estrogen provides vaginal health, lubrication, and protection from sexual pain. Diminished estrogen production in the transition/menopause renders these genital tissues highly susceptible to atrophy [169–172].

Following exposure of peripheral genital tissue to decreased estradiol atrophic changes can be identified, many of which can lead to sexual arousal issues. Genital tissue structural changes and cellular dysfunctions that occur in the genital tissues as a result of estrogen deficiency are as follows. Specifically in the vagina, estrogen deficiency leads to vaginal atrophy and an alteration of the normally acidic vaginal pH that usually discourages growth of pathogenic bacteria. In an estrogen rich environment, glycogen from sloughed epithelial cells is hydrolyzed into glucose and then metabolized to lactic acid by normal vaginal flora. In the postmenopausal women, epithelial thinning reduces the available glycogen. The change to an alkaline pH value leads to a shift in the vaginal flora resulting in the likelihood of vaginal yeast infections, discharge, odor, and sexual pain. In addition atrophy of the various vaginal tissues occurs including the epithelium, vascular, muscular and connective vaginal tissues. This leads to the vaginal vault becoming pale or colorless in appearance with loss of multiple folds or rugae normally present in the estrogenized vagina. The atrophy of the lamina propria blood vessels leads to diminished blood flow to the tissues, decreased lubrication, vaginal dryness, and sexual pain. Thinning of the vaginal epithelial

layer leads to lowered elasticity and increased bleeding of vaginal tissues. When coital activity is attempted in the presence of estrogen deficiency, the marked shortening and narrowing of the vaginal vault may make sexual activity unpleasant, unsatisfactory, and painful [173–175].

Estrogen deficiency also adversely affects other genital tissues. The clitoral hood may become phimotic and the glans clitoris may atrophy and become fibrosed with persistent estrogen deficiency and diminished genital blood flow. The labia majora atrophy as there is decreased subcutaneous fat and skin elasticity. It is common for women to experience itching and pain as tissues undergo atrophy. The endocervical glandular tissue produces less mucin further contributing to vaginal dryness.

Estrogen deficiency also adversely affects the bladder and urethral meatus. Women frequently note dysuria, urinary frequency, urgency, incontinence, postcoital urinary tract infections, and sexual pain. In particular, prolapse of the urethral mucosa out the urethral lumen is highly associated with estrogen deficiency states. It is not uncommon for women with urethral prolapse to note spotting of blood on the toilet paper after wiping following voiding. The abnormal voiding history is often accompanied by a unique sexual history. Women with urethral prolapse often have the ability to have full sexual pleasure and satisfaction during self-stimulation of the clitoris; however, during sexual activity with the partner or with a mechanical device, she experiences pain and/or urgency to urinate and/or inability to have orgasm secondary to distracting pain. Physical examination of a urethral prolapse reveals a beefy red, erythematous, protruding, inflamed, edematous mucosa, prolapsing from the meatus in different degrees. Conservative treatment options include topical or systemic estrogens. If necessary, surgical excision may be required [176–178].

Local estrogen therapy can effectively restore vaginal epithelium and relieve atrophy within weeks to months. Several studies have shown restoration of vaginal cytology and improvement of vaginal atrophy and dryness. The conservative treatment involves the use of local topical vestibular and/or intravaginal estrogen [179–183].

Neurotransmitters and Female Genital Sexual Arousal

Female genital sexual arousal is a complex event associated with vasocongestion and changes in the hemodynamics of clitoris and vagina and is controlled by a host of parasympathetic and sympathetic neurotransmission. Several studies have provided detailed discussion of the physiology and neurophysiology of central regulation of genital arousal. This chapter will focus on peripheral neurotransmitters. There are limited data concerning the regulatory mechanisms modulating genital tissue smooth muscle tone and how these neurologic mechanisms are altered by disease states.

Immunohistochemical studies in vaginal and clitoral tissues have demonstrated the presence of nerve fibers containing tyrosine hydroxylase, choline acetyltransferase, neuropeptide Y, vasoactive intestinal polypeptide, peptide histidine methionine, nitric oxide synthase, calcitonin gene-related peptide, and substance P. Currently, the most data exist for adrenergic, vasoactive intestinal polypeptide and nitric oxide signaling systems to play important roles in regulating genital blood flow. Data exist that suggest that different female genital organs share these adrenergic, vasoactive intestinal polypeptide and nitric oxide signaling pathways [184, 185].

Adrenergic Neurotransmitters: In the nonstimulated state, low genital blood flow and high vaginal wall tone are largely the result of norepinephrine release from sympathetic nerves that cause vascular and nonvascular smooth muscle contraction in peripheral genital organs. After sexual stimulation has ended, termination of the genital engorged state is also the result of adrenergic system stimulation. Expression of alpha 1 and alpha 2 adrenergic receptors in female genital tissues has been demonstrated. Exogenous norepinephrine causes dose-dependent contraction in organ bath tissue strips of clitoral corpus cavernosum and vagina. Contraction to norepinephrine has been shown to be attenuated by the alpha-adrenergic receptor antagonists, prazosin and phentolamine in isolated strips of rat vaginal tissue [186].

Nitric Oxide: Following sexual stimulation, nitric oxide–cGMP signaling appears to be a critical mechanism regulating clitoral and vaginal blood flow. In experiments in isolated clitoral cavernosal tissue strips, nonadrenergic, noncholinergic relaxation to electrical stimulation was potentiated by a phosphodiesterase type 5 inhibitor. Immunoreactivity for PDE type 5 was localized in the endothelium and smooth muscle of blood vessels in human vaginal tissue. Genital engorgement and vaginal blood flow were both increased by administration of a phosphodiesterase type 5 inhibitor. It is not clear, however, if there is a role for nitric oxide mediation of relaxation of the nonvascular smooth muscle in the vagina [187–189].

Neuropeptides: Vasoactive intestinal polypeptide is likely involved in the regulation of clitoral and vaginal vascular and nonvascular smooth muscle tone. Exogenous vasoactive intestinal polypeptide has been shown to cause a concentration-dependent increase in vaginal blood flow. In vitro organ bath studies have showed that vasoactive intestinal polypeptide facilitates vaginal and clitoral smooth muscle relaxation. Peptide histidine methionine is a vasoactive intestinal polypeptide precursor and is colocalized in nerve fibers with vasoactive intestinal polypeptide. In the vagina, peptide histidine methionine can cause relaxation of the nonvascular smooth muscle by acting through the same receptors as vasoactive intestinal polypeptide. Neuropeptide Y has been detected in human vagina. Due to its primary localization within nerve fibers near blood vessels, it has been postulated that neuropeptide Y regulates blood flow in the vagina [190–193].

In summary, norepinephrine binds to alpha 1 and alpha 2 adrenergic receptors and results in a cascade of signaling that produces smooth muscle contraction, especially in the clitoris and the vagina. Stimulation of the hypogastric nerve results in attenuation of blood flow to the genital. In contrast, nitric oxide activates guanylyl cyclase in clitoral and vaginal tissues, increasing cyclic guanosine monophosphate resulting in relaxation of vascular and nonvascular smooth muscle. Similarly, vasoactive intestinal polypeptide has been shown to increase blood flow and the proposed mechanism involves activation of G-protein coupled receptors which activates adenylyl cyclase and increases cAMP, thus modulating vascular and nonvascular smooth muscle contractility and contributing to increased blood flow.

Vascular Blood Flow

Female sexual arousal is a complex neurovascular process that depends on a multitude of factors. In some women, changes in genital responsiveness (e.g., vasocongestion) with arousal may appear normal yet these women may suffer from female sexual arousal disorder. Slow oscillations in vaginal blood flow have been shown to correlate with subjective physiological arousal. In women with female sexual arousal disorder, slow oscillations in vaginal blood flow showed diminished responsiveness.

There is an increased awareness for the role of physiologic factors mediating female sexual arousal and a new appreciation for the role of organic pathophysiologic conditions resulting in female sexual arousal disorders. Vascular insufficiency states have been associated with disorders and diseases of the penis (erectile dysfunction), however, the association between vascular insufficiency and female genital arousal disorders in women has received limited attention. A developing hypothesis is that following sexual stimulation, diminished arterial inflow may contribute to impaired genital arousal as manifested by inadequate genital engorgement [194, 195]. This is seen clinically in many vasculopathic women with both atherosclerosis and claudication.

Atherosclerosis of the ilio-hypogastric-pudendal arterial bed was developed following injury to the intima with a balloon catheter. Animals were maintained on a high cholesterol diet. When compared to control animals, animals with atherosclerotic lesions had significantly diminished vaginal and clitoral blood flow following pelvic nerve stimulation, as well as reduced development

of pressure in vaginal and clitoral tissues. Upon histological examination, clitoral and vaginal tissues from atherosclerotic animals exhibited diffuse fibrosis [194, 195].

Specific pathophysiological processes have yet to be explicitly demonstrated in vaginal or clitoral tissues. It does seem likely, however, that the development of atherosclerotic plaques within genital blood vessels along with the progression of atherosclerotic disease would be similar to what has been described elsewhere. Atherosclerotic blood vessels that have developed significant stenosis may not be able to maintain sufficient perfusion such that female genital tissues are exposed to chronic ischemia and hypoxia.

Summary

Female sexual arousal disorder is defined as the persistent or recurrent inability to attain or maintain sufficient sexual excitement that causes personal distress. Women diagnosed with sexual arousal disorder may have sexual complaints of diminished vaginal lubrication, increased time for arousal, diminished vaginal and clitoral sensation, and difficulty with orgasm. These conditions may exist, in part, due to disruptions in the normal endocrine, vascular, and/or neural regulatory mechanisms with concomitant changes in genital tissue structure or cellular organization.

The female peripheral genital arousal responses are dependent upon the structural integrity of all the genital tissues. Genital arousal involves intricate neurovascular events regulated by various local neurotransmitters, vasoactive agents, vasoconstrictive agents, androgen, estrogen and progestin sex steroid hormones, growth factors, endothelial factors, epithelial factors, and other issues such as blood vessel integrity. Future research into the cellular and molecular mechanisms of normal female genital sexual arousal physiology, and of the abnormalities that occur with female genital sexual arousal disorder, will help improve the biologic management of women with sexual health concerns.

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Chapter 6
Physiology of Erection

Alan W. Shindel and Tom F. Lue

Keywords Corpus cavernosum • Smooth muscle • Endothelium • Nitric oxide • Adrenaline

Introduction

Penile erection is the process by which the flaccid phallus becomes engorged and rigid, thus facilitating sexual intercourse. The mechanisms and means by which the penis becomes erect have been a source of fascination, superstition, and interest for humans throughout recorded history. It is only within the past 40 years that the physiological and molecular pathways that mediate this critically important process have been elucidated. With improvements in our understanding of the physiology of erection, the medical community has been able to potentiate and improve sexual function in ways scarcely imagined in the past.

The complex interrelationships of the various component tissues of the penis permit the process of penile erection. In this chapter we will briefly review the current state of the art with respect to understanding of the physiology of penile tumescence and detumescence at the molecular, tissue, and organ level. Readers desiring a review of penile anatomy are referred to Chap. 1. Readers who desire a more comprehensive understanding of the molecular physiology of penile tumescence and detumescence are referred to the excellent recent review article by Prieto [1].

Penile erection requires a complex interplay of various organ systems, most importantly the neurological and vascular systems. The endocrine system and skeletal muscle play important adjunctive roles in the process of penile erection and in maintaining penile functionality. Further more, psychological state and interpersonal factors can have a tremendous impact on erectile functionality. Given the numerous organ systems involved in mediating penile erection, it is not surprising that a substantial number of somatic and psychological illnesses are linked to ED.

Neurological Regulation of Erectile Function

Cerebral Control of Penile Erection

Penile erection may be mediated by both peripheral and central mechanisms. Centrally mediated erections occur secondary to erotic stimuli or thoughts. Central nervous system (CNS) structures, specifically the medial preoptic area (MPOA) and the paraventricular nucleus (PVN) of the hypothalamus, also play an important role in the regulation of penile erection [2]. Dopamine appears to play a critical role in the erection-inducing capacity of both the MPOA and the PVN, likely through stimulation of oxytocin. Potentiation of dopaminergic function enhances penile erection as well as ejaculatory function,

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although side effects of currently available dopamine agonists have limited their utility in the management of ED [3, 4]. CNS release of norepinephrine has also been demonstrated to play a role in penile tumescence, as evidenced by the erectogenic effect of the alpha-2 receptor antagonist yohimbine [5].

In a study of visually evoked penile erection in response to erotic video clips, brain activation was seen in the bilateral inferior temporal cortices, right insula, right inferior frontal cortex, and left anterior cingulate cortex. Through descending projections, these brain centers are thought to modulate the process of erection by effects on centers in the thoracic and sacral spinal cord. Based on these results it has been postulated that visually evoked sexual arousal has three components associated with neuroanatomic regions: (1) a perceptual-cognitive component that recognizes visual stimuli as sexual (occurring in the bilateral inferior temporal cortices); (2) an emotional/motivational component that processes sensory information with motivational states (occurring in the right insula, right inferior frontal cortex, and left cingulate cortex); and (3) a physiologic component that coordinates endocrine and autonomic functions (occurring in the left anterior cingulate cortex) [6]. In situations involving nonvisual sexually arousing cues, it may be speculated that other centers integrate stimuli and transmit erectogenic impulses via similar common pathways downstream.

Autonomic Control of Penile Erection

Penile erection is mediated principally by the parasympathetic nervous system, although centrally mediated suppression of the sympathetic nervous system also plays a role. The primary parasympathetic innervation of the penis is from the sacral nerve roots S2–4 [7]. It has been demonstrated that men with sacral spinal cord lesions sometimes maintain the capacity for penile erection, although such erections are typically of lesser rigidity than what is observed in healthy men. These centrally mediated erections may occur in men after spinal cord injury in response to sexually arousing stimuli; similarly, erections have been detected in animals with sacral spinal cord injury after electro-stimulation of the MPOA or by administration of apomorphine [8]. Interestingly, these cerebrally induced erections do not occur in men with spinal cord lesions above T9, suggesting that central inhibition of sympathetic tone to the penis is the mechanism underlying psychogenic tumescence [9]. Reflexogenic erections (mediated by direct penile stimulation) may be produced in men with spinal cord lesions above T9 [10]. This effect is thought to be secondary to preservation of the sacral reflex arc which mediates erectogenic response to tactile stimulation of the penis in these men [11].

Somatic Nervous System and Penile Erection

Although the parasympathetic nervous system is of primary importance in producing penile erection, the somatic nervous system also plays a role; the somatic dorsal nerves of the penis form the first portion of the sacral nerve circuit that synapses with parasympathetic sacral neurons responsible for tumescence. This circuit is of critical importance in the induction of a reflexogenic erection mediated by genital touch rather than nontactile erotic stimuli [11]. The somatic nervous system is also responsible for contraction of the bulbospongiosus and ischiocavernous muscles during maximal arousal, leading to engorgement of the corpus spongiosum and the glans penis during the rigid erection phase as well as ejaculation at peak arousal. Contraction of these muscles is coordinated in Onuf's nucleus in the S2–4 spinal segments [11].

Tissue Level Mechanisms of Penile Erection

The penis is normally in a flaccid state, mediated by tonic contraction of the corporal tissues and cavernous arteries. In this state the penis is moderately hypoxic (pO_2 30–40 mmHg) [12]. With sexual arousal, there is dilation of the cavernosal arteries

and progressive engorgement of the erectile sinusoids of the paired corpora cavernosa with fresh arterial blood (pO_2 70–100 mmHg), causing an enhancement in penile girth and a modest increase in penile rigidity. With increasing influx of blood the sinusoids expand to the point at which they compress the sub-tunical plexus (located between the spongy erectile tissue and the fibrous tunica albuginea). Compression of the tunical emissary veins quickly follows, leading to a near complete abolition of venous blood flow out of the corporal bodies and a fully erect penile shaft (full erection phase) in which intracavernous pressure routinely exceeds 100 mmHg. During the full erection phase there is typically a slight engorgement of the corpus spongiosum and glans penis mediated by compression of the deep dorsal vein and circumflex veins of the penis by the corporal bodies and Buck's fascia. Full engorgement of the corpus spongiosum and glans does not occur during the full erection phase due to the relatively thin nature of the tunical investment of the corpus spongiosum; this does not permit tight compression of the venous drainage channels surrounding it. Glanular and spongiosal engorgement increases during the maximal (or rigid) erectile phase, during which the glans penis and corpus spongiosum are engorged with blood via contractile action of the bulbospongiosus and ischiocavernous muscles [11].

It is readily apparent that abundant smooth muscle content is required to modulate the contracted or relaxed states of the corporal tissues. Elastin has also received recent attention as a potentially important mediator of penile function. It has been demonstrated in several studies that decline in elastin and/or smooth muscle content is associated with erectile dysfunction in human men [13, 14]. While smooth muscle and elastin are generally conducive to erectile function, collagen and fibrotic processes are associated with erectile dysfunction [15].

Molecular Mechanisms of Penile Erection

Release of the neurotransmitter nitric oxide (NO) from the nitrergic cavernous nerve terminals is the initiating step in the molecular pathway leading to penile erection [1]. Neuronal NO is produced by activity of the enzyme neuronal nitric oxide synthase (nNOS) by reaction of oxygen and l-argininine. NO activates the soluble protein guanylate cyclase, which in turn cleaves GTP to cyclic GMP [16]. Cyclic GMP has a number of down-stream effects mediated primarily by protein kinase G (PKG), including closure of membrane bound calcium channel which prohibit entrance of extracellular calcium, opening of membrane-bound potassium channels which leads to cellular hyperpolarization, and sequestration of intracellular calcium in the endoplasmic reticulum. cGMP and PKG have also been demonstrated to play a role in inhibition of inositol triphosphate (IP_3) generation, inhibition of Rho-kinase, stimulation of myosin light chain phosphotase (MLCP), and phosphorylation of heat shock proteins [17, 18]. With hyperpolarization and a decline in intracytoplasmic calcium concentration, there is a decline in the concentration of the calcium/calmodulin complex, which interacts with myosin light chain kinase (MLCK). With decline in activity of this MLCK, myosin light chain tends to be dephosphorylated by the action of myosin light chain phosphatase (MLCP). Uncoupling of the actin and myosin cross-bridges occurs, leading to muscular relaxation and vasodilation [19].

Stimulation of guanylate cyclase by neuronally derived NO is believed to be the initial signal transduction cascade in the *initiation* of penile erection [20, 21]. NO release continues to play an important role in the maintenance of penile erection via continued release from endothelial cells by the action of endothelial nitric oxide synthase (eNOS); eNOS is activated through an Akt-dependent mechanism due to shear stress from increased blood flow past the endothelium [22]. It is thought that endothelium-derived NO is the principle source for NO necessary to *maintain* penile erection [1].

Figure 6.1 characterizes the basic NO-cGMP related mechanisms underlying penile erection.

Although NO is the best known and studied molecular mediator of penile erection, a number of non-NO mediated signal transduction pathways have been identified as potential contributors to this process.

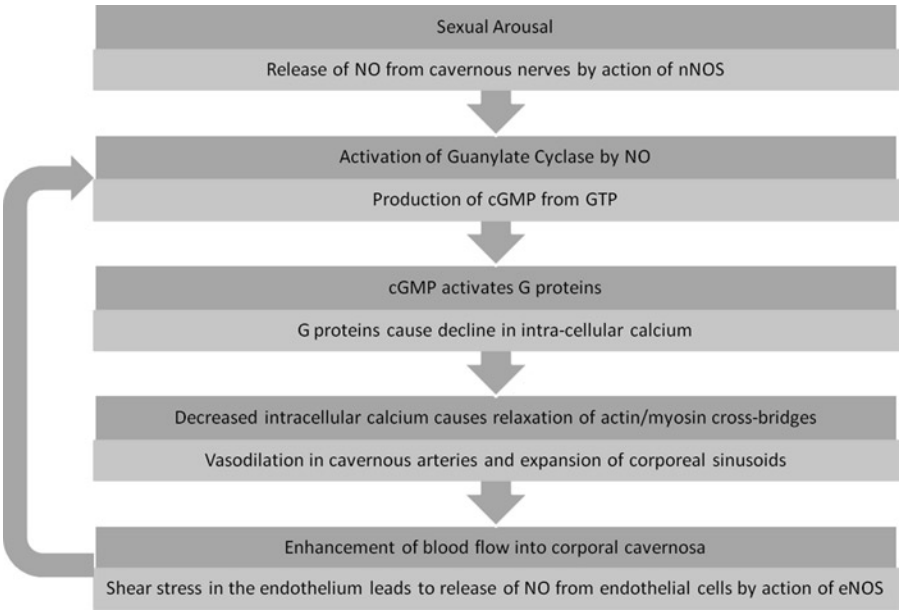

Fig. 6.1 Physiology of erection – tumescence mechanisms

1. Cholinergic neurons have been identified in cavernous nerves and appear to play a supporting role in erection [23]. It has been elucidated that acetylcholine acts both by inhibition of detumescing adrenergic nerve terminals and by direct activation of endothelial cell receptors, leading to an increase in endothelial cell production of inositol triphosphate (IP3) [24]. IP3 activates the eNOS, which produces NO from the substrate l-arginine; this endothelium-derived NO contributes to activation of guanylate cyclase in smooth muscle cells [11].
2. Carbon monoxide (CO) is a breakdown product of hemoglobin by the action of the enzyme heme oxygenase (HO). CO shares many properties with NO, including the capacity to activate guanylate cyclase. Induction of HO activity has been demonstrated to enhance erectogenic response to the phosphodiesterase type 5 (PDE5) inhibitors, and inhibition of HO activity has been shown to attenuate the action of all three PDE5 inhibitors in vivo [25, 26].
3. Prostaglandins (PG) are a family of eicosanoids that have numerous biological effects mediated in part by a large variety of receptor sub-types. In the penis, PG_{E1} and PG_{E2} have been demonstrated to induce vascular relaxation after binding to their specific receptors, EP2 and/or EP4 [27]. After receptor binding, these molecules lead to activation of adenylate cyclase and production of cAMP. cAMP activates one of several cAMP specific kinases and has downstream effects similar to cGTP. Interestingly, other PG sub-types are known to stimulate smooth muscle contraction via indirect activation of phospholipase C [28]. While the role of PG in mediation of physiological erection is at this time unclear, it is well known that intracavernous administration of PG_{E1} is highly effective in inducing penile erection in humans [29].
4. Additional compounds elaborated by the endothelium that are thought to play a role in maintenance of penile erection include endothelium-derived hyperpolarizing factor (EDHF), prostacyclin (PGI2), vasoactive intestinal peptide (VIP), and endothelin (which may have both constrictive or relaxant properties dependent on receptor type activation). These compounds have all been demonstrated to induce vasodilation but their precise role in normal erectile physiology is unclear [1, 11].

Penile Detumescence

Loss of penile erection occurs after ejaculation or with cessation of sexual arousal. Penile detumescence involves return of the penis to the resting state and is mediated in large part by reversal of the erectogenic stimuli previously discussed. While removal of sexual stimulus is an important part of this process, a number of factors play important roles in expediting this return to baseline.

Tissue Level Mechanisms of Penile Detumescence

At the tissue level, the process of detumescence occurs over three phases. There is an initial increase in intracavernous pressure as the cavernous arteries and corporal sinusoids contract against the engorged corporal spaces. With contraction of these arteries, there is decreased compression of the emissary veins and sub-tunical venous plexus. As the compressive force decreases venous outflow increases. This process permits a slow, followed by a rapid, phase of detumescence [30].

Neuronal Regulation of Penile Detumescence

While removal of the erectogenic stimulus is the principle means of reversing penile erection, tonic flaccidity of the penis appears to be mediated by different mechanisms, principally the sympathetic nervous system via fibers derived from the T10–T12 nerve roots [7]. Nerve terminals derived from these roots have been shown to innervate the cavernous arteries and trabeculae of the cavernous tissue. In addition to providing tonic suppression of erection, the sympathetic discharge that accompanies ejaculation is thought to play a role in reversing penile erection by opposing parasympathetic tone.

Central control of penile detumescence seems to rely largely on serotonin, although the relationship is complex. Activation of the 5-HT_{2C} serotonin receptor has been shown to potentiate erection, whereas activation of the 5-HT_{1A} receptors inhibits erection [31].

Molecular Mechanisms of Penile Detumescence

With cessation of the parasympathetic stimulus a slow reversal in penile erection occurs. Cessation of cGMP production and breakdown of existing cGMP by PDE5 is likely the primary mechanism of posterection detumescence [32]. The importance of PDE5 in detumescence is underscored by the efficacy of highly selective inhibitors of PDE5 (PDE5I) in improving erectile function in men with ED [33].

Norepinephrine appears to be the principal erectolytic neurotransmitter and acts by binding to alpha-1 receptors on the cell membrane of cavernous tissue smooth muscle [34, 35]. Alpha-1 receptors stimulate activation of a G protein coupled pathway leading to an increase in cellular inositol triphosphate (IP3) concentration. IP3 has myriad effects on calcium metabolism, including enhancing release of calcium from the sarcoplasmic reticulum and opening of extracellular calcium channels. Calcium binds to calmodulin and then forms a complex with MLCK; it is this complex that phosphorylates the regulatory myosin light chain at the serine-19 residue. With phosphorylation of this residue, actin–myosin cross-bridge formation is potentiated using cellular ATP as an energy source. This leads to muscle contraction. At the same time, alpha-2 receptors inhibit the activity of adenylate cyclase, inhibiting production of cyclic AMP from GTP. In addition to neuronally mediated mechanisms of G protein activation, endothelium-derived substances including endothelin, prostaglandin $F_{2\alpha,}$ angiotensin II may also activate the G protein cascade leading to IP3 production and increased intracellular calcium.

Effects that are independent of calcium concentration also account for some degree of vasoconstriction that is observed in penile smooth

muscle. These effects are thought to be mediated in large part by the action of RhoA, a small G protein that activates Rho-Kinase. Rho-Kinase phosphorylates and thus inhibits activity of smooth muscle myosin phosphatase. With a decline in phosphatase activity against smooth muscle myosin, the actin–myosin cross-bridges tend to stay contracted and vasoconstrictive tone is maintained [36]. It is thought that this "calcium-sensitizing" pathway is responsible for maintaining penile vascular contraction tonically with minimal expenditure of cellular energy [37]. A simplified algorithm for the molecular mechanisms underlying penile detumescence is presented in Fig. 6.2.

Psychological Factors and Penile Detumescence

Psychogenic causes were thought by Masters and Johnson to be the primary cause of the vast majority of cases of ED [38]. While no longer considered the primary etiology in most cases of ED, psychogenic disorders are prevalent to some extent in virtually every case of difficulty with penile erection. Furthermore, comorbid depression, anxiety, and relationship stressors may compromise erectile function. While the fundamental issue in cases such as these may be a psychological one, the physiological manifestation of psychogenic ED is based on organic factors. The most parsimonious explanation for these observations is that sympathetic nervous system activation, which accompanies most stress reactions including depression, tends to potentiate the various sympathetically mediated erectolytic pathways of the penis [39]. Indeed, it has been demonstrated that norepinephrine levels tend to be higher in men with psychogenic ED compared to healthy controls and men with organic ED; furthermore, higher levels of norepinephrine are observed in men with psychogenic ED who do not respond to PG_{E1} injection compared to those with psychogenic ED who do respond [40]. Experimentally, the sympathetic nervous system has the capacity to inhibit papaverine induced penile erection in dogs [41]. Another relatively logical explanation is that psychological states may lead to an exaggeration of the intrinsic central-mediated inhibition of sacral

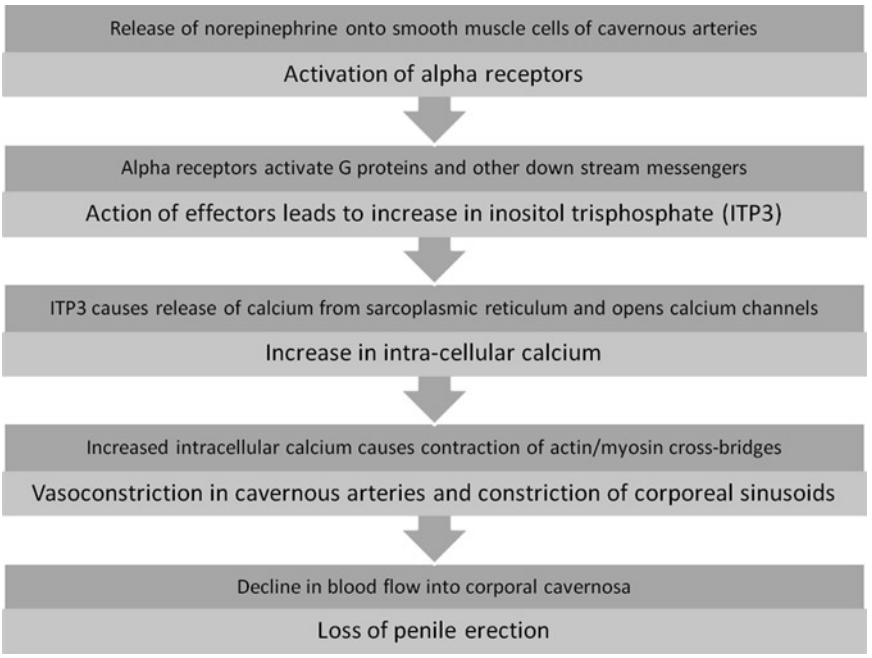

Fig. 6.2 Physiology of erection – detumescence mechanisms

erectogenic stimuli [42]. In the setting of enhanced sympathetic activation and suppression of parasympathetic activity it is not surprising that erectile function is often compromised. It maybe hypothesized that any stimulus which tends to increase cavernous tissue tone will produce a similar effect.

It is clear that a psychorelational situation conducive to sexual activity is essential in the production of reliable erections in men. Although the mechanisms are at this time unclear, the role of psychological state in the process of penile erection is of great importance.

Endocrine Factors and Penile Erection

It has been well established that men with hypogonadism tend to have poorer erectile function, although the precise mechanisms for this finding are unclear. As testosterone (T) has a substantial effect on libido, it may be speculated that low levels of testosterone may contribute to decreased interest in sex and hence more difficulty focusing on sexual activity and maintenance of erection during sexual situations [43]. While T is associated with changes in libido, its' direct effects on erection are questionable. In a meta-analysis of 17 clinical trials of T therapy, a significant improvement in erectile function was noted in young men with ED and low T levels; in older men with low T and all men with low-normal or normal levels there was no statistically significant change [44].

While the libido-inducing effects of T likely play some part in potentiating penile erection, T may play a direct role in maintaining penile tissue. Evidence to support a role for T in maintaining penile tissue integrity include observations that castrated animals or those that have been treated with antiandrogens tend to have declines in arterial inflow, increased rates of venous leak, increased cellular apoptosis, decreased smooth muscle content, and reduced erectile capacity [45–48]. At the molecular level, T has been shown to regulate expression of NOS isoforms in the penis [48]. Further studies are required to properly elucidate the role of T in normal erectile physiology but it seems clear that T is an important component in normal erectile functioning.

Conclusion

Penile erection is mediated by a complex interaction of excitatory and inhibitory mechanisms. Penile tumescence is determined by the relative activity of these various stimuli. Given the complex nature of erectile regulation, it is not surprising that numerous biological, psychological, and situational factors can have a profound effect on a man's capacity for penile erection.

The pace of discovery regarding mechanisms of penile erection continues to quicken, and it is near certain that our knowledge of penile and erectile physiology will continue to improve over time. It is our hope and belief that this will lead to continuous improvement in our ability to care for men with erectile problems in the future.

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Chapter 7
Physiology of Ejaculation

Pierre Clément and François Giuliano

Keywords Ejaculation • Emission • Serotonin • Dopamine • Spinal cord • Spinothalamic tracts

Introduction

The human sexual response can be described as a cycle formed by successive distinct, although intimately connected, phases. These are desire, excitation, orgasm, and resolution. In the human male, the orgasm phase actually refers to ejaculation and the intense pleasurable feeling that normally accompanies it. A correct ejaculatory response in human male engaged in sexual intercourse with a female partner is obligatory, although not sufficient, for reproduction. A correct ejaculation can be defined as forceful propulsion of seminal fluid out of the body through the urethral meatus (antegrade ejaculation). Ejaculation consists of the synchronized succession of physiological events that form two distinct phases: emission and expulsion. Emission corresponds to the secretion of the different components of the seminal fluid from accessory sex glands and testes. The composition of the seminal fluid is complex and contains, besides spermatozoa, a variety of enzymes, sugars, lipids, oligo-elements, and other substances. This mixture provides spermatozoa with a nutritive and protective milieu promoting their survival and movement during their run through the female reproductive tract to the ovule. The seminal secretions are secreted in a specific sequence into the posterior urethra via phasic contractions of the glands and the relative ducts. This is followed by seminal expulsion, which occurs in the form of intense rhythmic contractions of pelvi–perineal striated muscles. Concluding the ejaculatory response and marking the sexual climax, arises orgasm, a complex neuropsychophysiological process that translates in intense cerebral discharge but also whole-body physiological changes. The orgasmic response is intimately connected to the ejaculatory response but this will not be addressed here as another chapter is dedicated to this aspect of the male sexual response. It is nevertheless of crucial importance to state that orgasm can occur without ejaculation in certain conditions like after radical prostatectomy or after lesion of the sympathetic innervation to the seminal tract following retro-peritoneal lymph node dissection in testicular cancer.

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Peripheral Anatomical Organization

At the peripheral level, the ejaculatory response involves several organs and other anatomical structures belonging to the urogenital tract which take part to the process in a coordinated manner.

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Depending on the phase of ejaculation they participate in two types of anatomical structures can be distinguished.

Organs Participating in Emission

Epididymis

This highly coiled tube joins the back of the testis through an enlarged extremity, the head (or caput). The head of the epididymis is followed by a medial segment, the body (or corpus) of the epididymis, and then by the distal extremity, the tail (or cauda). In the epididymis, spermatozoa undergo final maturation as they acquire motility and fertilizing capacity [1]. Contractions of the smooth muscle layer of the epididymis are responsible for the progression of spermatozoa throughout the epididymal lumen until they reach the caudal segment where they are stored prior to ejaculation. The epididymis is continued by the ductus deferens.

Ductus (or Vas) Deferens

It extends from its junction with the caudal part of the epididymis to the ejaculatory duct formed by the fusion of the ductus deferens with the seminal vesicle ductus. The ejaculatory ducts open onto the prostatic urethra at close proximity of the prostate gland ducti to form the verumontanum. The terminal portion of the ductus deferens is dilated and tortuous (ampulla) and is capable of storing spermatozoa. At the time of emission, intense contractions of the smooth muscle cells in the wall of the ductus deferens are responsible for a rapid peristaltic transport of spermatozoa from the caudal epididymis to the ejaculatory duct.

Seminal Vesicles

They are a pair of tubular glands lying posterior to the bladder which epithelium is made of goblet cells and stroma is composed of smooth muscle layers. The fluid is expressed by epithelial cells into the single tube that is comprised in each seminal vesicle. The emitted fluid can be stored within the lumen of the seminal vesicle until emission occurs. At that time, the fluid is injected into the ejaculatory duct via strong contractions of smooth muscle cells. Seminal vesicles are responsible for the secretion of 50–80% of the entire ejaculatory volume. The seminal vesicle fluid is rich in fructose, the main source of energy for spermatozoa. However, it is unlikely that seminal vesicle secretions provide the energy required by spermatozoa for their long travel in the female reproductive tract since spermatozoa are propelled with a first fraction of the sperm that contains mainly prostatic secretions.

Prostate Gland

It is more often considered as divided into five lobes (anterior, posterior, median, and two laterals) that surround the proximal urethra (prostatic urethra) from the bladder neck to the urogenital diaphragm. The prostate gland can be seen as a tangle of fibromuscular tissue that encircles and invests the tubulo-alveolar epithelium. Epithelial cells release prostatic fluid into about twenty ducts that open onto the prostatic urethra via a slit-like aperture in the verumontanum. At the time of emission, contractions of the smooth muscle cells eject the prostatic secretions into the urethra where they mix with most of the spermatozoa to form the first fraction of the sperm. Prostatic fluid represents 15–30% of the total amount of seminal fluid expelled during ejaculation. The slightly alkaline secretions from the prostate gland contain high concentration of sugars and zinc providing spermatozoa with higher motility and longevity.

Bulbo-Urethral (or Cowper's) Glands

These glands are paired structures composed of tubulo-alveolar epithelium invested by a layer of striated muscle. Bulbo-urethral glands are embedded in the urogenital diaphragm and open into the membranous portion of the urethra at the base of the penis. Bulbo-urethral glands are actually activated

during sexual arousal and their secretions have a cleaning and lubricating role in the urethra to facilitate sperm flow to the meatus.

Organs Participating in Expulsion

Bladder Neck and Urethra

The bladder neck, which corresponds to an area of thickened smooth muscle fibres at the junction between bladder and urethra, is essential for antegrade ejaculation. The strong contractions of the bladder neck that firmly tighten bladder outlet prevent seminal fluid backflow into the bladder when pelvic floor striated muscles contract. The male urethra can be divided into three main segments that are, from the bladder neck to the urethral meatus, prostatic, membranous, and anterior urethra. Of great importance during ejaculation is the membranous urethra. The smooth muscle cells layer forming the membranous urethra wall is surrounded by a layer of striated muscle (the external urethral sphincter or rhabdosphincter). At the time of expulsion, relaxation of the external urethral sphincter, but also of smooth muscle fibres throughout the urethra, facilitates semen flow to the meatus.

Striated Muscles

The pelvic floor striated muscles, including the ischiocavernosus, bulbospongiosus (or bulbocavernosus), and levator ani, are activated during the expulsion phase of ejaculation. More particularly, the bulbospongiosus muscle, which encircles the base of the penis (bulb), has a preponderant role in the ejection of semen out of the urethra. Intense contractions of this muscle also contribute to the orgasmic feeling.

All the pelvic viscera listed above receive specific autonomic (both sympathetic and parasympathetic for most of them) and somatic innervations (Fig. 7.1) that drive messages allowing synchronized functioning of the organs involved in ejaculation.

Neural Pathways

Afferents

The main sensory afferents involved in ejaculation are represented by the dorsal nerve of the penis, a sensory branch of the somatic pudendal nerve. The dorsal nerve of the penis carries impulses from sensory receptors harboured in the penile skin, prepuce, and glans up to the upper sacral and lower lumbar (in rodents) segments of the spinal cord [2, 3]. Sensory terminals present in the glans are made of free nerve endings in majority but also of encapsulated receptors, named Krause-Finger corpuscles [4]. Those corpuscles, capable of responding to low-frequency vibrations, facilitate the ejaculatory reflex upon mechanical stimulation of the penis. In addition, Krause-Finger corpuscles excitatory inputs driven by myelinated fibres can be potentiated by sensory messages coming from various peripheral areas such as penile shaft, perineum, and testes. In different mammalian species, a relatively sparse sensory innervation of the ductus deferens, prostate gland, and urethra has been evidenced which reaches the spinal cord via the pudendal nerve [5, 6]. A second afferent pathway is constituted by fibres travelling along the hypogastric nerve and, after passing through the paravertebral sympathetic chain, enters the spinal cord via thoracolumbar dorsal roots [7]. Spinal terminals of the bipolar primary sensory neurons, which cell bodies are located in dorsal ganglia, are found in the medial dorsal horn and the dorsal grey commissure [8, 9].

Efferents

Efferent inputs commanding the peripheral events of the ejaculatory response are driven by sympathetic, parasympathetic, and somatic systems. The soma of the preganglionic sympathetic neurons are located in the intermediolateral cell column and in the central autonomic region of the thoracolumbar segments (12th thoracic and

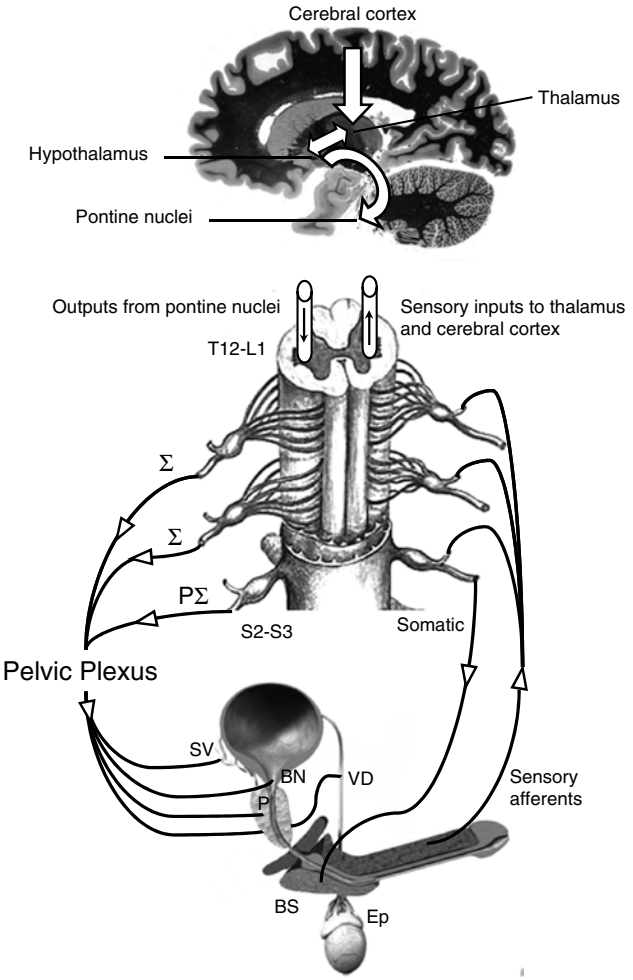

Fig. 7.1 Neural pathways controlling ejaculation. Sympathetic (S), parasympathetic (PS), and somatic nerves originating in lumbosacral spinal nuclei command the peripheral anatomical structures responsible for ejaculation. Sensory afferents originating in genital areas are integrated at the spinal and brain levels. Activity of spinal preganglionic and motor neurons is under the influence of peripheral and supraspinal inputs. *BN* bladder neck; *BS* bulbospongiosus muscle; *Ep* epididymis; *P* prostate; *SV* seminal vesicle; *VD* vas deferens

1st lumbar segments) of the spinal cord [10, 11]. The sympathetic fibres, emerging from the spinal column via the ventral roots, relay in the paravertebral sympathetic chain. The fibres then proceed either directly via the splanchnic nerve or after relaying in the coeliac superior mesenteric ganglia via the intermesenteric nerve to the inferior mesenteric ganglia [12]. Emanating from the inferior mesenteric ganglia is the hypogastric nerve that lies in the extraperitoneal connective tissue lateral to the rectum. The pelvic plexus (also known as the inferior hypogastric plexus) is formed by the merging of the hypogastric nerve and the parasympathetic pelvic nerve. The pelvic plexus lies lateral to the third anterior sacral foramina with its midpoint at the tips of the seminal vesicles. From the pelvic plexus arise fibres innervating the anatomical structures involved in ejaculation.

The cell bodies of the preganglionic parasympathetic neurons are located in the intermediolateral cell column of the sacral segments (first to third segments) of the spinal cord in an area referred to as the sacral parasympathetic nucleus

(SPN) [13]. The SPN neurons send projections, travelling in the pelvic nerve, to the postganglionic cells located in the pelvic plexus.

Efferents of somatic motoneurons, which cell bodies are found at the sacral or lumbosacral spinal level in the Onuf's nucleus, exit the ventral horn of the medulla and proceed via the motor branch of the pudendal nerve to the pelvic floor striated muscles, including bulbospongiosus, ischiocavernosus, and levator ani muscles as well as external urethral sphincter [14]. The pudendal nerve enters the perineum via the pudendal canal in the lateral wall of the ischiorectal fossa. Normal activity of these muscles, as measured with EMG electrodes, is maintained in patients subject to cystoprostatectomy, vesiculectomy, and urethrectomy [15].

Synchronisation of the activity of autonomic and somatic nervous systems, which is necessary for correct ejaculatory response to occur, takes place in the spinal cord with specific brain structures having an essential influence.

Central Nervous System Network

Spinal Organization

Cell bodies of neurons that send outputs to pelvic viscera involved in ejaculation are distributed in thoracolumbar and lumbosacral spinal cord as described above. An additional spinal centre, also known as the spinal generator for ejaculation (SGE) has been recently identified in the male rat that seems to orchestrate the activity of autonomic and somatic neurons [16] (Fig. 7.2). SGE is composed of cells that reside around the central canal, in laminae X and VII medial of the spinal lumbar segments 3 and 4 and that contain galanin, cholecystokinin, and enkephalin [17]. Because these cells were previously identified as projecting to the parvocellular subparafascicular nucleus of the thalamus, they are referred to lumbar spinothalamic (LSt) cells. LSt cells also project to the sympathetic and parasympathetic preganglionic neurons innervating the pelvis [16] as well as to the motoneurons of the dorsomedial nucleus innervating the bulbospongiosus muscles [18]. In addition, fibres of the sensory branch of the pudendal nerve terminate close to LSt cells [9], although a direct connection has not been proved yet. Finally, recent investigations in anaesthetized male rats have demonstrated that electrical stimulation of SGE elicits a complete ejaculatory response allowing the collection of mobile spermatozoa [19]. All these data support a crucial role for LSt cells that orchestrate secretory and motor outputs. They are also likely involved in the orgasmic response as a relay for sensory stimuli from the periphery to the brain structures where the pleasurable feeling raises. Integrity of these spinal nuclei is necessary and sufficient for the expression of ejaculation as demonstrated by the induction of ejaculation after peripheral, spinal, or pharmacological stimulation in animals with spinal cord transection and humans suffering from spinal cord lesion [20, 21]. Despite recent decisive progress, further advances are required for clarifying some aspects of SGE functioning. Indeed, whether several populations of neurons, including LSt, exist in SGE is still unclear, and descending brain modulating pathways on SGE are still to be identified.

Supraspinal Organization

As a centrally integrated and highly coordinated process, ejaculation involves cerebral sensory areas and motor centres which are tightly interconnected (Fig. 7.3). Research teams have used immunohistochemistry directed against Fos protein, which is the product of the immediate early gene *c-fos* rapidly transcribed once a neuron is activated, to reveal brain structures specifically involved in ejaculation [22, 23]. As a whole, experimental data collected in different species strongly suggest the existence of a cerebral network specifically related to ejaculation that is activated whatever the preceding sexual activity, i.e. mounts and intromissions in rats. The brain structures belonging to this cerebral network comprise discrete regions located within the

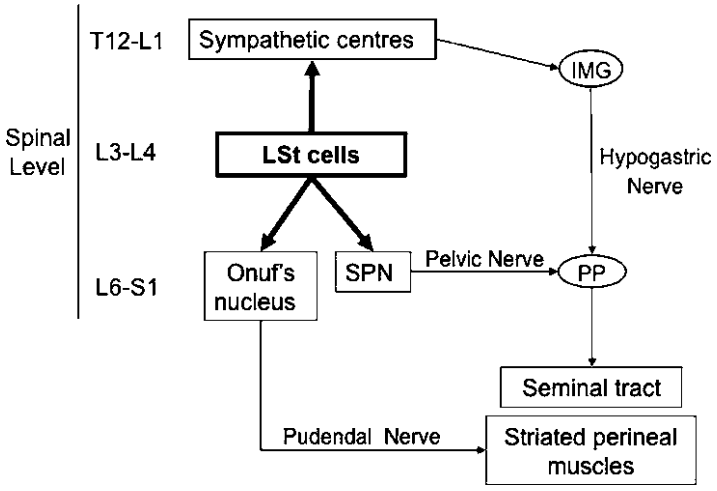

Fig. 7.2 Schematic view of LSt cells situation and connections to spinal centres of ejaculation in the male rat. *IMG* intermesenteric ganglion; *PP* pelvic plexus; *SPN* sacral parasympathetic nucleus

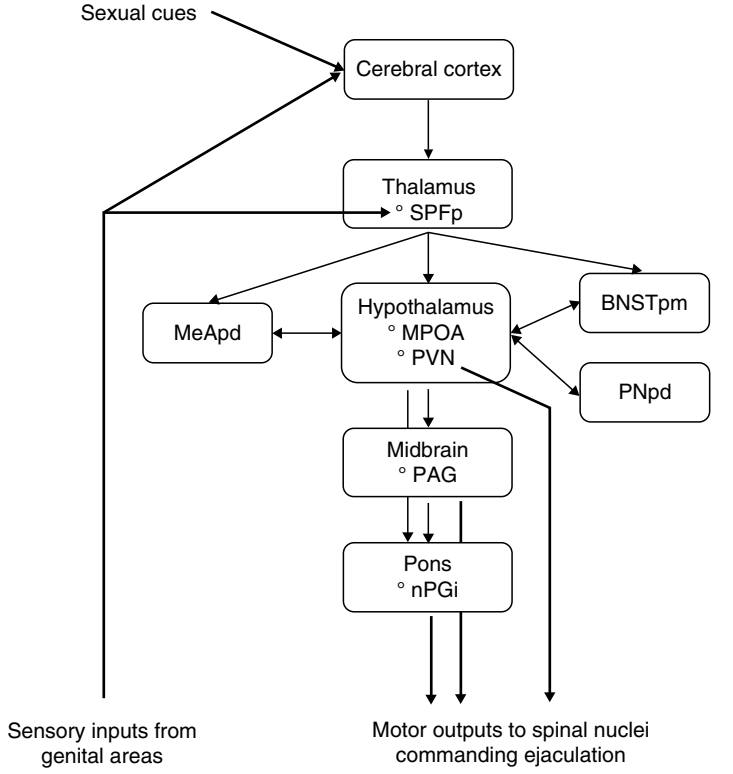

Fig. 7.3 Diagram of brain structures and putative central pathways involved in ejaculation. *BNSTpm* posteromedial bed nucleus of stria terminalis; *MeApd* posterodorsal medial amygdaloid nucleus; *MPOA* medial preoptic area; *PAG* periaqueductal grey; *nPGi* paragigantocellular nucleus; *PNpd* posterodorsal preoptic nucleus; *PVN* paraventricular thalamic nucleus; *SPFp* parvicellular part of the subparafascicular thalamus

posteromedial bed nucleus of stria terminalis (BNSTpm), the posterodorsal medial amygdaloid nucleus (MeApd), the posterodorsal preoptic nucleus (PNpd), and the parvicellular part of the subparafascicular thalamus (SPFp). Reciprocal connections between those substructures and the medial preoptic area (MPOA) of the hypothalamus, a brain area known as essential in controlling sexual behaviour [24], has been reported in anatomical and functional studies [23, 25].

The pivotal role of MPOA in ejaculation has been documented in several experiments where both emission and expulsion phases of ejaculation were abolished after MPOA lesion [26] and elicited after chemical [27, 28] or electrical [29, 30] stimulations of this brain area. Neuroanatomical studies failed to reveal the existence of direct connections between the MPOA and the spinal ejaculatory centres (autonomic and somatic nuclei, and SGE). However, it was shown that MPOA projects to other brain regions involved in ejaculation such as the paraventricular hypothalamic nucleus (PVN) [31], the periaqueductal grey (PAG) [32], and the paragigantocellular nucleus (nPGi) [33]. The PVN has long been known as a key site for neuroendocrine and autonomic integration [34]. Parvocellular neurons of the PVN directly innervate autonomic preganglionic neurons in the lumbosacral spinal cord [35, 36] and pudendal motoneurons located in the L5–L6 spinal segment in rats [9]. PVN also sends direct projection to nPGi in the brainstem [37]. Bilateral chemical lesion of the PVN with NMDA was associated with one-third reduction in the weight of the seminal material ejaculated [38]. Retrograde and antegrade tracing studies have shown that SPFp sends projections to BNST, MeA, and MPOA [3, 39] and receives inputs from LSt cells [17]. These data suggest a pivotal role for SPFp although functional investigations are lacking. The other forebrain structures which have been proposed, based on Fos pattern of expression, to take part in regulation of the ejaculatory process in rat are MeA, BNST, and PNpd [22, 25]. Their precise roles remain unclear but they may be involved in the relay of genital sensory signals to the MPOA.

In the brainstem, different nuclei have received increasing attention. A strong inhibitory role for nPGi, which projects to motoneurons and interneurons in the lumbosacral spinal cord [40, 41], on ejaculation has been suggested in several rat experimental models [40, 42]. Behavioural data provide further support to this view by showing increased expression of Fos protein in nPGi of male rats copulating but not in animals repeatedly (>2 times) ejaculating [22, 43]. An inhibitory influence on ejaculatory reflex was demonstrated for PAG [44]. Actually, as established in neuroanatomical studies, PAG constitutes a relay between MPOA and nPGi [25, 45]. Thus, it can be suggested that a baseline brain inhibitory tone on spinal mechanism of ejaculation exists and its release is required for ejaculation to occur. However, a brain excitatory influence on spinal control of ejaculation also likely exists since intracerebral administration of dopamine agonists can trigger ejaculation in anaesthetized rats, outside sexual context and in the absence of genital stimulation [46–48]. Clearly, midbrain structures exert a regulating function on ejaculation but further investigations are required for revealing the details of the mechanism.

Neurochemical Regulation

A variety of transmitters distributed throughout supraspinal and spinal sites are essential for sexual behaviour. However, the exact role of these various substances in ejaculation is difficult to define because of the wide range of sexual parameters (other than ejaculatory ones) affected, species differences, conflicting results depending on the site in the CNS where the transmitter acts, and the existence of multiple receptor subtypes. Here, we will describe the transmitters that have received a particular attention and whose mechanisms of action are clarified in some aspects.

Dopaminergic Control

Over the last decades, an extensive body of research has indicated that dopamine (DA) plays an important role in the central regulation of the male sexual response [49, 50]. To date, five DA

receptors (designated D1–D5) have been structurally characterized and classified into two distinct families (D1-like comprising D1 and D5 receptors and D2-like comprising D2, D3, and D4 receptors) based on their, respectively, positive and negative coupling with adenylate cyclase activity. The involvement of D2 and/or D3 receptors in male rat sexual motivation is well established. The D2/D3 antagonist haloperidol reduces the interest of a male rat towards an oestrous female and sexually conditioned stimulus [51, 52]. D2-like receptors, which include D2, D3, and D4 subtypes, but not D1-like receptors, which include D1 and D5 subtypes, mediate the pro-erectile activity of DA agonists [53]. Induction of erection by a selective D4 agonist was recently reported in conscious rats [54] although the participation of D2 and D3 receptors cannot be ruled out. In rats, stimulation of D2-like receptors was shown to facilitate ejaculation [55, 56] and can even trigger ejaculation in anaesthetized rats [46, 57]. In an effort to better characterize the role of D3 receptors in male sexual behaviour, the effects of the preferential D3 receptor agonist 7-OH-DPAT were studied. When injected systemically, this compound facilitates ejaculation without affecting sexual arousal [58, 59]. In addition, 7-OHDPAT induces ejaculation in anaesthetized rats when delivered into the cerebral ventricles or into MPOA and this effect is reversed by D3 but not D2 preferential antagonists [47, 48]. Very recently, the use of a highly selective D3 receptor antagonist shed light on the role of D3 receptors. Blockade of those receptors results in specific inhibition of the expulsion phase of ejaculation that translates in lengthened ejaculation latency in male rats free to copulate with sexually receptive females [60]. It appears therefore that a particular component of the brain dopaminergic pathway is especially involved in the control of a specific aspect of the ejaculatory response.

Serotonergic Control

A great body of evidence supports the inhibitory role of cerebral serotonin (5-HT) on ejaculation [61, 62]. The selective serotonin re-uptake inhibitors (SSRIs), widely prescribed as antidepressants, induce increase in 5-HT tone, especially after repeated administration, and have long been known to impair sexual functions and more particularly ejaculation in men. Advantage has been taken from these observations for the development of pharmacological management of premature ejaculation and, at the time of writing, the SSRI dapoxetine has received marketing authorization for this condition in Europe and other parts of the world. The exact mechanism of action for SSRIs to impact ejaculatory function is to be clarified but these compounds very likely act in the brain to inhibit ejaculation [63]. At the spinal level, 5-HT rather seems to exert an activating role on ejaculation. The amphetamine derivative *p*-chloroamphetamine, which causes sudden release of 5-HT in the synaptic cleft, triggers ejaculation in anaesthetized rat with complete spinal cord lesion [64]. In addition, increased spinal 5-HT levels, following intrathecal delivery of serotonin or SSRI, facilitate expulsion reflex in anaesthetized rats [63]. Different 5-HT receptor subtypes may have opposite action on ejaculation. Amongst the 14 structurally distinct 5-HT receptor subtypes identified to date, 5-HT1A, 1B, and 2C subtypes have been shown involved in the control of ejaculation [65]. It is however unreliable to ascribe one particular influence of 5-HT receptor subtypes on ejaculation since a number of data indicate that they either activate or inhibit the ejaculatory response depending on their location in the CNS.

Oxytocinergic Control

The nonapeptide oxytocin (OT) is a major hormone secreted by the hypothalamic–neurohypophyseal system. A couple of decades ago, increasing evidence demonstrated that OT also plays a role as a neuropeptide in the CNS [66]. Quantification of the level of expression of the immediate early gene product Fos protein revealed a link between ejaculation occurrence and the neuronal activity of OT neurons in the PVN [67]. However, the use of such a biological marker makes it impossible to determine the causative link between OT system and ejaculatory response. Several pharmacological studies

using OT receptor ligands clarified the situation and indicated a facilitating role of OT on ejaculation. OT acts in accessory sex glands containing OT receptors but also vasopressin receptors [68, 69] and, more importantly, in the brain [70, 71] where the neuropeptide may interact with dopaminergic system [72].

Human Brain Functioning

Noninvasive functional brain imaging techniques with relatively high spatial and temporal resolutions have been used for identifying the brain areas involved in the human sexual response. The discrimination of the different components of the sexual response (e.g. arousal, erection, ejaculation) is complicated because of the intimate relationship between them. However, correctly designed experimental paradigms render possible the specific study of neuronal activity in relation with ejaculation. To our knowledge, only one brain imaging study has been performed to date that aimed at investigating the changes in regional cerebral blood flow in human during ejaculation [73]. This study used positron emission tomography (PET) in healthy male volunteers who received penile stimulation from their female partner until ejaculation occurred. At the time of ejaculation, the strongest activation was found in mesodiencephalic transition zone including ventral tegmental area (VTA), SPFp, medial, and ventral thalamus. Those thalamic areas are known to be associated with rewarding processes, visceral sensory responses, and control of pelvic floor motoneurons and sympathetic preganglionic neurons throughout the spinal cord. Notably, the VTA contains A10 DAergic cell group belonging to the mesolimbic system and has previously been shown activated in human during cocaine or heroin rush [74, 75]. These observations make the VTA a key element of the neuronal substrate for orgasm. In addition, based on data collected in rats (as described in supraspinal organization), SPFp can also be suggested as an important relay in the human male orgasmic response. Quite unexpected is the intense increase in blood flow in an extended zone (vermis and cortex) of the cerebellum during ejaculation. In addition to its primary role in motor and coordination control as well as proprioception, the cerebellum has also been shown involved in sensory and emotional processing [76] and thus its activation concomitant to ejaculation may be related to the orgasmic response. In their PET imaging study, Holstege and collaborators noted that amygdala was deactivated during ejaculation, as indicated by decreased blood flow. This element of the limbic system is essential for the processing of emotional reactions [77] and, as demonstrated in previous imaging studies in men, is also deactivated during cocaine rush [74] and in correlation with sexual arousal [78]. The release of amygdala influence on other brain areas may constitute the neuronal substrate for the euphoric state related to different contexts including orgasm. It is to be noticed that some results of the brain imaging study of Holstege and collaborators are in disagreement with data obtained in rodents using Fos immunohistochemistry [22, 23]. Most notably, BNST and subregion of the MPOA, which were found specifically activated in relation with ejaculation in male rats, do not display changes in blood flow. The lack of MPOA activation during ejaculation was also found in Fos study performed in monkeys [79] and let us suggest the lesser importance of this structure in the control of the ejaculatory response in primates. Human imaging studies have provided key data for the understanding of the brain functioning during ejaculation and orgasm but also its participation to other aspects of the sexual response like erection and sexual arousal [78, 80]. However, further investigations in men are required for determining how the spinal neuronal network controls the autonomic, somatic, and sensory responses during ejaculation.

The Trigger for Expulsion

Sensory inputs have been shown sufficient to provoke expulsion reflex or even complete ejaculatory response with forceful expulsion of semen. In an experimental paradigm developed

in anaesthetized rat with transection of the spinal cord at T8 level, urethral distension by accumulating liquid perfused into the urethra elicited rhythmic contractions of bulbospongiosus muscles [21]. In anaesthetized and intact rat, pudendal nerve (motor branch innervating bulbospongiosus and ischiocavernosus muscles) firing was measured in response to electrical stimulation of the dorsal nerve of the penis and pelvic nerve which convey sensory information from penis and urethrogenital tract, respectively [81]. More recently, it was shown that electrical stimuli delivered to the pelvic afferents carried by the intermesenteric nerve can evoke the expulsion reflex after an obligatory relay in the brain [82].

In humans also, contractions of bulbospongiosus muscles identified with electromyographic electrodes were evidenced following electrostimulation of the penile dorsal nerve, mechanical distension of the posterior urethra, and magnetostimulation of the sacral root [83–85]. These procedures are currently used in routine to evaluate the integrity of neural pathways controlling ejaculation and have also served as basis for developing a method that produces ejaculation in patient with neurogenic anejaculation. This method, namely penile vibratory stimulation, consists in placing a vibration-delivering device on the glans of the penis, either the dorsum or frenulum, and applying 2.5 mm amplitude vibrations for 5–15 min in 1–3 series [20, 86]. Penile vibratory stimulation allowed to obtain complete ejaculatory response in more than 50% of men with spinal cord injury [20]. Despite the number of experimental and clinical data available, the exact neurophysiological event that can be regarded as the trigger for expulsion is still not clearly identified. A theory, proposed by Marberger [87], stipulates the triggering event as the build up of a prostatic pressure chamber created by seminal secretions entering the posterior (bulbous) urethra with concomitant closure of the bladder neck. The resulting distension of the bulbous urethra, communicated through sensory pathways to spinal ejaculatory centres, causes a series of rhythmic reflex contractions of the pelvic striated muscles responsible for forceful propelling of urethral content. However, several lines of evidence, recently discussed in greater details [88], actually contradict it. Indeed, it has been demonstrated that:

1. Anaesthesia of urethra by infusion with lidocaine did not prevent bulbospongiosus muscle contractions elicited by urethral distension in rat [89].
2. Pharmacological inhibition of seminal emission by alpha adrenergic receptor antagonists did not prevent occurrence of pelvic striated muscle contractions resulting in dry ejaculation nor did it alter the related orgasmic sensation [90, 91].
3. Endorectal ultrasonography studies undertaken in healthy volunteers did not evidence the formation of a prostatic pressure chamber before semen expulsion [92, 93].
4. Distension of urethra with small volume of saline is unable to provoke bulbospongiosus muscle contractions [85] suggesting that in case of dry ejaculation another mechanism takes place to trigger expulsion phase.
5. In patients after cystoprostatectomy, pattern and intensity of perineal striated muscle contractions were found similar to that measured pre-operatively despite the absence of emission in those patients [15].

Altogether these findings indicate that the expulsion phase of ejaculation can occur in the absence of urethral stimulation and that the prostatic pressure chamber concept does not provide a definitive answer on the identity of the expulsion trigger. The purpose here is not to reject the fact that stimulation of the urethra can initiate contractions of pelvic striated muscles – there are clear evidence in favour of this phenomenon – but we rather postulate this expulsatory reflex as a secondary mechanism which may take place, in the absence of any sexual cue, to prevent possibly deleterious accumulation of seminal fluid within the urethrogenital tract. The search for another possible site triggering ejaculation has given rise to interesting studies. The recent identification in rat of a spinal ejaculatory generator in adapted position for integrating peripheral and supraspinal inputs and commanding autonomic

and motor outputs responsible for ejaculation seems promising [16]. The confirmation for the existence of such an integrative spinal site in human remains to be done. Nevertheless, the close similarity between human and rat physiology of ejaculation makes very likely the existence of a human spinal generator for ejaculation.

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Part II
Disorders of Sexual Function

Chapter 8
Classifying Female Sexual Dysfunction

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Keywords Arousal • Orgasm • Pain • Sexual Pain • Sexual Desire • Classification • Definition

Introduction

Over the past decade classification of female sexual dysfunction (FSD) has undergone intense scrutiny and revision, which mirrors the present understanding of women's sexual function and behaviour.

Women's sexuality is multifaceted, rooted in biological, psychological, and social factors. Numerous epidemiological studies have shown that women's sexual function and dysfunction are influenced by various factors: *biological factors* include medical and psychiatric diseases (e.g. depression, neurological diseases, urogenital diseases), hormonal changes, menopausal status, pharmacological treatment (e.g. antidepressants), substance abuse, and medical therapies (e.g. pelvic radiation, surgical procedures); *psychological factors* include sexual development, personality, sexual experiences including abuse, body image, sexual education, and coping strategies; *contextual factors (social)* include ethnic and religious norms, economical and household factors, contraception issues, relationship with partner, life stage stressors, family issues, and partner's health and sexual health [1–7].

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Classification of sexual dysfunctions is a difficult and challenging task, and the classification of FSD is no exception. The consensus of what is considered as healthy (normal) or dysfunctional is changing and varies according to different paradigms that are themselves derived from the perceived normal reference, the subjective nature of sexual experience, and different perspectives on sexuality and its conceptualization [8]. All may vary within different cultures and over changing time periods. Sexual behaviours that were previously considered normal (lack of sexual desire in women) are now considered as dysfunctional, and women with high level of sexual interest were considered nymphomaniac as short as a century ago, are today considered as normal and desirable.

Consequently the definitions of FSD are not constant, but evolving and an ongoing discussion of them continues to take place. Despite the fact that classifications are evolving and difficult to define, they are necessary. They serve the purpose of conceptualizing the current understanding of sexual behaviour and function, both functional and dysfunctional. They make the clinician capable of differentiating between transient sexual complaints, which are part of normal life from sexual dysfunction, a distressing and persistent sexual problem. They facilitate communication between the clinician and the patient and between clinicians, as they create the common basis for clinical work. A well-defined classification is also necessary for research and measurement of treatment outcome, development of assessment

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instruments, and new treatment modalities. On the economics level, classifications are necessary for treatment and reimbursement in most health care systems around the world.

Historical Overview of the Development of Classification of FSD

The DSM System

Very early, the sexual dysfunctions were included and defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM). In the first edition (DSM-I) in 1952 there was a section on sexual deviations but without a description/term of sexual dysfunction [9]. In the second edition (DSM-II) the section psychophysiologic disorders included two sets of diagnostic terms for sexual dysfunction, dyspareunia, and impotence [10]. Both DSM-I and DSM-II reflect psychodynamic psychiatry; however, the perception of the sexual problems was that it was psychophysiologic in nature [8].

In 1966 Masters and Johnson published their book, *Human Sexual Response* [11] and later *Human Sexual Inadequacy* [12]. They introduced the sexual response cycle, a linear model based on physiological observations. The model was divided in successive stages: *excitement* being the physiological genital arousal, *plateau*, and *orgasm* followed by *resolution*. Kaplan [13] and Lief [14] later drew awareness to sexual desire, describing a psychological process embracing sexual thoughts and sexual fantasies preceding the physiological processes described by Masters & Johnson. This also reflected the clinical experience that the primary complaint of women was not a problem with genital response or sexual performance, but lack of sexual interest/desire. On the basis of this a triphasic sexual response model was developed describing: desire, excitement, and orgasm (and resolution) (Fig. 8.1). Subsequently the sexual dysfunctions were then linked to each phase and since then the phases have been the basis of how we describe

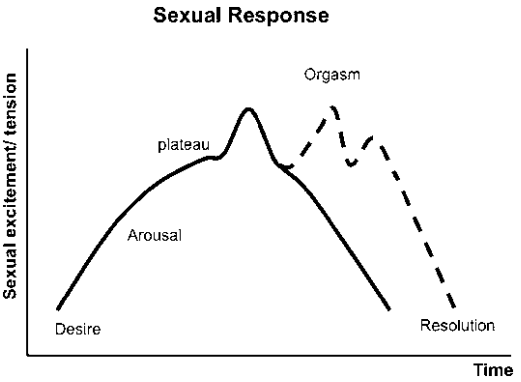

Fig. 8.1 The sexual response cycle. Adapted from Masters and Johnson [11], Kaplan [13]

and classify sexual dysfunctions. DSM-III [15] included the psychosexual disorders: *inhibited sexual desire*, *inhibited sexual excitement* (frigidity), and *inhibited orgasm* which all are linked to the three phases and *functional dyspareunia* and *functional vaginismus*, which were added as a fourth category.

In the revised edition, DSM-III-R [16], the term inhibited was dropped and what was in the previous editions described as a psychosexual dysfunction was now termed a "sexual dysfunction". In the DSM-III-R the terms lifelong or acquired; and generalized or situational; and psychogenic or psychogenic/biogenic were introduced for the first time as a further subtype classification of each dysfunction to make a more precise description of the dysfunction.

DSM-IV [17] and DSM-IV-TR [18] considerably changed the picture. An entire section was devoted to sexual disorders in this edition. The concept that psychological inhibition was the primary cause of psychopathologic disorders was abandoned, and the psychosexual disorder was described as "disturbances in sexual desire and in the psychophysiology, changes that characterize the sexual response cycle" [8]. In addition more emphasis was put on the distress and interpersonal difficulties caused by the sexual disorder.

Consequently the sexual disorder was described using three criteria: The A criterion, the disturbance itself, the B criterion, which requires that "the disturbance causes marked distress or interpersonal difficulty" and the C criterion, which

indicates that the disturbance is not "better accounted for by other Axis I disorders (except another sexual dysfunction) and is not due exclusively to the direct physiological effect of a substance abuse or a general medical condition" [18]. The determination as to whether the condition warranted a diagnosis was made by the clinician, taking into account factors that affect sexual functioning such as age and the context of the person's life [18] (Table 8.1).

Taking into account that there was growing evidence that medical conditions and substance use can affect sexual function, DSM-IV-TR also included the diagnosis Sexual Dysfunction due to a General Medical Condition, Substance-Induced Sexual Dysfunction, and Sexual Dysfunction not otherwise specified [18].

Definitions Reconsidering the DSM Definitions

The DSM-IV diagnoses have been challenged during recent years based on several critiques. It has been argued that the DSM diagnoses have failed in several aspects: It is inaccurate to present male and female dysfunctions as parallel representations of the same phenomena, that sexual response does not follow the linear model, and it can be difficult to separate desire and arousal and there may be interaction between the phases. Furthermore the described sexual behaviour is directed towards the heterosexual couple and intercourse is the reference. Moreover, it has been pointed out that important factors, such as emotional and interpersonal aspects are ignored, neglecting the effect of past and current sexual experiences, relationship, contextual factors, social factor, and many other parameters known to affect women's sexuality [8]. What is also important is that the separation between primarily medical or psychological factors seemed unjustified. With the knowledge we have today, it is recognized that it is very often impossible to separate the aetiology of the dysfunction into what is caused by biological or psychological causes since a substantial overlap very often exists.

The First Consensus Conference

On the basis of the focus on these limitations a consensus conference was organized by the American Foundation for Urological Disease in 1998 to review and suggest an update of the classification of FSD [19]. The committee included European and North American academic and clinical experts from several disciplines. Despite the fact that they continued to rely on the traditional model of sexual response, they suggested modifications of the DSM-IV diagnoses as outlined in Table 8.1. Most importantly, they added receptive desire as a crucial part of women's sexual response based on research showing that women may experience spontaneous sexual desire and fantasies, although many do not experience this regularly, but instead are receptive to sexual stimuli. They also emphasized the importance of sufficient sexual stimulation and arousal as essential to the diagnosis of orgasmic disorder. They introduced a third sexual pain category, non-coital sexual pain. Finally, they struggled with the difficulties of describing sexual arousal. Traditionally arousal has been seen as the bodily signs of arousal (lubrication, genital swelling, etc.). However, the fact that several studies have shown that the correlation between genital responses and subjective arousal is very inconsistent, resulted in a definition including objective and subjective arousal as described in Table 8.1.

Circular Model Versus a Linear Model and the Second Consensus Conference

Despite the suggested changes, dissatisfaction remained with the revised diagnoses. In the models described above, women's sexual response is described as a linear progression of phases based on the Masters & Johnson/Kaplan model, dominated by different physiological responses, initiated by desire, followed by arousal, and then orgasm. This model was challenged by Basson [20]. In her model (Fig. 8.2)

Table 8.1 Definitions of female sexual dysfunction

	DSM-IV (TR). Criterion A[a] [18][b]	Consensus conference 2000 [19]	Revised definitions from AFUD/AUAF International Consensus Committee 2003[c, d] [21]
Hypoactive sexual desire disorder (HSDD)	Persistent or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgement of deficiency or absence is made by the clinician, taking the factors that affect sexual functioning such as age and the context of the person's life into account	The persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, which causes personal distress	Sexual desire/interest disorder Absence of or diminished feelings of sexual interest or desire, absence of sexual thoughts or fantasies and a lack of responsive desire. Motivations for attempting to become sexually aroused are scarce or absent. The lack of interest is beyond a normative lessening with life cycle and relationship duration
Sexual aversion disorder	Persistent or recurrent extreme aversion to and avoidance of all (or almost all) genital contact with a sexual partner	Persistent or recurrent phobic aversion to and avoidance of sexual contact with a sexual partner, which causes sexual distress	Extreme anxiety and/or disgust at the anticipation of/or attempt to have any sexual activity
Female sexual arousal disorder (FSAD)	Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement	The persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement, or genital (lubrication/swelling) or other somatic responses	Genital sexual arousal disorder Absence of or impaired genital sexual arousal. Self-report may include minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from nongenital sexual stimuli Subjective sexual arousal disorder Absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur Combined genital and subjective arousal disorder Absence of or markedly diminished feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation as well as absence of or impaired genital sexual arousal (vulval swelling and lubrication) Persistent genital arousal disorder Spontaneous, intrusive, and unwanted genital arousal (e.g. tingling, throbbing, pulsating) in the absence of sexual interest and desire. The awareness of subjective arousal is typically but not invariably unpleasant. The arousal is unrelieved by one or more orgasms and the feelings of arousal persist for hours or days

(continued)

Table 8.1 (continued)

	DSM-IV (TR). Criterion A[a] [18][b]	Consensus conference 2000 [19]	Revised definitions from AFUD/AUAF International Consensus Committee 2003[c, d] [21]
Female orgasmic disorder (FOD)	Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of FOD should be based on the clinicians judgement that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives	Persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress	Despite the self-report of high sexual arousal/excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations or markedly delay of orgasms from any kind of stimulation
Sexual pain disorders			
Dyspareunia	Recurrent or persistent genital pain associated with sexual intercourse. The disturbance is not caused exclusively by vaginismus or lack of lubrication	Recurrent or persistent genital pain associated with sexual intercourse	Persistent or recurrent pain with attempted or complete vaginal entry and/or penile-vaginal intercourse
Vaginismus	Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse	Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress	Persistent difficulties to allow vaginal entry of a penis, a finger, and/or any object, despite the woman's expressed wish to do so. There is variable involuntary pelvic muscle contraction, (phobic) avoidance, and anticipation/fear/experience of pain. Structural or other physical abnormalities must be ruled out/addressed
Noncoital pain disorder	NA	Recurrent or persistent genital pain induced by noncoital sexual stimulation	NA

NA non-applicable

[a] The definition also has to include: Criterion B: The disturbance causes marked distress or interpersonal difficulty and criterion C: The disturbance is not better accounted for by another axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance abuse or a general medical condition

[b] Subtypes: lifelong/acquired, generalized/situational

[c] Subjective distress should be measured and rated as: none, mild, moderate, or severe

[d] It is recommended that the following three classes of specifiers are included and considered when making the diagnosis:

1. Negative upbringing/losses/trauma, past interpersonal relationships, and cultural/religious restrictions
2. Current interpersonal difficulties, partner's sexual dysfunction, inadequate stimulation, and unsatisfactory sexual and emotional contexts
3. Medical conditions, psychiatric conditions, medications, and substance abuse

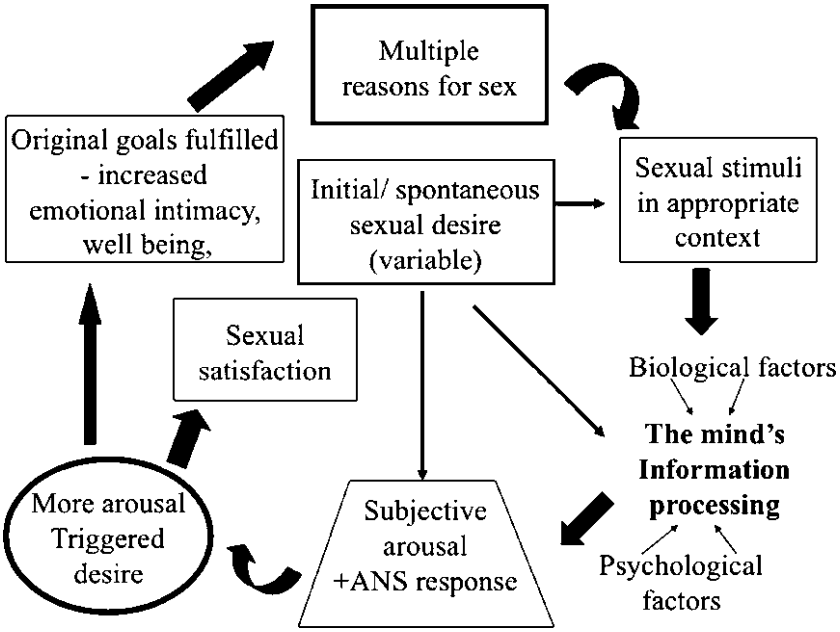

Fig. 8.2 Circular response cycle of overlapping phases: desire may or may not be present initially: it is triggered during the experience. The sexual and nonsexual outcomes influence future sexual motivation. *ANS* autonomic nervous system. Copied with permission from Lippincott Williams & Wilkins from Fig. 2: Basson [42]

she describes a circular model and a sexual response, not necessarily initiated by intrinsic physical sexual desire. In this model women's sexual response is more based on willingness to find or be receptive to sexual stimuli. Desire is a part of arousal triggered by stimuli that has a sexual meaning. This leads to the circular model, which shows several motivations to be sexual, and where arousal can occur before recognition of desire. Furthermore, the lack of specificity of the various presentations of arousal was viewed as problematic, since arousal can be described as genital and/or subjective/mental as well as the fact that these entities typically are due to different causes and dysfunction in these requires different interventions. Consequently, a second consensus conference was assembled by the Sexual Health Council of the American Foundation of Urological Diseases in 2003. As with the first consensus conference the panel consisted of an international group of clinicians and academics from several different disciplines within sexual medicine [21]. They reviewed the literature and suggested new and revised definitions of FSD as displayed in Table 8.1.

First hypoactive sexual desire disorder (HSDD) was renamed "women's sexual interest/desire disorder" reflecting the circular model where it is suggested that many women engage in sexual activity for other reasons than intrinsic physical desire as described above. On the basis of this it also included sexual motivation as a normative part of women's sexual interest, emphasizing that desire is not necessarily manifested by spontaneous sexual fantasies or thoughts [8]. Furthermore the new definitions acknowledged that there are fluctuations in sexual desire and these are influenced by age, relationship duration, life events/phases, and contextual factors and suggested that the sexual function is viewed in the context of these factors. Another considerable change was in the definitions of female sexual arousal disorders (FSAD). On the basis of the observations that genital arousal does not always strongly correlate with subjective arousal [22–24], the committee suggested addition of the categories: genital sexual arousal disorder, subjective sexual arousal disorder and combined genital and subjective sexual arousal disorders [21].

The definition of vaginismus was also changed significantly as it was found that there is no

evidence for the belief that the condition is caused by spasms of vaginal muscle. It is rather a reflexive, involuntary contraction of the pelvic muscles in addition to the thigh muscles. In addition it was suggested that the fear was towards any attempt to insert an object, thereby not only relating it to intercourse [21].

Finally the consensus group suggested a new category of arousal disorders based on clinical experience, namely persistent sexual arousal disorder (PASD). This condition describes a group of women who complain of excessive and persistent vaginal and clitoral arousal in the absence of sexual desire and which do not subside with one or more orgasms. The feelings are unwanted and intrusive [25, 26]. The name of the disorder has subsequently been changed to persistent genital arousal disorder (PGAD) and many studies have tried to describe its aetiology and characteristics [27–29].

In addition to these new suggestions for FSD, the consensus committee recommended that three classes of specifiers are included as outlined in Table 8.1 and that distress be measured as it is an important descriptor of the disorder and has implications for treatment motivation and outcome. During the last several years, the importance of distress when describing women's sexual problems has been shown to be of significant importance when describing FSD in epidemiological studies. If describing dysfunction per se, the prevalence of any given dysfunction will inevitably be very high in most populations, as demonstrated by several epidemiological studies reporting the prevalence of FSD to be as high as 55–60% in the general female population [30–32]. However, research has shown that inclusion of sexual distress in the definitions of FSD results in a lower prevalence of 15–20% in the general female population [33–35].

DSM-V a Suggestion for New Definitions

The two consensus definitions are certainly an improvement compared to earlier definitions. The major advance is the inclusion of the model of the women's sexual response cycle and the fact that they were more evidence-based than previous definitions. Despite the fact that the new definitions provide us with a more specific and refined view of women's sexual function and dysfunction, they may not fully reflect women's sexual response. Recently, it has been advocated that one single model may not adequately describe all women's' sexual response. Sand & Fischer reported that when asked to choose between a description based on Masters & Johnson, Kaplan, or Basson's models, an equal number of women chose each model [36]. Women with different characteristics (age, menopausal status, and with/without FSD) may endorse different models and the women may change in how they regard their sexual response over time. Consequently, the future challenges will be in defining FSD embracing all the different ways women experience their sexuality over a lifespan.

It is also to be noted that both consensus definitions only remain recommendations for new definitions. Even though they are used in research, clinical practice and other settings they still need to be adapted by the DSM or World Health Organization's International Classification of Diseases (ICD-10).

DSM-V

A revised version of the DSM system is under consideration. The DSM-V is expected to be finished in 2013. In the revision process, a working group on Sexual and Gender Identity Disorders has been established with the purpose of reviewing the existing DSM definitions, reviewing the literature and introduce revised evidence-based definitions. This group has published their definitions preliminary recommendations on sexual desire disorder, arousal disorder, pain disorder, aversion disorder, and orgasmic disorder as outlined in Table 8.2. The group is suggesting extensive changes in their recommendations of new definitions of FSD.

Table 8.2 Suggested new definitions of female sexual dysfunction in the DSM-V diagnostic manual [37–41]

	Criteria A	Criteria B	Criteria C	Specifiers
Sexual interest/arousal disorder (or sexual arousability disorder)	Lack of sexual interest/arousal of at least 6 months duration as manifested by at least four of the following indicators: 1. Absence of/reduced interest in sexual activity 2. Absence of/reduced sexual/erotic thoughts or fantasies 3. No initiation of sexual activity and is nor receptive to a partner's attempts to initiate 4. Absence of or reduced sexual excitement/pleasure during sexual activity (on at least 75% or more of sexual encounters) 5. Desire is not triggered by any sexual/erotic stimulus (e.g. written, verbal, visual, etc.) 6. Absence of/reduced genital and/or nongenital physical changes during sexual activity (on at least 75% or more of sexual encounters)	The disturbance causes clinically significant distress or impairment		1. Lifelong or acquired 2. Generalized or situational 3. Partner factors (partner's sexual problems, partner's health status) 4. Relationship factors (e.g. poor communication, relationship discord, discrepancies in desire for sexual activity) 5. Individual vulnerability factors (e.g. depression or anxiety, poor body image, history of abuse experience) 6. Cultural/religious factors (e.g. inhibition related to prohibition against sexual activity) 7. Medical factors (e.g. illness/medications)
Sexual aversion disorder	See text for details			
Female orgasmic disorder (FOD)	At least one of the two following symptoms: 1. Delay in, or absence of orgasm 2. Markedly reduced intensity of orgasmic sensations	Symptom(s) must have been present for at least 6 months and be experienced on 75% or more occasions of sexual activity	The problem causes marked distress or interpersonal difficulty	1. Lifelong or acquired 2. Generalized or situational 3. Partner factors (partner's sexual problems, partners health status) 4. With concomitant problems in sexual interest/sexual arousal 5. Relationship factors (e.g. poor communication, relationship discord, discrepancies in desire for sexual activity) 6. Individual vulnerability factors (e.g. depression or anxiety, poor body image, history of abuse experience) 7. Cultural/religious factors (e.g. inhibition related to prohibition against sexual activity) 8. Medical factor (e.g. illness/medications)

(continued)

Table 8.2 (continued)

	Criteria A	Criteria B	Criteria C	Specifiers
Genito-pelvic pain/ penetration disorder	See text for further details Persistent or recurrent difficulties for 6 months or more with at least one of the following 1. Inability to have vaginal intercourse/penetration on at least 50% of attempts 2. Marked genitor-pelvic pain during at least 50% of vaginal intercourse/penetration attempts 3. Marked fear of vaginal intercourse/penetration or of genitor-pelvic pain during intercourse/penetration on at least 50% of vaginal intercourse/penetration attempts 4. Marked tensing or tightning of the pelvic floor muscles during attempted vaginal intercourse/penetration on at least 50% of occasions	The disturbance causes marked distress or interpersonal difficulty		With a general medical condition (e.g. lichen sclerosis, endometriosis)

Sexual Desire and Arousal Disorders

The group suggests that the diagnoses HSDD and FSAD are merged into one diagnose, sexual interest/arousal disorder. They base their recommendation on some empirical research suggesting a lack of differentiation between sexual desire and (subjective) arousal in women and the high degree of overlap between FSAD and HSDD [37, 38]. As it can be seen from Table 8.2, they try to cover all aspects of desire (spontaneous and receptive desire) in the new definition. In the recommendation, the disorder needs to cause clinically significant distress (B criterion) and finally they recommend that the disorder is further described using specifiers as listed in Table 8.2.

Sexual Aversion Disorder (SAD)

One major problem for the recommendations for SAD is the relative few cases of SAD published and the lack of epidemiological studies. On the basis of this the group suggests three options for the DSM-V definition.

Option 1 is to remove SAD from DSM-V and expand the definition of vaginismus to include women with sexual aversion [39]. This is based on the findings that some women with vaginismus experience aversion to sexual activity.

Option 2 is to remove SAD and make the recommendation that cases of genital contact phobia are captured under the diagnosis of specific phobia in another section of DSM-V.

Option 3 is to keep SAD in the DSM-V as a sexual dysfunction, despite the lack of empirical data. The group sees this as the least desirable option based on the lack of epidemiological data and the overlap with specific phobia.

Female Orgasmic Disorder (FOD)

The group recommends that FOD is characterized by an A criterion that describes the orgasm, a B criterion that establishes a time period of the dysfunction and a frequency of occurrence, and a C criterion which includes distress and finally specifiers [40] as described in Table 8.2. The recommendation is trying to de-emphasize the

physiological aspects of orgasm as they find the evidence of distinct physiological changes to be variable, and, secondly, they argue that the subjective experience is the reason why women seek treatment for orgasm problems and not the lack of physiological changes. It should be noted that they also underline that both the physiological and the subjective changes experienced by the women during orgasm vary significantly.

Dyspareunia

In their recommendations the group suggests major changes of the definitions of sexual pain disorders and suggests three different options [41]:

Option 1 is to classify dyspareunia together with pain disorders instead of with sexual dysfunctions. They underline the lack of evidence to suggest that dyspareunia is a sexual dysfunction and state that: "the pain is not sexual; the sex is painful" [41].

Option 2 is to collapse the two categories of vaginismus and dyspareunia into one. This is suggested on the basis that the original separation of the two disorders was not empirically based [41].

Option 3 is the suggestion of a new category, including dyspareunia and vaginismus, named genito-pelvic pain/penetration disorder. They base this new definition on an A criterion describing the dysfunction and a B criterion which is the distress criterion and finally further diagnosing using specifiers [41] as outlined in Table 8.2.

Conclusion

As it can be seen from the above overview definitions of women's sexual problems and the models used to describe women's sexual response are constantly changing. It is evident that today changes in the definitions must be evidence based. Fortunately, an increasing body of research in the field of women's sexual function and dysfunction is being published which hopefully will enable us to make more accurate and clinically relevant definitions of FSD clarifying and adding new knowledge to the psychological, physiological, interpersonal, social, and contextual factors that influence women's sexuality. Whether the suggestions for new definitions in the future DSM-V will be accepted remains unknown, as they are only suggestions and at the present time they are debated intensively. However, it should be recognized that the basic domains of desire, arousal, orgasm, and pain will undoubtedly continue to make up the foundation of our classifications of FSD combined with a measurement of distress.

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Chapter 9
Hypoactive Sexual Desire Disorder

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Keywords Desire • Libido • HSDD • questionnaires • FSFI

Diagnosis

Hypoactive Sexual Desire Disorder (HSDD) is diagnosed when an individual indicates persistent or recurrent blunted levels of sexual desire and/or a lack of sexual fantasies that cause marked distress and/or interpersonal difficulties [1]. This diagnosis is intended to include only individuals who experience dissatisfaction with their low levels of sexual desire. Women with this condition will often report that they "want to want" more sex, while women with low levels of sexual desire that do not meet HSDD criteria will indicate no bother or concerns with the frequency of their sexual desire. The subjective experience of distress caused by low desire is a critical component of the diagnosis of HSDD because many individuals are not alarmed by low levels of sexual desire. Indeed, an epidemiological study conducted in Australia demonstrated that 32% of women who are 20–70 years old report low sexual desire, but only 16% report distress caused by the low sexual desire [2].

Few studies have empirically evaluated variations in levels of sexual desire in women. A recent study on frequency of sexual fantasies, which is an aspect of sexual desire, reported that, on average, women experience sexual fantasies between once-twice per month to once a week [3], although an older study on the frequency of sexual fantasies reported that, on average, women experience two sexual fantasies per day and the majority of these fantasies are activated by outside cues [4]. Because of this great variance between women, the DSM-IV-TR [1] diagnosis relies on reports of distress caused by the low desire. Nevertheless, it is possible that individuals who desire sex once a year and are content with their levels of sexual desire and sexual activity may not be diagnosed with HSDD. Conversely, individuals who desire sex 3 times a week, but are distressed by this frequency may be diagnosed with HSDD. To add to the confusion, the DSM-IV-TR [1] indicates that a diagnosis can be made when the low levels of sexual desire cause interpersonal difficulties. Because of this criterion, if a woman is in a relationship with a partner with a much greater level of sexual desire than hers and the discrepancy in desire is causing relational distress, she would nevertheless receive a diagnosis for HSDD. However, if the same woman were in a relationship with a partner whose desire was more similar to hers, she would not meet criteria for HSDD. These caveats seriously question the theoretical assumption that "abnormal" levels of sexual desire can be identified and reliably assessed.

Theoretically, sexual desire has been conceptualized as the motivating mechanism behind sexual activities. This impetus is central to the survival of the species. The chronic and distressing experience of inhibited sexual desire can

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adversely affect quality of life, lead to high levels of personal distress, and cause relational difficulties [5]. Women who experience a loss of sexual desire might be faced with the choice of engaging in sex without feeling desire, but capitulate because they fear losing their partners, or experience guilt for withholding an important part of a satisfying relationship and harbor feelings of inadequacy and poor self-esteem – all of which could impair mental health. Because of the guilt often associated with inhibited sexual desire, women report they no longer express affection or touch their partners. For example, they often report withholding a hug, kiss, or casual touch, such as holding hands, because they are afraid this would mislead their partners to think they want to engage in sexual activities. The guilt of "starting what they cannot finish" prevents them from exchanging innocent forms of affection and this leads to greater distance in the relationship.

It has been well documented in the literature that inhibited sexual desire has relational consequences beyond the sexual realm. For example, studies have shown that couples reporting low frequencies of physical intimacy score lower on relationship adjustment and relationship satisfaction as compared to couples with higher frequencies of physical intimacy [3, 6]. However, the directionality of this relationship remains debated [7]. It is important to note that the frequency of sexual activities per se may not be the problem and that a decrease in frequency of sexual activities may cause greater distress in couples whose sexual lives are dramatically affected by HSDD as compared to couples who are satisfied with a low frequency of sexual activities. When couples experience different levels of sexual desire, there is often resentment on the part of the partner who has high levels of desire, while the partner with little or no sexual desire feels guilt and shame. Couples are often left to grapple with a cyclical and nonproductive conversation to make a change, each not knowing how to move out of their preferred sexual stance. In the long term, this cycle, with or without professional intervention, is likely to erode the relationship.

To prevent this dysfunctional cycle where HSDD fosters resentment and greater sexual dysfunction, information regarding potential changes and shifts in sexual desire over a lifetime can be incorporated in a preventive health education or sexual education program. Healthcare providers may be instrumental in reducing sexual dysfunction by simply educating their patients about sexual desire changes that may be the result of an illness, medication, surgery, or psychiatric condition, or even changes that result from life changes such as pregnancy or menopause. Having realistic expectations for changes in sexual health is an important aspect of health care that can help prevent sexual desire problems and can also help managing treatment and medication doses. Indeed, treatment-induced inhibition of sexual desire is one of the most commonly cited reasons for treatment discontinuation even for conditions that cause high levels of emotional distress, such as depression, and for drugs that provide an important function in women's lives, such as hormonal contraceptives. Indeed, research on antidepressants showed that 42% of men and 15% of women discontinue the medication over perceived beliefs of sexual adverse effects [8].

In summary, severe personal and relational distress caused by changes in sexual desire can be addressed by healthcare providers through simple education of how treatment, surgery, and illnesses can affect sexual desire. By providing accurate information to the patients, the healthcare provider can have a significant impact on the prevention of dysfunctional patterns in the relationship that can lead to chronic sexual dysfunctions. Moreover, accurate information about changes in sexual desire associated with a treatment can help prevent treatment discontinuation and promote overall quality of life not only for the patient, but also for her partner.

Theoretical Models of Sexual Desire

The HSDD diagnosis is based on the early models of the sexual cycle. Masters and Johnson [9] were the first to conceptualize the model of the sexual cycle to begin with sexual arousal and continue with plateau, orgasm, and resolution.

Kaplan [10] revised Masters and Johnson's original theoretical model by adding sexual desire in the beginning of the cycle (i.e., prior to sexual arousal). To date, Kaplan's model is considered controversial. The debate is centered on whether desire and sexual arousal are distinct experiences, with desire always *preceding* sexual arousal.

A more recently proposed model of female sexual response posits that desire is experienced after sexual arousal [11]. In this model (often called the Circular Model), it is proposed that the woman experiences sexual arousal after her partner approached her with sexual cues and stimulation. The sensation of sexual arousal leads to positive associations with sexual behavior and these associations motivate desire for further sexual stimulation. Once the sexual activity has led to satisfying emotional and physical sexual experiences, the woman internalizes the desire for future sexual activities that, she anticipates, will lead to similar sexual rewards. The emotional and physical rewards resulting from sexual activity are the sources of spontaneous motivation for later sexual activities. Therefore, sexual activities that fail to provide satisfying physical and emotional rewards may diminish sexual desire in women [11]. According to this model, the treatment of sexual desire is contingent to the experience of satisfying sexual activities.

A third model, proposed by Levine [12], emphasizes that variations in individuals' experiences of sexual desire provide more clinically relevant information than just frequency of sexual thoughts or fantasies. According to Levine's theory, an overall frequency of sexual thoughts or fantasies is less relevant than information changes in the cues that activate sexual desire. For example, according to this model, a clinician would benefit from assessing whether a woman who used to experience sexual desire after a romantic dinner is no longer feeling sexual desire after similar activities. Thus, an assessment of how a woman used to respond to a sexual cue (e.g., a specific scent, romantic experiences, erotic material, seeing a partner acting competently) is more important than the assessment of overall frequency of sexual thoughts. This model, originally developed through extensive clinical experience, has found support in a recent empirical study [13]. A group of 50 women identified 125 different cues of sexual desire that were analytically grouped into four cue types based on the responses of a second group of 874 women of 17–72 years old (Table 9.1; 13). The four analytically derived types of sexual cues are reminiscent of the 11 sexual cues that Levine identified based on his clinical observations. Later, a study on premenopausal and menopausal women showed that individuals with HSDD endorsed significantly fewer cues than women without HSDD [14]. The combination of clinical and empirical evidence for this model provides unique support for the validity of perceived sexual cues as meaningful contributing factors of HSDD. The next step will be to establish whether increasing the variety of sexual cues and modulating the sensitivity to sexual cues (e.g., lowering the threshold of desire activation in the presence of a sexual cue) could alleviate HSDD symptoms.

Today, desire continues to be understood as a motivating force to engage in activities that can lead to sexual satisfaction [14]. From a behavioral perspective, motivation is the driving force behind the initiation and maintenance of goal-oriented behavior [16]. However, sexual desire does not always directly precede the behavior it motivates, and sexual behaviors may occur in the absence of desire. There are a number of reasons women may not act on their sexual desire, for example, social norms or fear of pregnancy. On the other hand, sexual desire aside, women may engage in sexual activities, for instance, to ensure the fidelity of a mate, to spite someone, or to succumb to peer pressure [17]. The distinction between sexual desire and frequency of sexual behaviors connected to desire [3] makes the assessment of desire more complicated than it may initially appear.

As noted above, the theoretical model for sexual desire proposed by Basson argues that spontaneous sexual desire is not the norm in women, but rather it is the product of sexual arousal. An empirical study that asked women whether they identified more strongly with the model proposed by Kaplan (the model proposing that desire always precedes sexual arousal) or the model

Table 9.1 Type of cues of sexual desire

Type of cues	Examples of cues
Emotional bonding	Feeling a sense of love with a partner
	Feeling a sense of security in your relationship
	Your partner is supportive of you
	Your partner does "special" or "loving" things for you
	Feeling a sense of commitment from a partner
	Your partner expresses interest in hearing about you
	Talking about the future with your partner
	Feeling protected by a partner
	Experiencing emotional closeness with a partner
	Feeling protective of a partner
Explicit/erotic	Watching an erotic movie
	Reading about sexual activity (e.g., pornographic magazine)
	Watching or listening to other people engaged in sexual behavior/activity
	Talking about sexual activity or "talking dirty"
	Watching a strip tease
	Sensing your own or your partner's wetness, lubrication, or erection
	Asking for or anticipating sexual activity
	Hearing your partner tell you that he or she fantasized about you
	Having a sexual fantasy (e.g., having a sexual dream, daydreaming)
	You experience genital sensations (e.g., increased blood flow to genitals)
Visual/proximity	Seeing someone who is well dressed or "has class"
	Seeing/talking with someone powerful
	Being in close proximity with attractive people
	Seeing/talking with someone famous
	Seeing a well-toned body
	Seeing/talking with someone wealthy
	Watching someone engage in physical activities (e.g., sports)
	Seeing someone act confidently
	Seeing/talking with someone intelligent
	Flirting with someone or having someone flirt with you
Romantic/implicit	Whispering into your partner's ear/having your partner whisper into your ear
	Dancing closely
	Watching a sunset
	Having a romantic dinner with a partner
	Watching a romantic movie
	Being in a hot tub
	Touching your partner's hair or face
	Giving or receiving a massage
	Laughing with a romantic partner
	Smelling pleasant scents (e.g., perfume/cologne, shampoo, aftershave)

From McCall and Meston [13].

proposed by Basson found that women with a sexual dysfunction identified more with the latter and women with no sexual dysfunction identified more with the former [18]. Future studies are needed to assess whether (1) the tendency to identify with a specific model can be a factor in developing sexual dysfunction and (2) whether women's perceptions of their sexual response cycle can change as their sexual functioning develops and changes over time. Both models are currently utilized in clinical settings. A useful tool for clinicians may be to present both models to a patient and ask her to identify the model that reflects her personal experience. Presenting the patient with this option opens the opportunity for education on different perspectives of sexuality and provides a

theoretical framework to conceptualize sexual symptoms, goals, and expectations of treatment.

In sum, the debate on whether desire precedes or follows arousal is implicitly a discussion on the nature of sexual desire. The perspective that some women experience sexual desire before sexual activities implies that a woman may experience spontaneous sexual desire, suggesting that desire can be activated by internal forces and may not necessarily be based on outside cues. Examples of spontaneous sexual desire are sexual fantasies that emerge during the day, or the night, and are not activated by any external stimulation. Conversely, the circular model, proposing that sexual desire occurs after sexual arousal, supports the idea that women's sexual desire is naturally derived from outside cues or is reactive in nature. In other words, this model questions the importance of spontaneous sexual thoughts or fantasies. Establishing the definition of normal sexual desire as internally vs. externally derived determines what is perceived as "abnormal" and thus directs the focus of treatment. Although an in-depth explanation of this pressing discourse is beyond the scope of this chapter, an understanding of these two conflicting positions can be useful for understanding the utility of different treatment modalities and the aspects of desire to include in a preliminary HSDD assessment.

Assessment of HSDD (Table 9.2)

A number of instruments developed for the assessment of HSDD are available to the public. Clinics not specialized in the treatment of sexual dysfunction can utilize a brief screener of HSDD to identify women who are more likely to experience problems with sexual desire. There are two such screeners currently available: the Hypoactive Sexual Desire Screener [19] and the Decreased Sexual Desire Screener [20]. Both screeners exhibit good sensitivity and specificity, meaning that the instruments are able to correctly identify people with the disorder. Individuals scoring positive on the screener, and indicating interest in greater support in this area, can complete aimed questionnaires that measure severity of sexual symptoms. According to a recent review of 28 questionnaires for female sexual functioning [21], the Female Sexual Functioning Index [22] and the Sexual Function Questionnaire [23] were recommended for both clinical and research use for women who may have sexual dysfunctions [21]. Although these questionnaires cannot be a substitute for a thorough interview covering the sexual, psychological, and medical history of each patient, they are adequate measures of severity of the sexual problem and provide the clinician with population-based norms on levels of distress associated with low desire. Clinical cutoffs based on population norms allow clinicians to quickly assess the severity of the symptoms in relation to the larger population.

Questionnaires assessing distress and satisfaction can be utilized to provide a measure of the impact of the problem on the patient's daily life. Measures of distress/satisfaction can also be useful to set goals for treatment and to track treatment-related improvements. Among the available published measures for sexual satisfaction, the Sexual Satisfaction Scale for Women [24] is one that captures both satisfaction and distress with sexual functioning. Although norms for women with and without HSDD are available, currently the scale lacks cutoffs for clinical levels, therefore it is best used to monitor treatment-related improvements.

A more comprehensive sexual health history can uncover important diagnostic information not fully captured by brief questionnaires. For example, potential etiological factors of low sexual desire can emerge from an interview that includes questions about the relationship dynamic. A personal interview also provides an opportunity to assess whether the low levels of desire are lifelong, the product of a slow decline, or whether a reduction followed a specific triggering event. For instance, a crisis caused by infidelity, a lifelong issue, or perhaps a slow decline since menopause can be important factors in the assessment and treatment of HSDD. If the change was sudden, other issues can be

Table 9.2 Topics addressed during a complete assessment of hypoactive sexual desire disorder

Topics to target during HSDD assessment
1) Ensure patient understands the definition of desire. Desire is both spontaneous desire for sexual activities and the tendency to respond when a partner initiates sexual activities
2) Assess whether levels of sexual desire are lower than wished by the patient (not necessarily her partner)
3) Assess whether the low level of sexual desire causes distress or bother in the patient (not necessarily her partner)
4) Investigate whether the levels of desire have always been low (lifelong) or if they were higher at some point (e.g., in pervious relationship or earlier in current relationship, before menopause, before pregnancy, or before a specific event)
a) Investigate the circumstances of the event
b) Explore the pattern of change (sudden or gradual change)
c) Establish the amount of change noticed by the patient
5) Assess the attribution for the low sexual desire by the patient
6) Assess relationship satisfaction, ability of the couple to communicate emotional material, points of disagreement, and power distribution within the couple
7) Determine the major points of life stressors in the patient and her coping style
8) Inquire about relevant past sexual experiences including a history of sexual abuse and childhood trauma including emotional and physical abuse
9) Assess emotional responses to sex that could affect sexual desire, including beliefs that could lead to guilt, shame, and anxiety

explored during an interview, for example, whether the patient experienced a recent illness, a change in medication, or whether problems emerged within the romantic relationship, with alcohol or substance use, or as aftermath of a sexually abusive experience. Other clinically meaningful information that can be explored during an interview include whether the low desire causes personal or interpersonal distress (or both), and whether partner's sexual health is playing a role in the low desire of the patient. Moreover, interviews aid in identifying other coexisting sexual dysfunction, including whether desire was an antecedent or consequence of the accompanying sexual dysfunction. As we will discuss later, it is common for women with sexual arousal dysfunction to experience concurrent low sexual desire. In such cases, determining whether the sexual arousal dysfunction occurred prior to, in concurrence with, or after the decline in sexual desire may help identifying important etiological factors to target during treatment.

In addition to clinical interviews, laboratory tests can provide useful information for treatment of HSDD. The most commonly used laboratory tests include an assessment of abnormally low androgens levels. Usually, laboratory exams include an assessment of free testosterone, DHEA-S, and DHEA. Patients' androgens levels can be compared to population-based norms; however, information on intrapersonal drops in androgen has been identified as more accurate information. An assessment of medical conditions associated with estrogen and androgens abnormalities can also be useful. For examples, conditions resulting in amenorrhea, oligomenorrhea, polycystic ovarian syndrome, and diabetes have been linked to impaired levels of sexual desire and it would be appropriate to treat these conditions before attempting the direct treatment of sexual desire, since the low desire may be a symptom of a larger problem rather than a circumscribed and independent condition.

Differential Diagnosis

Low sexual desire is often observed in people experiencing other psychiatric conditions such as depression, anxiety disorders, and eating disorders [25–28]. In addition, low levels of sexual desire are commonly reported by women who also experience other types of sexual dysfunction, including female orgasmic disorder, female sexual arousal disorder, and sexual pain disorders.

Identifying whether HSDD is part of a more complex sexual or psychological cluster of symptoms or whether it is a symptom independent of other pathology is a requisite part of a complete HSDD diagnosis.

The high coexistence of HSDD and other types of sexual dysfunction [22] can be best understood if we look at desire as a motivating force to pursue or engage in gratifying sexual experiences [15]. If desire is the motivation to engage in behaviors that lead to sexual rewards, any obstacle to the rewarding aspect of the sexual experience, or with motivating mechanisms in general, can potentially have an adverse effect on sexual desire. For example, a woman who experiences difficulties becoming sexually aroused or reaching an orgasm is not likely to experience the physiological pleasure associated with sexual activities and this could lead to a reduction in motivation for sexual activities. It is also possible for the inverse to be true and problems with desire could eventually lead to low arousal or problems with orgasm and sexual pain. From a treatment point of view, factors that maintain HSDD may be equally (or more) important than initiation factors. Therefore, understanding the factors that perpetuate the dysfunction in the present moment is central to the assessment. For example, levels of sexual desire may have dropped after a series of sexual experiences that failed to lead to orgasm. After numerous unsuccessful and frustrating sexual experiences, the woman may feel a loss of desire along with the difficulty in reaching orgasm. In such a case, the orgasm is the primary dysfunction that subsequently caused the development of HSDD; therefore, treating the desire problem alone may not be sufficient. At the same time, treating the orgasm without addressing the low desire caused by feelings of anxiety, sadness, inadequacy, and disappointment may overlook an important aspect of her sexual health. Thus, a clear understanding of what started the sexual problems needs to be addressed along with the exploration of potential maintaining factors.

Female sexual arousal disorder and HSDD are particularly difficult to distinguish because women often do not intuitively differentiate arousal from desire. However, women are not the only ones confused about the desire-arousal distinction. As we have discussed above, experts are still debating whether desire and arousal should be considered two distinct experiences [29]. Currently, desire is defined as the experience of longing or wanting to engage in sexual activities, whereas subjective sexual arousal comprises the sensations that women experience during sexual stimulation. Questions to distinguish between problems with arousal, orgasm, and desire are listed in Table 9.3. Although these questions have not been empirically validated, they are commonly used in clinical practice and they can be quite informative.

It should be noted that despite the importance to ascertain the temporal precedence between HSDD and the other types of sexual dysfunction, to date, very little is known about the coexistence of desire and other diagnoses and even less is known about the importance of treating desire in relation to other sexual difficulties. Indeed, it is unclear if it is possible to maintain normal sexual desire in the presence of chronic sexual arousal or orgasm problems.

Problems of sexual desire are highly prevalent in women experiencing clinical depression. Indeed, the diagnostic criteria for depression include loss of sexual desire as part of the vegetative symptoms of this condition. Individuals with major depression lose interest in many pleasurable experiences, including sexual activities. According to the DSM-IV-TR [1], the occurrence of reduced sexual desire as part of a depressive episode precludes the diagnosis of HSDD because the change in desire is conceptualized as part of a more generalized loss of motivation and interest. Nevertheless, the relationship between loss of desire and depression is poorly researched and quite complex. For example, young college students experiencing depressive symptoms within the clinical levels for major depression reported a strong interest and desire to masturbate, yet, interestingly, they also reported reduced interest in engaging in sexual activities with a partner [30, 31]. These findings suggest that individuals experiencing major depression do not completely lose interest

Table 9.3 Questions to differentiate between HSDD and other sexual dysfunction

If I had a pill that increased your level of sexual arousal (how much your body gets turned on during sexual activities) do you think your desire would increase as well?
If I had a pill to increase the frequency and/or the intensity of your orgasms, would your sexual desire increase as well?
Was there a time when it was easier to become sexually aroused than now? If so, what was your sexual desire then, and what was the relationship like during that time?
Was there a time when your orgasms were more intense and more frequent than now? If yes, what was your sexual desire then?
[If the individual indicated that she is also experiencing sexual arousal or orgasm problems] What started first, the problems with sexual desire or the problems with sexual arousal/orgasm?

for activities that lead to sexual reward. The loss of sexual desire for these women may be specific to a subset of sexual activities that include partners (potentially as an extension of social isolation often experienced with depression).

To complicate the relationship between HSDD and depression, the literature has shown robust evidence for a relationship between antidepressant medication use and decreased sexual desire, with women on antidepressants being 2.2–2.5 times at greater risk for sexual dysfunction [32, 33]. The standard critique of studies correlating antidepressant use with blunted desire is that sexual disturbances are part of the diagnostic criteria for depression and this redundancy complicates our ability to accurately measure prevalence of sexual dysfunction in this population. This sound critique is overshadowed by stringent exclusion criteria in most studies that limit the extrapolation of findings from a specific sample (e.g., no comorbid medical or psychiatric conditions, no concurrent use of other psychotropic medications, and restricted duration of antidepressant use). Years of research have targeted selective serotonin reuptake inhibitors (SSRIs) as primary culprits for antidepressant-induced reductions in desire based on the astoundingly high prevalence of impaired sexual desire associated with these medications, yet some serotonin-norepinephrine reuptake inhibitors (SNRIs) show equally dismal rates of reduced desire (see [33] for review). Data on newer antidepressants with highly specific mechanisms of action (i.e., flibanserin, a 5-HT1A agonist, 5-HT2A antagonist, and a D4 partial agonist) indicate that future antidepressants may not adversely impact sexual desire, but may indeed facilitate levels of desire [34].

It is also possible that when the depression abates due to psychotherapy (individual and/or couple therapy), and the use of SSRIs, then partnered sexual relationships improve. For example, Mary was 54-year-old married woman who had been postmenopausal for several years before she sought help. Her primary complaint was that after her surgery for uterine cancer, she had no sexual desire. She was in a satisfying marriage of 26 years with a husband who was very supportive and not demanding of sexual contact. They both were affectionate with one another and shared kisses, hugs, and touching one another in nonintercourse encounters. However, during an initial attempt at vaginal intercourse, she experienced a great deal of pain. They were both very anxious that they might never be able to have intercourse again. During Mary's diagnosis and treatment for cancer, she and her husband had not been given any information about how the treatments and surgery might affect their sexual relationship.

Mary had depressive episodes prior to her diagnosis of uterine cancer and had not been treated. After a thorough evaluation, it was decided that couple therapy would be the best modality for treatment as the issue was both relational as well as personal. Mary brought up the idea of trying antidepressants as she had a mother who was depressed most of her life. Mary knew a great deal about the current family of medications that were available and wished her mother had been able to take advantage of them. She felt confident that without being

depressed, she would be more willing to engage in sexual contact with her husband even if she did not feel much desire. Prior to the surgery, she had always been orgasmic and willing to engage in intercourse. She felt she would enjoy sex once she and her husband were engaged even if she felt no desire going into the encounter. A pelvic physical therapist was suggested for dealing with vaginal pain, pelvic floor strengthening, and building confidence for vaginal containment. Couple therapy enhanced their ability to communicate about sexual issues and to develop a broader repertoire for sexual expression. While their relationship was stable, therapy enhanced their ability to communicate about expectations regarding sex and allowed them to become a more "intimate team" working together to meet the challenge of "good enough sex" after cancer [35].

HSDD Prevalence in Epidemiological Studies

Population-based studies indicate that 29–39% of women report low or no sexual desire in the previous month [2, 36, 37], and between 15 and 34% report that the low desire causes distress [2, 38, 39]. These rates elucidating that low sexual desire is not experienced as distressful by all women. Rates of low sexual desire are independent of age up until age 50. After age 50, the rates of low sexual desire and distress caused by desire increase noticeably. A study of Swedish women found that rates are double in the 50–60-year-old cohort compared to younger women. The age trend found in Sweden is comparable to what has been reported in population-based studies in Iceland and Morocco [40].

The only incidence studies available to date were conducted in Finland and Sweden in the early 1990s. These studies found between 40 and 45% of women report a decrease in sexual desire within the prior 5 years [41]. Due to the lack of information on levels of distress, it is not possible to deduce the actual incidence of HSDD from this study, although we would expect reduced reports of distress in these incidence rates, based on prior studies of desire frequency and distress [39].

Factors Implicated with Sexual Desire

The complexity of HSDD is reflected in the myriad of mechanisms that the literature has linked to sexual desire. Although we attempt here to highlight the independent effect of biological, psychological, and relational factors, it is important to note that, in the patient, these three domains do not manifest independently from each other, and at times, may not be distinguishable from one another. The impact of each separate variable on low sexual desire is difficult to isolate. We have discussed, for example, how in Mary's case, a lifelong struggle with depression provided an impairment in her serotonergic system. Cancer provided additional psychological and physiological problems. In this case, the depression and cancer worked together to provide low sexual desire, physiological impairments to intercourse, and relational issues.

Biological Factors

From a biological perspective, it is undeniable that sex hormones play an important role in sexual desire [30]. However, the relationship between desire, androgens, and estrogens is poorly understood. Even with this lack of clarity, there is persuasive data on the impact of sex steroid hormones on desire. Most of this information comes from studies on sexual desire during the menopausal transition. Developmental fluctuations in estrogens and androgens observed during menopause are associated with a decrease in sexual desire (for a review see 30). A few studies have found that for women with particularly low levels of androgens, an androgen patch [42] and injections [43] can be effective at increasing sexual desire. However, the safety of these treatments is under investigation and the

positive effects of such treatments are modest [44]. This evidence provides an indirect indication that abnormal decreases in androgen levels can negatively impact desire. However, increasing androgen levels in women not experiencing androgen deprivation is unlikely to lead to an increase in sexual desire [45]. Thus, androgens are better conceptualized as hormones that facilitate the normal fluctuations and peaks in sexual desire, rather than hormones that directly modulate desire.

Estrogens levels are also associated with sexual desire. In animal studies, sexual behavior is tightly connected to the estrous cycle and deprivation of estrogen (via ovariectomy or the use of estrogen antagonists) leads to the complete cessation of receptive behavior in the female rat [15]. In women, however, estrogen does not have such a clear effect on sexual desire. Normal fluctuations in estrogens during the menstrual cycle have been linked with fluctuations with desire in some studies, but not others [30]. Characteristics of estrogen receptors are also key in understanding the modulation of circulating estrogen. The regulation of estrogen receptors is modulated by progesterone and androgens. Therefore, it is often the combination of low estrogen and testosterone, rather than low estrogen per se, that has been associated with low sexual desire [46].

Given that sexual desire is comprised of essential motivating mechanisms to engage in specific behavior, other neurotransmitters implicated with the general motivation system are likely to affect sexual desire. Dopamine and endogenous opioids are some of the most studied neurotransmitters in the modulation of sexual desire [47]. Animal studies have found that opioid antagonists prevent female rats from learning that specific stimuli can lead to sexual satiation, indicating that when sexual activities are not paired with opioid release, sexual rewards are not perceived. As a result, learned sexual preferences and desire for access to sexually intact males will not be expressed [15]. Dopamine antagonists also impair the expression of sexual desire by altering the salience of sexual cues and the behavioral response to rewarding stimuli. Female rats given dopamine antagonists will not express sexual preferences for specific cues that they have previously learned to pair with sexual rewards [15]. Recent studies on humans have found that a compound that acts on both the dopaminergic and serotinergic systems, flibanserin (a 5-HT1A agonist, 5-HT2A antagonist, and a D4 partial agonist), increases levels of sexual desire in premenopausal women, providing further evidence for the role of dopamine in the modulation of sexual desire. Indeed, antipsychotics (most of which antagonize D2 receptors) are notorious for reducing the appreciation of pleasure [48].

Psychological Factors

Psychological well-being is highly correlated with sexual desire, and conversely, a lack of sexual desire can signal a problem in the area of psychological adjustment. In a study of 126 women seeking sex therapy, 50% were diagnosed with a coexisting psychiatric diagnosis [49]. An organism functions according to a hierarchy of needs, as first proposed by Maslow [50], and psychological maladjustment can adversely impact multiple levels of needs. From an evolutionary perspective, the suppression of sexual desire during states when the individual is fighting for survival ensures that reproduction occurs when energy and resources are available. It is therefore practical for people perceiving threat to their well-being to focus on self preservation over any other activity. In states where the individual is struggling with a threat to safety, physiological needs, such as procreation, are disrupted. Similarly, individuals who tend to be overly sensitive to stressors in their environment and may show an exaggerated response to stressors (i.e., individuals with mood or anxiety disorders) may show a reduction in sexual function that is not warranted.

Individuals suffering from depression, a disorder that disrupts primary physiological needs including sleep and eating, also report lower

levels of sexual desire compared to people with no depressive symptoms [51]. Women with HSDD are indeed more likely to have a history of major depression compared to women with no HSDD [52]. In addition to mood and anxiety disorders, other psychopathologies often accompanied by inhibition of sexual desire include schizophrenia and anorexia nervosa. The relationship between schizophrenia and sexual desire is poorly understood. From a theoretical point of view, it is feasible that impairment in the mesocortical pathway, a pathway associated with emotional processes and motivation, may be also responsible for the low level of sexual desire in patients with schizophrenia. However, the lack of empirical studies on this topic and the complexity of both schizophrenia and sexual desire prevent a clear acceptance or rejection of such hypothesis, at this point. Alternatively, the antipsychotics used to treat schizophrenia may depress appreciation of sexual reward, thereby blunting sexual desire.

The association between anorexia nervosa and desire may be implicated with the impairment in the hypothalamus-pituitary-adrenal (HPA) axis, a system closely connected with stress that is responsible for facilitating the release of resources to key organs involved in the fight and flight response. States of food deprivation affect this system and send signals that the organism is in a state of potential starvation. Resources are released in the body, which enters a survival state. It is plausible that during this state, the motivation system for functions not necessarily linked to immediate survival is shut down. This hypothesis is largely speculatory at this point given the lack of information available on sexual function in women with eating disorders.

Relationship

When sexual desire occurs within the context of a relationship, a woman's desire to engage in sexual activities may be affected by her sense of closeness and intimacy with her partner and her overall relationship satisfaction [7]. Quality of the relationship is also important for treatment outcome. A review of clinical outcome studies for desire [53] found that overall quality of the couple's nonsexual relationship and degree of physical attraction between partners were the first and third most commonly reported factors associated with positive treatment outcome, respectively.

In addition to the quality of the relationship, the sexual dysfunction and the health of the partner can affect a woman's sexuality. Data from longitudinal and cross-sectional studies found that poor health in the male partners of heterosexual women was associated with lower sexual desire functioning and greater overall sexual dysfunction in women [54, 55].

Cancer

The majority of the studies that investigated sexual function in cancer survivors focused on gynecological or breast cancer. In our review of Medline, PsychInfo, and PubMed databases for articles published in the past 50 years on cancer and sexual desire, only a handful of articles focused on nongynecological cancers (including lung, pituitary, and rectal cancers). Therefore, the majority of the information currently available on cancer and sexual desire must be understood as limited to these specific types of cancer populations as it is unclear whether these results would apply to other forms of cancer.

While the initial studies on breast cancer were mostly focused on the potential effect of mastectomy on women's body image and therefore on her sexuality, later studies [56, 57] painted a different picture and provided evidence that side effects of treatment (and especially radiotherapy) on sexual desire are more debilitating than the psychological effects caused by mastectomy. Because of the multifaceted nature of desire, and the multitude of systems affected by cancer and cancer treatment, we will discuss the effects of cancer and its treatment on the three components

of sexual desire preciously identified in our review of desire: biological, relational, and psychological.

Prevalence of Low Desire and HSDD in Cancer Patients

The prevalence of desire problems in cancer populations is elevated compared to national averages. In a sample of 20 women treated for gynecological cancer, 56% reported low levels of sexual desire and 35% of the 20 women had both depression and sexual dysfunction [58]. For patients with breast cancer, the rates of women reporting interferences with sexual desire (31%) are comparable to patients with gynecological cancer [59].

In a sample of 96 patients treated for ovarian, cervical, endometrial, vaginal, vulvar, and sarcoma cancer, 43% complained of HSDD and asked for clinical recommendations [60]. After 6 months, of all patients requesting clinical consultation, 70% reported improvement after complying with treatment recommendations, indicating that women were both interested in receiving support for the side effects on sexuality and demonstrated the motivation to follow through with such suggestions.

Direct Effects of Cancer on HSDD: Biological, Psychological, and Relational

Based on data from 817 women who had undergone breast cancer treatment, including chemotherapy, researchers found that the best predictors of sexual function and satisfaction postbreast cancer are: absence of vaginal dryness, emotional well-being, body image, quality of the relationship, and partner's sexual problems. These variables accounted for 33% of variance in sexual satisfaction in breast cancer survivors [61]. We will now look individually at main factors impacting sexual desire with the understanding that these factors often act in orchestration and not independently.

Biological

The only data available on the direct biological effects of cancer on sexual desire come from studies on cancer affecting the HPA axis. According to a study on 53 women with pituitary tumors, levels of sexual desire were inhibited or desire was lacking in approximately 80% of patients [62]. Levels of sexual desire were neither correlated with hyperprolactinemia nor with serum testosterone (although no data was presented on free testosterone, a measure of androgen that is more closely associated with levels of sexual desire), but age and presence of intrasellar tumors were positively associated with loss of sexual desire [62].

Psychological Factors

Depression is a common consequence of a life-threatening condition like cancer. Indeed, between 15 and 40% of individuals with cancer will experience depression or anxiety during the course of their illness [63]. Symptoms of depression are difficult to tease apart from physiological and treatment-related effects of cancer treatment (e.g., fatigue, changes in appetite and weight). Both clinical depression and treatment-related depressive symptoms may impair sexual desire. Sexual desire may be diminished following chronic depression, which is associated with altered HPA axis function and persistent immune activation [64], which, in turn, may compound the broad immune, endocrine, and metabolic changes associated with cancer and its treatment. Prominent psychological issues that arise in individuals suffering from cancer include feelings of grief and loss, existential anxiety related to death, adoption of poor coping strategies, problematic social support, and tolerance of prolonged treatment and cancer

recurrence. The combination of the stress caused by this life-threatening condition and cognitive vulnerabilities that may lead to depression can affect sexual desire.

Receiving a life-threatening cancer diagnosis can motivate a number of fears that directly, or indirectly, inhibit sexual desire. More often than not, a cancer diagnosis has a profound impact on not just the patient, but their spouse/partner as well, and it is likely to create ripples in the entire family system. Assessing a patient's sexual history and her baseline sexual functioning (i.e., before the surgery) and establishing a rapport with the patient and her spouse/partner are important steps for the healthcare provider interested in preventing or containing HSDD symptoms associated with treatment. In the case of gynecological cancer, fears specific to sexual activities may be particularly relevant for understanding sexual dysfunction. Schultz and van de Wiel [65] listed common feelings evoked by gynecological cancer that affect sexual desire: guilt, fear that the disease will reoccur, the wish to reject physical contact, the fear of damaging one's body, contaminating others, or losing the ability to procreate.

Fear and guilt are among the most commonly reported types of negative affect and are frequently addressed in the literature. Fears associated with cancer can have a direct effect on sexual function since it can activate avoidance of sexual activities. Guilt is more commonly experienced among women with cervical cancer because this form of cancer is linked to genital herpes, and thus a promiscuous sexual history may be likely among individuals with this type of cancer and this may lead to the feeling that she caused (and deserves) the disease. Negative affect caused by fear and guilt acts as a motivator to avoid sexual activities or any form of intimacy. This avoidance can counterintuitively lead to the strengthening of these negative emotions.

The psychological effects of cancer on the sexual desire of a woman are moderated by her view of herself as a sexual being, prior to the diagnosis [67]. The perception a person has of her self (self-schemas) provides a blueprint on how the individual perceives and responds to events. Schemas emerge from past experiences and the meaning that the individual gives to these experiences. At their basic level, schemas provide a framework on which the individual forms a sense of self that is coherent across time and situations. Studies have indeed found that a woman's sexual self-schema affects how the woman faces cancer and how her sexuality changes during treatment [66]. Although schemas are stable features of our identity, they are of particular interest for treatment since they can be modified through psychotherapy. In a series of studies on sexual self-schemas, Andersen and coworkers [66–68] found that endorsing adjectives that describe the self as embarrassed and sexually conservative, and not endorsing adjectives such as passionate, loving, romantic, open, and direct, predicted a decrease in sexual function at 4 and 8 months postcancer diagnosis [66]. A quick assessment of sexual self-schemas conducted at the time of diagnosis can aid in identifying individuals who are at higher risk for later sexual problems, who may therefore be good candidates for therapy.

Relational Factors

A life-threatening diagnosis can change a romantic relationship in a variety of ways. For example, if a partner or spouse is supportive and caring, the diagnosis will likely increase the sense of intimacy and commitment between the partners. These relationships can have a positive effect on both the individual and the prognosis of treatment. Indeed, supportive relationships are associated with better health outcomes for cancer survivors.

Alternatively, it is possible that the sexual dysfunction secondary to cancer treatment may upset the relationship, leaving the patient to deal with her medical condition and the relationship problems [69]. Patients who feel compelled to please their partners by trying to maintain their prediagnostic sexual life may engage in sexual activities despite a lack of sexual desire. Such behavior can lead to physically and psychologically painful sexual experiences, which eventually lead to resentment, thereby causing even

greater inhibition of sexual desire. For example, when Joan was diagnosed with leukemia, she had been married to David for 10 years. She was a high power attorney and came from a very wealthy and well-connected family. During those years, David had pressured Joan for sexual intercourse every day. At the time of diagnosis, the marriage was suffering from polarization around sexual frequency. Severe sexual desire incompatibility is associated with pair-bond dysfunction, a common issue in men who have compulsive sexual behaviors [70]. At this time, Joan also found out that David had an affair. Since Joan was already well practiced at "keeping David happy," she was determined not to risk a divorce by denying his sexual "needs." In this instance, cancer played a positive role when David, threatened by the loss of Joan to cancer, agreed to counseling. His pressure for sex also hid a needy, dependent man with well-hidden poor self-esteem who wanted sex to prove he was loved. The cancer diagnosis made him afraid Joan would die leaving him alone in the world. In spite of his affair, he needed the connection to Joan and the wealth and prestige she represented. During the diagnostic stage of the cancer, David's doctor suggested they talk with a mental health professional on the medical team. It was then that David and Joan started discussing and preparing for the sexual side effects that they were likely to encounter during treatment.

Effect of Cancer Treatment on HSDD

Not only can cancer directly affect sexual desire, but as mentioned above the interventions utilized to treat the cancer are likely to have adverse effects as well. Chemotherapy and radiation therapy in the treatment of gynecological cancer are the two most commonly documented interventions that impair sexual desire function.

Chemotherapy

Chemotherapy is accompanied by fatigue, nausea, and vomiting. These somatic symptoms can strongly inhibit sexual desire. For 50% of women, the sexual dysfunctions experienced during the active phase of treatment persist even after treatment [71, 72].

Radiation Therapy

Radiation for gynecological cancer is associated with higher sexual dysfunction than levels found in healthy controls, and sexual dysfunction increases after radiotherapy [73, 74]. This research hypothesized that the increase in sexual dysfunction following radiotherapy is partially explained by stenotic changes to the blood vessels in the vagina, vaginal shortening, necrosis, and vaginal adhesion or agglutination, where the elastic vaginal tissue is substituted by fibrous tissue present in 78–96% of women receiving radiotherapy [75, 76]. These changes in the vagina lead to lack of lubrication and problematic and painful intercourse, which then reduces sexual pleasure and therefore the incentive to further engage in sexual activities. Thus, even physiological changes associated with treatment can disturb normal motivation (i.e., desire) for sexual activities.

Moreover, radiation artificially induces menopause, thus reducing the production of testosterone [30]. It is important to note that studies have not always found an association between sexual desire and radiotherapy-induced changes in the vagina, when women were tested posttreatment. However, studies that tested desire 1 year posttreatment did report a reduction in desire [76, 77]. This posttreatment shift in desire suggests that the changes caused by radiotherapy may be delayed and therefore patients may benefit from consultation for sexual functioning *after* the termination of treatment. A qualitative study suggested that during treatment patients are mostly focused on their condition and dealing with the shock of receiving a life-threatening diagnosis than they are about their sexual functioning. During the later phases of treatment, quality of life becomes more important and survival is less of a pressing concern and it follows that women report a greater interest in information regarding their sexual function [78].

Breast Conservation

Breast conservation has been found to be consistently better for body image following a cancer diagnosis, but results are mixed for its effects on sexual desire. Initially it was believed that one of the major reasons for women to experience a loss in sexual desire, after breast removal, was due to the effect of mastectomy on body image. Recent studies have identified menopausal symptoms as a much stronger risk factor for HSDD in breast cancer survivors (c.f., 81). Two studies utilizing random assignment to mastectomy vs. breast conservation have reported fewer problems in sexual desire among women who underwent breast conservation therapy [80, 81]. However, six studies did not find greater sexual desire in women receiving breast conservation therapy compared to mastectomy.

Researchers have hypothesized that the benefit gained from a less severe loss in body image may be overshadowed by the fear that the cancer may return. For a study of breast cancer conservation with radiotherapy, a sample of 86 patients was recruited from an Italian general hospital. Forty-three percent reported they experienced a decrease in desire that they attributed to the treatment and 41% reported a decrease in sexual desire attributed to the disease [59]. Some women opt for breast reconstruction, and although some evidence points to greater body image satisfaction among them, it is not clear whether breast reconstruction can help a woman to increase her levels of desire since there is a lack of controlled studies. Another limitation of the available data is that women not interested in breast reconstructions usually do not participate in these studies. It is feasible that only women who experience greater body dysmorphia after the mastectomy choose breast reconstruction and therefore we cannot assume that all women would show a similar improvement in their sexual function after breast reconstruction.

Among breast cancer survivors, antiestrogenic medication could potentially have a negative effect on sexual desire [79]. A paucity of data exists on the sexual side effects of tamoxifen, which is the most common antiestrogen utilized for menopausal women with breast cancer. Two studies compared women currently taking tamoxefin to healthy women, in a trial for chemoprevention [59, 82]. These studies did not find a significant difference in sexual desire between groups, but they utilized a very crude measure of sexual desire. In these studies, the researchers asked participants to indicate whether they desired sex more or less than once per month. As indicated in our review of the definition of sexual desire, this information is not meaningful if not accompanied by subjective measures of distress. Given that there is no set frequency of sexual thoughts, the interpretation of this item is highly problematic. The arbitrary frequency of sexual desire selected for these studies (more or less than once per month) may cause a ceiling effect since many women with low sexual desire are likely to desire sex more than once per month. A third study utilizing a more sophisticated measure of sexual desire and comparing sexual function in women taking low vs. high levels of tamoxifen found that sexual desire increased more when the tamoxifen treatment was discontinued as compared to women who continued a low tamoxifen dose [83]. Separating the effects of tamoxifen from the effects of menopause is not easy and thus, at this point, we should interpret these results carefully, since we cannot exactly identify the effects of tamoxifen independently from the effects of menopause.

Overall, the studies on breast cancer treatment seem to indicate that body image is less salient for the sexual function of cancer survivors and that treatments that affect the production of steroids may have a stronger impact on sexual desire. Interestingly, little is known on the psychological vulnerabilities of individuals with breast cancer. Given that sexual dysfunction can be affected by biological, psychological, and relational factors, more studies are needed to explore potential vulnerabilities that may be specific to women going through breast cancer.

Oophorectomy

In addition to breast cancer, which is a prevalent type of cancer for women, oophorectomy, the surgical removal of ovaries, is the procedure that

is most commonly identified with a decrease in sexual desire. Removal of the ovaries, to all intents and purposes, induces surgical menopause. It is important to note that the literature consistently points to menopausal symptoms in response to the surgical removal of the ovaries as causing greater HSDD symptoms than natural menopause [84, 85]. This difference has been attributable to the fact that, during natural menopause, the production of testosterone continues, although at a much reduced rate, while surgical menopause causes a dramatic and definite cessation of androgen production. During surgical menopause, androgen levels drop to less than 50% of the normal production of testosterone in naturally menopausal women (for a review, see [86]). However, the changes in the sexual cycle caused by oophorectomy are quite pervasive and have been found to affect all aspects of sexual function, including sexual arousal, orgasm, and pain [84], and therefore it is difficult to identify whether the low desire is exclusively the product of the changes that affected the entire cycle or if there is a direct effect on desire per se.

Oophorectomy may affect sexual desire through the reduction in vaginal lubrication and thus a greater likelihood for damage to the vaginal epithelium during intercourse which leads to sexual pain. As we noted above, painful intercourse is, of course, a reason to be avoidant of sexual activities and can provide a lessening of sexual desire. Therefore, it is essential that preemptively, patients and their partners be advised about this outcome and be provided with information about pelvic physical therapy and lubricants which can mitigate painful vaginal issues.

Estrogen administered to women who have received oophorectomy can also have a negative effect on desire because estrogen increases levels of sex hormone-binding globuline (SHBG) levels, which cause the already low levels of testosterone to bind and not be physiologically active, therefore reducing the amount of testosterone available to bind with receptor sites involved with sexual desire. Indeed, in a perspective study on estrogen replacement therapy [87], individuals who underwent salpingo-oophorectomy or abdominal hysterectomy did not show any improvement in their postoperative sexual function after receiving estrogen replacement therapy.

Conclusions

In conclusion, the literature on HSDD in women with a history of cancer is in its infancy. Nevertheless, we can clearly see patterns emerging that point at essential impairments caused by the side effects of cancer treatments. While addressing sexual dysfunction in the early acute phase of a cancer diagnosis may be relevant only for a limited number of women, sexual dysfunction become more relevant for women after a year of treatment.

Sexual dysfunctions, and particularly hypoactive sexual desire, are complex phenomena regulated by biological, psychological, and relational aspects of the woman's life and, for this reason, the referral to a specialist in sexual medicine may be the best approach for an oncologist. Lately, we are seeing emergence of the inclusion of sex specialists on treatment teams. For example, since 2008, the University of Chicago has had a Program for Integrative Sexual Medicine Clinic for Women and Girls with Cancer. This is a program supported by the Department of Obstetrics /Gynecology, Section of Gynecology Oncology and the Cancer Research Center. Mental health professionals are also part of the oncological program at the University of Vermont Medical center. These are multidisciplinary programs which include an advance-practice nurse, a gynecologist, a psychologist and/or clinical sexologist, and a pelvic physical therapist with expertise in addressing pelvic floor issues and sexual problems in women with cancer. The focus is on generating new knowledge about sexuality and treatment of sexual problems in the context of cancer treatment and survivorship. For the oncologist who has limited time and resources, often just introducing the topic about sexual desire and providing a referral or titles of books (see Appendix) can help the patients and their partners gaining a perspective on their sexual health.

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Chapter 10
Disorders of Female Sexual Arousal

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Keywords Arousal • Hormones • Androgens • Testosterone • Estrogen

Case Example 1

Joanne, age 57, and 6 years postmenopause, first began experiencing difficulties with sexual arousal a few months after being diagnosed with cervical cancer. She was treated with a round of chemotherapy prior to undergoing a complete hysterectomy, after which her arousal difficulties significantly worsened. She recalled that following surgery, she was rarely able to become lubricated during attempts at sexual activity, and often experienced accompanying pain. Joanne and her husband began using topical lubricants, but Joanne reported that these led to only mild improvement. She also reported feeling chronically fatigued during this time, and ultimately fell into a moderate depression. By the time that she presented for treatment (1-year post surgery), Joanne was rarely experiencing feelings of sexual interest, and admitted that she had stopped initiating sexual activity with her husband, and was only occasionally responsive to his initiations. She also confessed that she had become increasingly self conscious about her body due to the physical changes she had noticed since her surgery, and found herself feeling preoccupied during sexual activity with fears that her husband no longer found her sexually attractive. In addition, Joanne noted that she had been unable to reach orgasm during any sexual activity over the past 3 months. Joanne appeared highly distressed about these changes and expressed interest in acquiring a prescription for Viagra to help ameliorate her difficulties.

Disorders of Female Sexual Arousal

Joanne is one of approximately 11.3 million Americans with a history of cancer [1] and, like an increasing number of survivors, she is struggling with adjustments to her quality of life following cancer treatment. Of particular interest to this chapter is that, among other things, Joanne is suffering from female sexual arousal disorder (FSAD), which has been traditionally defined as an impairment in a woman's ability to become physiologically aroused (genital lubrication and swelling) [2]. Her case illustrates the often complex interaction between sexual arousal problems and other issues, such as altered body image, depression and fatigue. In addition, individuals with chronic illnesses like cancer often have the added stressor of their illness trajectory and consequently, may feel uncomfortable

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addressing quality of life issues such as sexuality due to the belief that they should be focusing on "more important" things. Research indicates, however, that even for patients with advanced cancer, quality of life is as important or more important than the length of life [3]. While sexual health is an integral component of quality of life, relatively little research has addressed this issue in cancer patients, particularly in female cancer patients. A recent review of the literature found that of 257 articles examining self-reported sexual functioning in cancer patients, 76% were aimed at men with prostate cancer, whereas only 15% examined women with breast or gynecological cancers (the remaining 9% examined functioning in other types of cancers) [4]. The limited data evaluating sexual functioning in women with cancer is heavily weighted towards breast and gynecological cancers. In addition, the data that is available on sexual arousal is often based on one or two questions in a self-report survey that do not make the distinction between mental and physiological sexual arousal, making it difficult to truly understand the breadth of female sexual arousal problems in this population. These limitations, however, are not specific to studies on women with cancer, but also appear in the literature on FSAD in the general population.

Definitions and Problems

Diagnostic Criteria for Female Sexual Arousal Disorder

The past three decades have witnessed significant challenges to the legitimacy of diagnostic classifications of FSAD. In particular, substantial debate has focused on the relative importance of subjective versus physiological excitement as a diagnostic marker of sexual arousal. As mentioned earlier, FSAD is defined in the DSM-IV-TR [2] in physiological terms as an impairment in the genital lubrication-swelling response of sexual excitement (refer to Table 10.1 for diagnostic criteria and their limitations). In addition to the criteria presented in Table 10.1, the DSM-IV-TR text also includes the qualifier that "occasional problems with sexual arousal that are not persistent or recurrent or that are not accompanied by marked distress or interpersonal difficulty are not considered to be Female Sexual Arousal Disorder." (p. 501). Furthermore, it is noted that a diagnosis of FSAD should not be made if the arousal problems are due to "sexual stimulation that is not adequate in focus, intensity and duration" (p. 501).

Models of Sexual Response

As with the other sexual disorders, the current conceptualization of FSAD derives from the traditional linear human sexual response model that describes sequential stages of desire, arousal, plateau, orgasm and resolution [5, 6] (refer to Fig. 10.1). However, over recent years, this model has been subject to much criticism and alternate models have been put forward that take into consideration multiple motivations for initiating and accepting sexual activity, contextual factors in sexual response, and the highly overlapping and non-universal sequence of sexual responses phases [7] (refer to Fig. 10.2). This multi-faceted circular model of sexual response is based a growing literature that demonstrates the shortcomings of a purely physiological linear model [8–14].

The high degree of overlap amongst the different phases of sexual response in women has resulted in a high comorbidity in sexual dysfunctions, particularly between disorders of arousal and desire, which researchers are now suggesting may be one and the same [15, 16]. Indeed, there is currently no empirical evidence to support the distinction between these constructs, and women themselves report extreme difficulty differentiating these responses [16]. At present, it is unclear whether it is possible to find pure or primary cases of FSAD (without other coexisting sexual dysfunction) [17, 18], leading some to question whether FSAD should even be considered a distinct diagnostic entity [19].

Table 10.1 DSM-IV-TR diagnostic criteria for FSAD and their limitations

Diagnostic criteria	Limitation
Persistent or recurrent inability to attain, or maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement. The arousal response consists of vasocongestion in the pelvis, vaginal lubrication and expansion, and swelling of the external genitalia	The ambiguity of the requirement that symptoms be "persistent and recurrent" places excessive reliance on clinician judgment to decide what these terms mean. Decisions may negatively affect clinical and epidemiological research The criterion of genital arousal impairment as the sole diagnostic marker of FSAD is insufficient and not supported by research
The disturbance causes marked distress or interpersonal difficulty	Whether distress is considered as a diagnostic requirement dramatically affects prevalence estimates of FSAD; rates are inflated when distress levels are not assessed
The sexual dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition	The feasibility and utility of determining the *exclusive* cause of a sexual problem is not high. In most cases, causes are multifactorial or difficult to determine
Specifiers: (a) onset – lifelong type vs. acquired type; (b) Context – generalized Type vs. situational type; and (c) Etiology – due to psychological factors vs. due to combined factors	Although clinically useful to specify onset and context, these distinctions have rarely been made in epidemiological researchSpecification of etiological factors is often impossible, and of limited utility

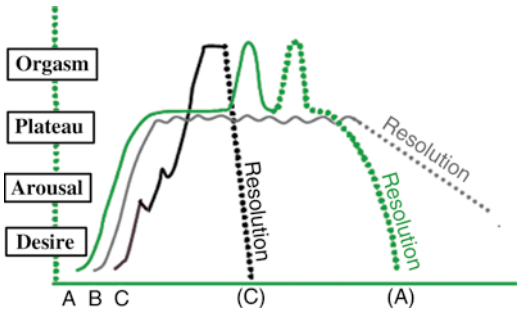

Fig. 10.1 Masters and Johnson model of sexual response. Adapted from Kaplan [5]

Problems with the DSM conceptualization of FSAD

While consensus has not yet been reached about how to best capture the complexity of female sexual experiences, the formulation of more flexible and context-based models has served to highlight some fundamental limitations in our current diagnostic conceptualization of FSAD (presented in Table 10.1). In particular, the requirement of an impaired genital response (i.e., lubrication/swelling), to the neglect of subjective feelings of excitement, as the sole diagnostic marker of an arousal disorder (Criterion A) has been demonstrated to be overly narrow and thus inadequate (refer to Graham [20] for more details). Specifically, contrary to women's clinical and epidemiological reports of insufficient genital arousal, studies employing vaginal photoplethysmography (VPP) [21] an indirect measure of genital arousal – have rarely found significant differences between medically healthy women diagnosed with sexual arousal disorder and healthy control women [22, 23]. In addition, research indicates that even women without self-reported arousal difficulties commonly experience desynchrony (low or non-existent correlations) between subjective and genital measures of sexual arousal [22]. Numerous theories have been offered to account for this phenomenon, including women's lesser awareness of the genital changes accompanying their arousal; the lesser importance placed by women on genital arousal cues in their appraisals of subjective arousal; the insufficiently arousing nature of the erotic stimulus used in the laboratory context; and the limitations of the tools used to measure sexual arousal in women [22]. While the reasons for desynchrony have not been established, it is clear that the criterion of genital response alone is insufficient to diagnose arousal problems in women.

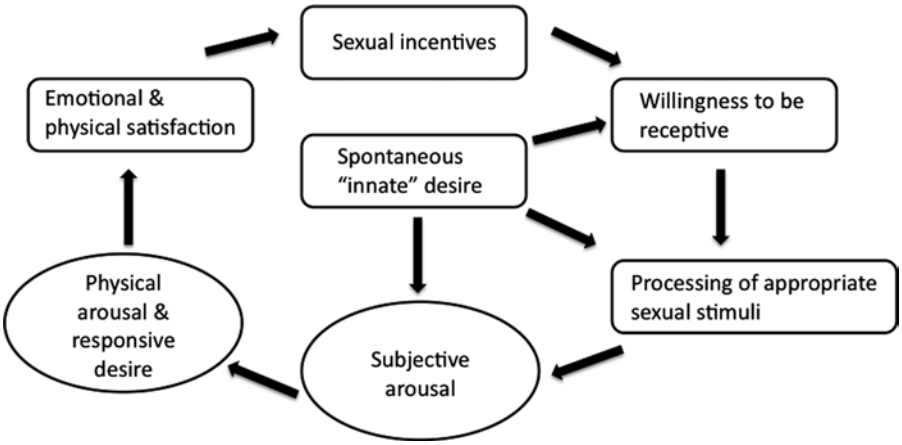

Fig. 10.2 Basson's circular model of female sexual response. Adapted from Basson [142]

Proposed Criteria for the DSM-V

Given the above limitations, and the lack of evidence to support the distinction between arousal and desire, it has recently been recommended that the diagnostic categories of sexual desire and arousal disorders be collapsed under the new category heading of "Sexual Interest/Arousal Disorder" [20]. In addition, it has been advised that a polythetic approach be applied in the diagnosis of this disorder to recognize the heterogeneity in women's expressions of low sexual interest/arousal, and to avoid prioritizing one symptom presentation over another. These suggestions have been incorporated into the symptom criteria that have been proposed for the DSM-V (refer to Table 10.2 for proposed criteria).

Table 10.2 Proposed DSM-V criteria for sexual interest/arousal disorder

Lack of sexual interest/arousal, of at least 6 months duration, as manifested by at least 3 of the following indicators[a]:
Absent/reduced interest in sexual activity
Absent/reduced sexual/erotic thoughts or fantasies
No initiation of sexual activity and is not receptive to a partner's attempts to initiate
Absent/reduced sexual excitement/pleasure during sexual activity (on at least 75% or more of sexual encounters)
Absent/reduced genital and/or non-genital physical changes during sexual activity (on at least 75% or more of sexual encounters)
The disturbance causes clinically significant distress or impairment
Specifiers:
Lifelong or acquired
Generalized or situational
Partner factors (partner's sexual problems, partner's health status)
Relationship factors (e.g., poor communication, relationship discord, discrepancies in desire for sexual activity)
Individual vulnerability factors (e.g., depression or anxiety, poor body image, history of abuse experiences)
Cultural/religious factors (e.g., inhibitions related to prohibitions against sexual activity)
Medical factors (e.g., illness/medication)

[a] Recommendations for duration and severity of symptom occurrence (e.g., three indicators occurring for at least 6 months) currently rest on sparse empirical evidence.

Epidemiology

Lifetime Prevalence of FSAD

Despite the recent publication of several large-scale epidemiological surveys with nationally representative and cross-cultural samples, the prevalence of arousal difficulties in women

remains unclear. Estimation of prevalence rates of FSAD has been complicated by various factors including the ambiguity of FSAD diagnostic criteria (e.g., regarding what should be considered reflective of "adequate" sexual stimulation); its frequent comorbidity with other sexual disorders (e.g., low desire and orgasmic difficulties); methodological limitations in assessing arousal difficulties (e.g., discrepancies between self-report vs. objective evidence) and the challenges in determining the etiology of arousal problems via survey methodology (e.g., as due to a medical condition, inadequate stimulation, or other contextual variables) (for a review, see [20]). In addition, prevalence rates vary dramatically depending on whether the presence of "distress" or "interpersonal impairment" is evaluated or required for disorder diagnosis; the duration of sexual problems and/or the recall period specified; the age, culture and reproductive status of the women sampled; and how arousal difficulties are operationalized (e.g., as problems with lubrication versus subjective feelings of excitement/pleasure or other physiological responses) [20]. With respect to the latter, the majority of survey studies have assessed problems exclusively with lubrication. Given that impaired genital responsiveness may not be a valid diagnostic criterion of FSAD in medically healthy women (due to the minimal evidence of an impaired potential to become genitally aroused), studies defining arousal difficulties in these terms have arguably produced prevalence rates of questionable validity.

With these qualifications in mind, prevalence rates of arousal difficulties have ranged in studies from approximately 7–31% (averaging around 14%) for women between the ages of 16–75, with rates varying as a function of age, level of distress, and duration of the difficulty (i.e., rates are higher for older women, and for those with short-term difficulties and mild/no distress) [24–27]. In a study with women between the ages of 18–44, it was estimated that while 9.2% of women had short-term difficulties with lubrication, only 3.7% had persistent problems (lasting at least 6 months) [28]. Finally, one of the few epidemiological studies with older, postmenopausal women from 29 different countries found prevalence rates of "occasional" lubrication difficulties ranging from 16.1% (Southern Europe) to 37.9% (East Asia), and of "frequent" problems ranging from 4.7 to 12.1%, with higher rates found in women between the ages of 50–59, than those aged 40–49 [29]. There is currently no epidemiological information available on the prevalence rates of subjective sexual excitement difficulties, particularly as distinguished from subjective appraisals of genital arousal.

Prevalence of FSAD in Cancer Patients

As compared to medically healthy women, the female oncology population has higher rate of difficulties with sexual arousal, with estimates ranging from 25 to over 50% depending on the type of cancer [30]. In a recent study, Huyghe and colleagues examined men and women with a variety of cancers and found that 36% of the women noted problems with sexual excitement and pleasure following cancer diagnosis, and 46% of them reported a problem with vaginal lubrication after cancer diagnosis and treatment [31]. Tierney and colleagues found similar rates in women undergoing neo-adjuvant chemotherapy for hematologic cancer with 36% reporting problems with arousal and pleasure, and 29% noting difficulties with vaginal dryness [32]. Finally, a study examining sexual functioning in women during the first months following breast cancer treatment showed that 28% of respondents indicated serious problems in at least one area of sexual functioning [33].

Similar to patients in the earlier stages of diagnosis and treatment, long-term cancer survivors also report difficulties with arousal. At a median follow up period of 8 years, one third of patients surviving chronic myeloid leukemia indicated decreased sexual functioning as compared to the general population [34], as did sexually active survivors of gynecologic cancer at a 2-year follow up [35]. In addition, Speer and colleagues

noted that long-term survivors of breast cancer had significantly lower scores on the Female Sexual Function Index (FSFI) than women in the general population, however, they scored significantly higher than medically healthy women who suffered from FSAD [36]. In one exceptional study, however, Greenwald et al., found that over 90% of long term cervical cancer survivors had enjoyable sex lives though questions specific to sexual arousal were not asked [37].

Correlates of FSAD

The relationship between different physiological and psychological factors to sexual arousal problems is often overlapping. This is particularly true of patients with cancer where comorbid problems will interact with each other to exacerbate arousal disorders. For example, a patient undergoing chemotherapy may experience a decrease in libido and increased vaginal dryness as a result of her medication, but she may also be exhibiting symptoms of depression, a disorder has frequently been associated with sexual dysfunction. It is likely that neither the chemotherapy nor the depression is entirely responsible for the arousal problems, but rather, they interact with each other and with other aspects of the patient's life (e.g., relationship with her partner and other life stressors) to bring about the sexual arousal disorder.

Physiological Correlates

Until recently, there had been little examination of the physiological factors underlying sexual arousal difficulties in women. While the past decade has witnessed a surge of interest in the pathophysiology of FSAD, the relationship between physiological risk factors and arousal difficulties in women remains understudied, and hence, poorly understood. The research currently available supports an association between female sexual dysfunction and a number of medical and health related factors (e.g., hormonal, vascular, neurological, pharmacological). Specifically, arousal difficulties in women (i.e., decreased lubrication) have been associated with medical conditions such as reproductive cancers (e.g., breast, ovarian, cervical), diabetes, hypertension/cardiovascular disease, neurogenic or neurological impairment, estrogen deficiency, ovarian failure, vulvovaginal atrophy or connective tissue damage, urinary incontinence and lower urinary tract problems, multiple sclerosis, hyperprolactinaemia, hypothyroidism, and congenital adrenal hyperplasia (for reviews see [38–41]). Many of these factors also have a strong independent association with age, making aging an even stronger risk factor for arousal difficulties in women. Although certain phases of the menstrual and reproductive life cycles (e.g., menopausal and postpartum status) have also been correlated with lowered arousal [42–44], results have been inconsistent, and the relationship between these factors is poorly understood. While decreased lubrication in postmenopausal women is typically attributed to lowered estrogen levels, there is some evidence indicating that decreased estrogen is associated with vaginal atrophy, but not vaginal dryness [45].

Aside from medical health conditions, medical and surgical treatments for various health conditions (e.g., cancer treatments, hysterectomies/oopherectomies), and certain pharmacological treatments have also been associated with arousal difficulties in women. In particular, psychiatric drugs such as antidepressants and antipsychotics, and health medications including antihypertensives, anticonvulsants, and H_2-blockers, have all been associated with arousal difficulties in women [40]. Finally, lifestyle factors such as tobacco/nicotine use have also been correlated with impaired genital response in women, as indicated by changes in VPA [46]. In contrast to research with women struggling with or being treated for medical or mental health conditions, research with medically-healthy, premenopausal women indicates that arousal difficulties in this group are more often associated with inadequate sexual stimulation than with physiological causes [47].

Physiological Considerations for Cancer Patients

While a tumor itself can directly affect sexual arousal through the restriction of blood flow to the genitalia or disruption to the production of hormones, it is often the treatment of cancer that has the largest impact on sexual functioning, with patients having reproductive cancers or hormonal imbalances experiencing the most direct symptoms [48]. Specifically, the most common treatments for cancer-chemotherapy, radiation therapy, hormone therapy and surgery, have all been associated with increased sexual dysfunction in women.

Due to the number of different chemotherapy drugs, doses and combination therapies, the specific mechanisms by which chemotherapy affects sexual arousal are not well documented. It is known, however, that chemotherapy can initiate ovarian failure, which in turn, reduces the amount of circulating estrogens and induces menopausal symptoms such as vaginal dryness, vaginal atrophy and shortening of the vagina, all of which negatively affect sexual arousal [39]. Reduced levels of estrogen have also been suggested to restrict genital vasocongestion through sympathetic innervation, which directly affects a woman's ability to become physiologically sexually aroused [49].

In line with this, a significant proportion of women undergoing chemotherapy report decreases in sexual arousal and desire, as well as increases in sexual pain [50]. Furthermore, it has been shown that women undergoing chemotherapy score worse overall on the FSFI than those undergoing other forms of treatment [51]. The effects of chemotherapy can be long term, with reports of decreased sexual functioning continuing more than 7 years after diagnosis and treatment [52]. In addition to the direct sexual side effects, chemotherapy also takes a strong physical toll on the body, with patients often reporting nausea, alopecia, fatigue, and pain, all of which can impair one's quality of life and desire to engage in sexual activity.

Similarly, hormone therapy has also been associated with vaginal atrophy, decreased lubrication, decreased libido and sexual arousal, and increased genital pain [53]. In contrast to the effects of chemotherapy, however, the sexual side effects of hormone therapy have been found to last as long as the treatment itself, and typically reverse upon treatment discontinuation.

Due to the local nature of radiotherapy, patients with cancers in the pelvic region are most likely to experience direct effects related to sexual functioning. For example, in women with cervical cancer, brachytherapy leads to fibrosis of the vaginal tissue and significant changes in the vaginal epithelium [54]. This may increase vaginal dryness and make intercourse painful, thereby decreasing sexual arousability. Furthermore, while re-epithelialization can occur within 6 months for most patients, the new tissue is histologically different and may lead to decreased blood flow and impaired genital response [55]. Congruent with this, women who were irradiated for cervical cancer demonstrated significantly lower sexual functioning than those who underwent surgery for the same cancer [56]. In addition to having a detrimental effect for women with gynecological cancers, radiation can also indirectly affect sexual arousal due to the pain and scarring of the skin at the site of radiation (e.g., nipple and breast pain for breast cancer) as well as due to more general side effects such as fatigue.

Surgical treatments may also differentially impact female sexual arousal depending on the site and type of operation. For example, a woman undergoing surgery to remove part of her calf due to sarcoma may not necessarily experience the same dampening in her sexual arousal as a woman undergoing full hysterectomy for cervical cancer. While the surgeries for both these women require recovery time and can alter their sense of body image, hence impairing sexual arousal, the woman undergoing a full hysterectomy will also have to deal with the hormonal fluctuations induced by early menopause. Even within the same type of cancer, different surgeries can affect a woman's sexual arousal in distinct ways. For example, a recent study has shown that women undergoing hysterectomy for cervical cancer had significantly better sexual functioning than those undergoing oopherectomy [37]. General side effects from surgery also include pain, infection, bleeding and loss of organ function, all of which

may influence the process of sexual arousal. More obvious contributors to sexual arousal difficulties are surgeries that require the removal of the vaginal wall or reproductive organs, such as hysterectomy or radical cystectomy [57]. Other surgeries which leave visible scars (e.g., on the face or neck), or those that require the creation of a stoma, can significantly affect an individual's sexual self-image and levels of self-consciousness [58]. Finally, the sexual side effects of some surgeries are long-lasting, with deterioration or decreased sexual functioning found 12 or more months after surgery [58, 59].

Psychological Correlates for FSAD

Although it is well known that psychological factors play a strong role in the etiology of female sexual dysfunction, there has been minimal examination of the influence of these variables on female arousal disorders specifically. The research that currently exists suggests that emotional variables such as negative affect or poor mental health status (e.g., anxiety, depression, low self-esteem, fatigue, disordered eating, distress) are commonly been linked with arousal difficulties in women [29, 60]. In particular, clinically significant levels of depression are consistently found to predict disorders of arousal as well as desire [61, 62]. Cognitive variables, such as negative sexual attitudes/expectancies about sexual interactions, and distraction from erotic cues (e.g., due to daily stressors, self-consciousness/"spectatoring," or negative body image) have also been found to predict dampened sexual arousal [29, 63–65]. Additionally, there is evidence that a history of sexual abuse is specifically associated with a higher incidence of arousal difficulties in women [26]. Some of the strongest predictors of reported arousal problems in women are relationship difficulties and partner variables [27, 66]. Specifically, relationship factors commonly associated with arousal difficulties include relational conflict, longer relationship duration, general dissatisfaction/distress, desire or sexual script discrepancies, lack of intimacy/trust, incompatibility, poor sexual stimulation, or an otherwise inappropriate/non-optimal sexual context [27]. Partner variables have included a partner's sexual dysfunction, inadequate sexual knowledge and/or poor sexual stimulation techniques [27]. Other psychosocial variables correlated with arousal problems include lower socioeconomic status, lower education level, unemployment, being married, and engaging less frequently in sexual activity [26]. It should be noted, however, that while all of the aforementioned variables have been found to be associated with arousal difficulties, correlations do not imply causality, and the mechanisms through which these variables are associated with arousal problems is still poorly understood.

Psychological Considerations for Cancer Patients

There are numerous ways in which the aforementioned emotional, cognitive and psychosocial factors contribute to sexual arousal disorder in women with cancer. It is estimated that anywhere from one third to half of oncology patients experience depression, 32% suffer from moderate to severe fatigue and 18% suffer from significant anxiety [67–69]. If we examine the Basson model of sexual response (see Fig. 10.2), female patients with either depression or anxiety may be more likely to focus on stimuli that is not conducive to sexual arousal or may mislabel physiological indicators of sexual arousal (e.g., increased heart rate) as an unpleasant or negative reaction. In addition to the effects of depression and anxiety on arousal in cancer patients, research indicates that pharmacological treatment with selective serotonin re-uptake inhibitors (SSRIs) is also strongly associated with impaired arousal [36, 70]. For example, though SSRIs have many advantages for cancer patients (e.g., low side effect profile, safe to use with chemotherapy), up to 96% of women taking SSRIs report some kind of impairment in sexual responding [70]. While different SSRIs may yield differential effects depending on their secondary binding properties, there are other antidepressants that have been associated with better sexual side effect profiles (e.g., Buproprion) [71, 72].

In addition to depression and anxiety, fatigue is a common side effect of cancer therapies that seems to persist well after treatment has ended. According to Vistad et al., 30% of cervical cancer survivors continued to suffer from chronic fatigue 5 or more years following radiotherapy as compared to 10% of general population [73]. Research indicates that patients with chronic fatigue have significantly lower quality of life, increased anxiety and depression and more physical complaints [73, 74]. However, given the comorbidity of fatigue with depression, anxiety and pain, it is difficult to ascertain the direct impact of fatigue on sexual arousal. As chronic fatigue significantly dampens levels of physical activity, it is conceivable that the general lack of energy felt by patients will have a detrimental effect on their sexual activity [75]. In non-cancer populations of chronic fatigue, however, no direct link has been established [76]. While some pharmacological treatments for cancer related fatigue can increase the incidence of sexual dysfunction (e.g., SSRIs and Modafinil), others have not been shown to have an adverse effect (e.g., Buproprion, corticosteroids, hematopoietics).

Impairments in mood and energy levels are often accompanied by adjustments to body image in cancer patients, particularly for those whose physical appearance has been altered by surgery or by the addition of a stoma [77, 78]. Negative feelings towards ones own body/appearance can significantly affect ones willingness to engage in sexual activity and may also decrease feelings of sexual arousal [35]. Body image can also interact with relationship functioning such that women report feeling more attractive and having better sexual encounters if they perceive that scars from cancer surgery do not bother their partners [79]. Additionally, a woman's sexual self-schema (how she views herself as a sexual being) can also affect sexual arousal. Cancer patients with positive sexual self-schema have been found to have significantly more frequent sexual activity, better sexual response, and higher sexual satisfaction than those with negative sexual self-schemas [80].

Finally, in examining the existence of sexual arousal problems in cancer patients, one cannot ignore the relational context in which the disorder occurs. Research has shown that married patients cope better with their cancer diagnosis than unmarried patients [81]. In addition, marital satisfaction in cancer patients has been found to be positively related to better sexual experiences [79, 82]. Moreover, Fobair et al. found that women who felt that their partners did not understand their feelings were significantly more likely to experience sexual arousal problems than those who did not. Similarly, Speer et al. found that relationship distress accounted for a significant proportion of the variance found in difficulties with sexual arousal in female cancer patients [33, 36].

While relationship functioning can influence the experience of sexual dysfunction, the diagnosis of cancer and its treatment can also have a negative impact on intimate relationships [37]. For example, studies have found that while patients and partners do not necessarily report changes in their ability to engage in sexual activities, more than half of women indicated that they were purposely avoiding intimacy [32].

One additional psychosocial consideration for female sexual dysfunction in cancer patients is the phase of life cycle in which it occurs. Arousal difficulties will likely affect patients differently depending on their stage of life, with younger patients having great need for guidance and counseling regarding sexuality, intimacy and fertility options [83, 84]. In addition, younger women who have menopause induced due to treatment are at greater risk for sexual dysfunctions and also are significantly more distressed by changes to their appearance than older patients who have already gone through menopause at diagnosis [85]. A review of the literature shows that childhood cancer survivors have lower rates of marriage, more negative attitudes towards sexuality and were limited in initiating intimate relationships as compared to the general population, highlighting the importance of addressing these issues in a clinical setting [86]. Furthermore, while patients at the end of their life may not necessarily engage in sexual intercourse, research indicates that sexuality and intimacy were an important part of their quality of life [87].

FSAD in Partners of Patients

It is important to note that FSAD does not only occur in the oncology patient, but can also be found in partners of patients with cancer. In a non-cancer sample, Fisher et al. found that women whose male partners had erectile dysfunction (ED) were more likely to report decreases in desire, arousal, orgasm and sexual satisfaction following the diagnosis of ED [88]. Similarly, in a population of men with prostate cancer, partners reported significantly greater sexual dissatisfaction than non-clinical samples [89]. Furthermore, partners of men with prostate cancer indicated high levels of sexual dysfunction that were negatively associated with marital satisfaction [90]. In addition to the effects on sexual dysfunction, research has also found that female partners of cancer patients are at greater risk for depression, which is a strong predictor of levels of sexual satisfaction [89, 91].

Assessment

Case Example 2

Sara is a 43-year-old woman recently diagnosed with stage 2 non-small cell lung cancer. At the time of assessment, she is awaiting surgery and has been referred to psychology due to increasing levels of anxiety, to the point where she is having difficulty sleeping at night and cannot function properly during the day. Sara has gone on sick leave from her job as a flight attendant and her partner of 8 years, Claire, has taken over most of the household tasks in an attempt to reduce Sara's stress. During the course of the assessment, Sara indicates that she has felt herself pulling away from Claire and is avoiding all forms of intimacy with her after a recent sexual encounter where she had difficulty becoming lubricated.

Case Example 3

Maude is 65 years old and has recently agreed to palliative treatment for metastatic breast cancer. Her husband of 40 years, George, is having a difficult time accepting Maude's prognosis and the couple find themselves arguing over a number of issues. During an assessment with the palliative case psychologist, it is discovered that a primary source of disagreement between the couple revolves around Maude's wish for sexual relations with her husband. Maude is embarrassed by her sexual desire and George emphasizes she should be focusing on more important things.

The standard recommendation for assessing sexual arousal difficulties in women involves a biopsychosocial approach, whereby a woman's personal history, physiological and psychological health, as well as her relationship functioning and environmental factors are considered in the case formulation [92, 93]. Within the context of cancer, arousal difficulties will present themselves amidst a myriad of physical and psychological difficulties as noted in the cases of Sara and Maude. It is important that the clinician recognize that under some circumstances, such as Sara's, the immediate focus of treatment should be dealing with the sleep and mood disorder, whereas in others, such as Maude's, it is appropriate to explore the source of the couple's disagreement. Additionally, while some cancer patients may not present with a sexual arousal disorder per se, they may experience significant guilt and embarrassment because they want to engage in sexual activity despite mortality and chronic health issues, and it is the clinician's job to normalize their experiences and present a nonjudgmental attitude. Finally, while both case examples raise distinct sexual issues, patients are often hesitant to discuss sexuality within the context of cancer because they fear that their doctors would be dismissive or embarrassed by the topic [94]. It is important, therefore, as a

health care provider, that one be comfortable with broaching the subject of sexuality with patients and that one demonstrate a willingness to openly discuss the topic.

Clinical Assessment of FSAD

Despite evidence of the desynchrony between women's reports of genital arousal difficulties and their objective genital response, to date, the assessment and diagnosis of female sexual arousal difficulties has unfortunately relied almost exclusively on a woman's self-report. This typically occurs in the context of the clinic (by treatment-seekers) and takes the form of a comprehensive clinical interview, in which diagnosis of sexual dysfunction is achieved via reliance on the clinician's judgment of the patient's self-reported difficulties. On occasion, self-report measures of female sexual functioning and physical exams are also used as diagnostic adjuncts [95].

In spite of the centrality of the clinical interview to making diagnoses, there is currently no widely used interview that has been standardized or psychometrically validated for the assessment of sexual dysfunction [96]. In view of this, clinicians and researchers have recently proposed numerous guidelines and recommendations to better structure the interview process and to maximize the potential for obtaining diagnostically useful information [92, 93, 95]. As part of these recommendations, the majority have advocated a biopsychosocial assessment of the woman's difficulties, with the caveat that the woman and her partner be interviewed both together *and* separately, in order to gather as much information as possible (see Table 10.3) [92, 93].

As an adjunct to the clinical interview, many clinicians may also employ one or more of a number of self-report measures of sexual functioning [96–100] (see Table 10.3 for examples). Most of these are global measures of sexual functioning, rather than dysfunction-specific, and may include a few items that are pertinent to the sexual difficulty in question (e.g., FSAD). The two measures that include a more detailed assessment of arousal difficulties are the FSFI [99] and the Sexual Function Questionnaire (SFQ) [100], both of which include eight questions devoted to arousal (four regarding genital arousal-lubrication, and four pertaining to general subjective arousal). While these measures provide a more comprehensive assessment of arousal difficulties in women, neither has been validated as a diagnostic tool for FSAD and clinical cutoffs for the domain score do not currently exist. Moreover, in view of the lack of concordance between a woman's reported arousal and her actual genital response, the reliability of the information provided by these measures is questionable. Finally, in addition to measures assessing sexual functioning, some clinicians may also choose to administer self-report measures of sexual satisfaction and relationship adjustment, in order to augment their comprehensive diagnostic assessment of arousal difficulties [95].

Last, in addition to self-report measures of sexual functioning, in many cases a clinician may also recommend a physical and pelvic exam as part of their diagnostic assessment of arousal difficulties (see Table 10.3 for details). In the case of medically healthy women, these exams typically do not identify a cause of the arousal difficulties, however, they may prove to be reassuring for the woman and her clinician. In the case of non-medically healthy women, a physical exam is highly recommended, however even when abnormalities are identified (e.g., estrogen deficiency), caution should be exercised in interpreting the results: the presence of an abnormality should not implicate it as the cause of the sexual dysfunction. Rather, such physical impairments represent one piece of information to be considered within the context of all the other biological, psychological and social factors assessed to influence the women's sexual experience. Finally, it is important to note that in all of the above cases, an examination of the genitalia in a *nonaroused* state can only be of limited value when it is the cause of the arousal difficulty that is in question.

Table 10.3 Multidimensional assessment of female sexual arousal disorders

Clinical interview Provides information on the presenting problem and possible contributing and maintaining factors	• Nature, extent, context of problem • Motivation for seeking treatment • Examination of biological factors ○ Health ○ Lifestyle ○ Hormone levels ○ Medical conditions ○ Surgeries ○ Physical trauma ○ Medication use • Individual psychological factors ○ Mental health ○ Emotional health ○ Thoughts and emotions during sex ○ Past sexual experiences ○ Trauma history • Social and relational factors ○ Ethnocultural and religious attitudes ○ Partner communication ○ Physical attraction ○ Sexual compatibility ○ Trust within the relationship ○ Partner sexual health, mental health, physical health ○ Partner reaction to problem
Self report measures Provides quantitative information on extent of sexual problem	• Female Sexual Function Index (FSFI) • Sexual Functioning Questionnaire (SFQ) • Brief Index of Sexual Functioning for Women (BISF-W) • McCoy Female Sexuality Questionnaire (MFSQ) • Derogatis Interview for Sexual Functioning (DISF)
Physical/pelvic assessment Provides information on physical features that may be contributing or exacerbating the problem	• Non-genital features ○ Estrogen deficiency ○ Connective tissue disease ○ Systemic disease ○ Disabilities ○ Disfigurement • External genitalia ○ Sparsity of pubic hair ○ Vulval skin disorders ○ Fissures in interlabial folds ○ Labial abnormalities • Introitus features ○ Signs of vulvar disease ○ Pallor ○ Friability or loss of elasticity/moisture from vulvar atrophy • Internal features ○ Pelvic muscle tone ○ Hypertonicity of muscles • Full bimanual features ○ Fixed retroversion of uterus ○ Uterine tenderness
Psychophysiological assessment Provides a measurement of genital functioning in an aroused state	• Thermography • Labial thermistor • Laser Doppler imaging • Clitoral ultrasonography • Vaginal photoplethysmography • Pelvic MRI

Hence, in light of this, it is recommended that a multidimensional approach be employed in the assessment of female sexual arousal difficulties, which incorporates not only the data from a clinician's comprehensive history taking interview, the medical practitioner's physical and genital exams, and the woman's self-report measures of sexual functioning, but also the researcher's psychophysiological assessment measures. There are currently a host of psychophysiological tools to measure female sexual arousal (see Table 10.3). The majority of these remain in their investigative infancy (particularly in terms of their diagnostic validity), and as such, have not yet been put to full clinical use (for review see [101]). However, some of these instruments, such as thermography [102, 103], hold great promise as diagnostic tools, as they overcome many of the limitations of previously used instruments and provide a more objective picture of the nature of a woman's reported arousal difficulties. Specifically, examining the genital arousal response during exposure to an erotic stimulus will provide invaluable information about what likely occurs physiologically for the woman when she is in a "real-life" sexual situation, which will be central to developing appropriate treatment plans. Thus, it is recommended that practitioners incorporate these tools as a routine component of the multidisciplinary package used to assess female sexual arousal difficulties.

Treatment Overview of FSAD

There is currently limited data available from controlled trials to support the use of any particular intervention for FSAD. However, it is generally recommended that treatment of FSAD follow a biopsychosocial approach, and incorporate components that address the physiological, psychological, and relational factors identified in the history to be contributing to the patient's sexual difficulties. Within the context of cancer, treatment of FSAD must take into consideration the possible interaction of biological interventions with the treatment of cancer itself. Additionally, in implementing psychological interventions, one must keep a broad definition of sexuality and understand that the traditional goal of directly increasing sexual arousal to aid in sexual intercourse may not be feasible or important to the cancer patient, but rather, the patient may wish to increase comfort with nudity following surgery, or to integrate sensual touch back into their relationship. Both these goals can lead to increased comfort with oneself and one's partner, and can thus indirectly increase a patient's ability to feel sexually aroused.

Biological Interventions

There are currently no medications that have been approved by the Food and Drug Administration (FDA) for the targeted treatment of FSAD. Several off-label applications of drugs for FSAD have recently been considered, but controlled studies are few in number, and the evidence regarding the effectiveness of these agents in the treatment of arousal difficulties remains inconclusive. Overall, these drugs fall within four general categories: topical creams/lubricants, vasoactive agents, neurotransmitter-acting agents and hormonal therapies.

Topical Lubricants

Most often, the treatment for women reporting difficulties with genital arousal has involved the administration of topical lubricants, creams, vitamin E, or mineral oils, all of which serve as cosmetic remedies for an insufficient lubrication response. The utility of these lubricating aids is limited, however, as they have no long-term effects on lubrication, nor do they impact vasocongestion, or genital arousal sensations, either/both of which may be impaired in women with reported sexual arousal difficulties [104]. While lubricants do not have an impact on improving the underlying cause of FSAD, they offer a relatively benign treatment option that is not contraindicated with treatment of cancer in women.

Vasoactive Agents

In view of the body of evidence supporting the efficacy of phosphodiesterase 5 inhibitors (PDE5s) in treating erectile difficulties in men, there have been parallel attempts to test these vasodilators in pre- and post-menopausal women with reported arousal difficulties. Controlled studies in this area have primarily concentrated on the utility of sildenafil citrate (Viagra) – a PDE5 inhibitor that functions to increase genital vasocongestion through nitric oxide mediated smooth muscle relaxation. Results from the majority of these studies have found that while sildenafil may produce increases in genital vasocongestion, it has no impact on subjective reports of arousal, desire or satisfaction [105, 106]. One exceptional study with estrogenised postmenopausal women, however, found that sildenafil did lead to increases in subjective arousal, perceived genital arousal, and orgasmic potential for women with demonstrated low vasocongestive response (as indicated by VPA) [107]. In addition, there is some evidence that the use of PDE5 inhibitors can improve genital vasocongestion in patients on SSRIs [108]. Hence, it may be that PDE5s, such as sildenafil, are useful for a specific subgroup of women with FSAD (i.e., those with objectively reduced genital vasocongestion), and may be of benefit to women with cancer who are experiencing sexual side-effects as a result of medication use.

In addition to research with the PDE5s, there has also been some investigation into the effectiveness of other vasodilating drugs that act to increase smooth muscle relaxation via nitric oxide-mediated processes (e.g., l-arginine, Zestra, Alprostadil cream), as well as drugs that inhibit adrenergic-mediated vasoconstriction processes (e.g., yohimbine, ephedrine, phentolamine) [104, 109–111]. Two of these randomized controlled studies found that while the pharmacological agents of yohimbine, l-arginine and ephedrine increased vaginal congestion (as indicated by VPA) in pre- and post-menopausal women with and without sexual arousal disorder, they had no significant effect on subjective ratings of arousal [104, 110]. In contrast, Ferguson and colleagues [109] found that Zestra (a botanical massage oil) led to increases in subjective levels of desire, arousal, orgasm, and sexual satisfaction, in women with and without FSAD. However, genital arousal levels were not measured in this study, and so direct comparison with other studies is not possible. Finally, studies on clonidine, an antihypertensive medication that acts as a selective adrenergic agonist (thus blocking sympathetic nervous system activity), has been found to dampen both physiological and subjective levels of arousal in premenopausal, sexually functional women [112], whereas Alprostadil (a vasodilator) [111] and phentolamine (an alpha adrenergic antagonist and vasodilator) have been found to produce mild increases in both physiological and subjective measures of arousal [113]. Hence, while evidence from these studies suggests that both nitric oxide and adrenergic systems are important in facilitating sexual arousal in women, the sexual response effects of the pharmacological agents targeting these systems remain inconclusive, owing in part to differences between these studies in sample composition and measurement tools.

Central Nervous System Acting Agents

While the majority of human research on arousal-enhancing pharmacological agents has focused on the use of drugs that amplify genital vasocongestion, there have also been recent attempts to test the effects of central nervous system (CNS)-acting agents (which act as neurotransmitter agonists or antagonists) on sexual response in women. The majority of this research has investigated the utility of dopaminergic drugs such as apomorphine or levadopa (dopamine agonists), as well as buproprion (a dopamine reuptake inhibitor and norepinephrine agonist). The results from these studies have, however, been mixed [72, 114, 115]. Specifically, while some researchers have found a facilitating effect of dopaminergic agents (i.e., apomorphine and buproprion) on the reported sexual functioning of women with low desire [72],

arousal and orgasm [114], a recent controlled study testing the impact of Levadopa in healthy subjects found no impact on arousal at all [115]. Finally, there are currently some initiatives underway to investigate the relationship between sexual arousal and other neurotransmitter systems (e.g., serotonoin, norepinephrine, adrenaline, and opioids), but the evidence is far from conclusive (for a review see [38, 116]). Overall, while some research suggests that dopaminergic and noradrenergic agents may facilitate sexual arousal in women, this finding is based on highly limited data. Few controlled studies currently exist in women, and methodological differences between these studies make it difficult to interpret discrepant results. Given that the available data seems to suggest that women's experiences of arousal are determined more by changes that occur 'mentally' than by changes that occur genitally, a surge in research on the neural mechanisms underlying experiences of female sexual arousal seems highly necessary.

Hormonal Agents

While androgen and estrogen therapies have been examined as treatments for sexual arousal difficulties in women, the risks of prescribing hormonal agents for women with cancer must be carefully weighed against the possibility of increasing the amount of circulating hormones, especially since the extent of improvement in sexual functioning from hormonal therapies remains questionable [85]. Even in non-oncology populations, the use of hormones to ameliorate symptoms of FSAD have been based on highly limited and conflicting research [38, 93]. While some of these studies have found general improvements in sexual responsiveness, desire, arousal, lubrication and satisfaction [117] others have found no benefit at all [118]. It is important to note that most of these studies have provided only brief tests of testosterone treatment in estrogenized women, and very few of these studies have made concurrent use of psychophysiological measures of arousal (such as VPA or thermal imaging). Thus, while there is evidence indicating that testosterone treatment may be effective in increasing desire, arousal and satisfaction in some women, the nature of the relationship between testosterone and sexual response is not well understood [116].

As with testosterone therapies, the role of systemic estrogen in improving sexual arousability is also unclear. The majority of research suggests that estrogen has little direct impact on sexual desire or subjective arousability, and studies examining the efficacy of estrogen alone in treating surgically menopausal women have not shown it to be successful [116]. In estrogenized postmenopausal women with vaginal atrophy or vulvar disease, estrogen creams, tablets or rings may be recommended on a short term basis [104], however, recent research suggests that these treatments can increase circulating levels of estrogen, which must be evaluated when prescribing their use in women with estrogen-receptor positive cancers [119].

Additional biological interventions for cancer patients: while all of the above may be considered for alleviating symptoms of sexual arousal disorder in women with cancer, two additional treatments have also been examined: EROS therapy and exercise. EROS therapy involves the use of a suction device that increases blood flow to the clitoris, and has been demonstrated to be beneficial in reducing arousal disorder symptoms and significantly improving FSFI scores in women with cervical cancer [120]. Additionally, Karvinen and colleagues found that cancer patients who met public health exercise guidelines demonstrated significantly better results regarding sexual functioning, body image and fatigue than those who were sedentary [121].

Psychological Interventions

While there are currently no randomized controlled trials of psychological interventions specifically designed for the treatment of arousal disorders [122], there is research suggesting the

benefits of psychoeducational interventions for female cancer patients with FSAD [123–126]. Psychological interventions typically incorporate a combination of general cognitive and behavioral techniques targeting the individual or relational difficulties identified in the clinical interview process. For example, individual psychological treatment may involve brief interventions to specifically address comorbid mood disturbances (e.g., depression, anxiety, body image dissatisfaction) interacting with the arousal difficulty. Treatment may also include psychoeducation about cancer and female sexual response, dilatation exercises and pelvic floor musculature exercises for conditioning the genital area following radiation or surgery, effective stimulation techniques, and contextual influences on sexual arousability (e.g., the detrimental effects of negative affect or cognitive distraction during sexual activity, and the need for appropriate erotic stimuli). In some cases, the impact of past sexual experiences (particularly sexual trauma) may need to be directly addressed through psychotherapy, and cognitive restructuring techniques may be employed to modify maladaptive sexual attitudes/beliefs, expectancies and myths/distortions.

In addition to individual psychotherapy, couple therapy is also recommended to address issues in the relationship (e.g., communication, trust, intimacy following cancer diagnosis, discrepancies in sexual scripts/expectations) that may be contributing to the woman's arousal difficulties. When working with cancer patients, standard behavioral and communication strategies can help the couple work through their sexual and relational difficulties. It is important for the therapist to work with the couple to identify their goals when dealing with FSAD, and to determine what their need is vis-à-vis increased sexual arousal. As mentioned earlier, the goal may not necessarily be to re-initiate sexual intercourse, but rather to broaden the couple's definitions of sexuality and intimacy within the context of chronic illness. Sex therapy techniques, such as sensate focus, can help the couple to begin body exploration, and increase communication and appreciation of pleasurable sensations. Sex education that is tailored to the patient's cancer can aid in teaching couples about the sexual changes that have occurred in the patient's body and how best to deal with them. Relaxation-based or mindfulness training can facilitate the experiencing of pleasure [127]. Finally, providing patients with reading material, such as information pamphlets or lists of resources is a relatively low cost way to educate individuals on some of the more common sexual side effects of cancer and how to deal with them. Research suggests, however, that the most effective educational pamphlets are ones that are tailored to the individual's needs, highlighting the importance of having reading material that targets specific problems and specific populations [128].

There are currently very few outcome studies examining the impact of the above therapeutic techniques on sexual functioning, and the few that exist have focused specifically on disorders of desire or orgasm, as opposed to arousal (for an exception, see [127]). For the most part, these trials have indicated general improvements in self-reported levels of sexual desire, subjective arousal, orgasm, mood/distress, relationship satisfaction and overall well-being [127, 129, 130]. However, more controlled research in this area, particularly regarding the efficacy of individual psychotherapy treatment components in treating arousal difficulties, is desperately needed.

Persistent Genital Arousal Disorder

Persistent genital arousal disorder (PGAD) is a syndrome characterized by high levels of spontaneous and unwanted genital arousal that occurs in the absence of sexual interest or desire [131]. Furthermore, these physical sensations do not resolve with orgasm and are not necessarily triggered by sexual activity [131]. While there is no mention of PGAD in the DSM-IV-TR, an international consultation on women's sexual functioning recognized that a number of women suffer from a particular constellation of symptoms that has come to be known as PGAD [13].

Leiblum and Nathan [132] were the first to describe PGAD and listed five features that have become the standard diagnostic criteria for this disorder:

1. Involuntary genital or clitoral arousal that persists for an extended period of time.
2. Physiological genital arousal does not resolve with one or more orgasms.
3. Genital arousal is unrelated to feelings of sexual desire.
4. Cause of persistent genital arousal is unknown.
5. Genital arousal is associated with moderate levels of distress.

They were also careful to distinguish PGAD from hypersexuality by the key component of a lack of sexual desire or mental sexual arousal. At present, there are no prevalence estimates on PGAD in the general population and the handful of research that exists on risk factors and etiology is entirely based either on self-report, case examples, or small pilot studies [133–139] (See Table 10.4 for correlates of PGAD).

To our knowledge, there has been no attempt to systematically study treatment for women with PGAD. Anecdotal reports suggest monitoring medication use, such as SSRIs, which women have reported to induce or relieve their symptoms; or trazadone, which has been demonstrated to cause priapism in some men [131]. In addition, life-style changes, cognitive-behavioral therapy, pelvic massage, social support groups and mood-stabilizing medications have been suggested, however, this is all based on single case examples with no empirical evidence to back up these claims [131].

Clearly, this is a disorder that requires more systematic study regarding its prevalence, etiology and treatment. While PGAD has never been studied in an oncology population, it is conceivable that some patients could exhibit these symptoms, depending on the type of cancer and treatment that they are receiving (e.g., transitional cell carcinoma as presented in DiGiorgi et al. [140], or high grade anaplastic astrocytoma as presented by Krychman et al. [141]).

Table 10.4 Clinical correlates of PGAD

Chronic fatigue
Depression
Panic attacks
Increased vaginal vasocongestion
Clitoral pain
Overactive bladder syndrome
Restless leg syndrome
Hypersensitivity of urethra
Hypersensitivity of genital area
Pelvic varices
Neuropathy

Conclusion

Disorders of female sexual arousal are multifaceted problems that are only beginning to be understood. Current conceptualizations highlight the overlap between arousal disorders and those of desire and orgasm and future diagnostic systems will likely collapse the categories into one. The research on female sexual arousal in cancer patients is limited and our understanding is clouded by questionnaires that do not differentiate between physiological and psychological arousal, a lack of physiological measurement of arousal in cancer patients, and poor control over multiple psychological, relational and physical variables that interact with arousal difficulties. Despite these limitations, it is clear that a significant proportion of female cancer patients suffer from sexual arousal problems. In dealing with patients who complain of arousal difficulties, it is recommended that a full psychosexual assessment be conducted that examines physiological issues such as cancer treatment and medication use, partner variables and relationship functioning, as well as psychological functioning. Treatment options can vary from broadening the patient's definitions of sexuality and sexual activity, to adjusting or prescribing different medications to ameliorate genital vasocongestion (see Fig. 10.3 for treatment summary). The study of sexual arousal disorders in women is still in its infancy and clearly, there are many

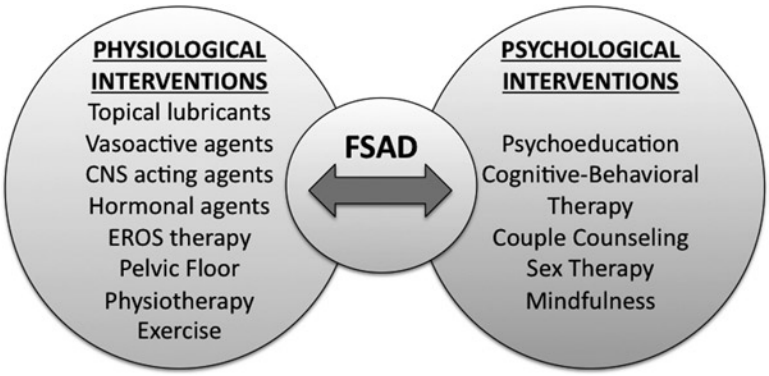

Fig. 10.3 Multidimensional treatment options for FSAD

interesting avenues of development that need to be pursued in order to provide us with a better understanding of the etiology, diagnosis and treatment of this issue, especially in populations with chronic illness.

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Chapter 11
Disorders of Female Orgasm

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Keywords Orgasm • Anorgasmia • SSRI medications • Sex therapy

Introduction

Both cancer and cancer treatments can have deleterious effects on women's ability to attain orgasm. The degree to which sexual functioning at large is impacted depends on a number of medical, psychological, and social factors including severity of the disease, treatment intensity and length, emotional status during cancer diagnosis and management, access to social support, and comorbid psychological problems. In this chapter, we discuss the diagnosis, prevalence, and treatment of female orgasmic disorder (FOD), with an emphasis, where possible, on how they pertain to women with current or past cancer. Orgasm is a fundamental component of sexual response in both men and women, and is affected frequently in humans from the studies of cancer survivors.

A summary of the specific ways in which cancer and its treatment can impact orgasm and sexual functioning at large is also provided.

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Definitions of Female Orgasm Disorder

The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) [1], defines FOD as the persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. In addition, the disturbance must cause marked distress or interpersonal difficulty. The diagnostic criteria also specify that the diagnosis of FOD should be based on the clinician's judgment that the woman's orgasmic capacity is less than that would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives.

It is important to note that the type or intensity of sexual stimulation required for obtaining orgasm varies widely across women. Orgasms have been reported to be induced by erotic stimulation of genital areas such as the breast/nipple, periurethral glans, or mons, in addition to the clitoris and vagina [2, 3]. Research indicates that stimulation via mental imagery, or fantasy, and hypnosis has been shown to induce orgasm [4, 5]. A few cases of spontaneous orgasm without an obvious source of sexual stimulation have been reported in the literature [6, 7]. Spontaneous orgasms have also been reported with the use of antidepressants [8–10].

The DSM-IV-TR subtypes are used to indicate the onset of orgasmic disturbance (lifelong vs. acquired), the context in which the disturbance occurs (generalized vs. situational), and whether the FOD is a result of psychological or combined factors. Most studies refer to orgasm problems in

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women as either *primary orgasmic dysfunction* or *secondary orgasmic dysfunction*. The term primary orgasmic dysfunction was introduced by Masters and Johnson [11] and has been used to describe women who report never having experienced orgasm under any circumstances, including masturbation. According to the DSM-IV-TR, this would refer to those women who meet criteria for lifelong and generalized FOD. Secondary orgasmic dysfunction relates to women who meet criteria for acquired and/or situational FOD.

Although situational FOD is understood to mean that orgasm difficulties occur in specific contexts, the clinical consensus is that achieving orgasm during intercourse with manual stimulation but not with intercourse alone would not meet criteria for clinical diagnosis, unless clinically significant distress is present. The inability to achieve orgasm when one wishes may result in sexual distress or dissatisfaction in women, but this is not always the case. Some women meet criteria for FOD and do not perceive their anorgasmia or reduced orgasmic capability as a problem nor do they report experiencing significant distress [12, 13]. If the disorder does not cause the women marked distress or interpersonal difficulty, a DSM-IV-TR diagnosis of FOD is not given.

While lifelong, generalized FOD is a clear diagnosis covering all sexual situations, a diagnosis of secondary orgasmic dysfunction (acquired and/or situational FOD) encompasses a wide range of clinical presentations. Women who were initially orgasmic but later obtain orgasms infrequently and women who achieve orgasms in only certain contexts, with certain types of sexual activity or with certain partners are examples of the heterogeneity found with secondary FOD.

A large proportion of women who meet FOD diagnostic criteria also meet the criteria for female sexual arousal disorder [14–16]. DSM-IV-TR criteria explicitly state that the absence or delay in orgasm must follow a *normal* sexual excitement stage produced by adequate sexual stimulation. Thus, women with comorbid FSAD and FOD may indeed have orgasm difficulties when sexual arousal is achieved. If adequate sexual arousal is not achieved, the lack of orgasm is due to FSAD, not FOD. Basson et al. [17] suggested the following revised FOD definition in order to address the fact that a DSM-IV-TR diagnosis of FOD precludes one of female sexual arousal disorder, and also to highlight the need for adequate arousal preceding the anorgasmia: "despite the self-report of high sexual arousal/excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations, or marked delay of orgasm from any kind of stimulation."

The World Health Organization's *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision, defines orgasm dysfunction in broader terms and without subtypes. According to the ICD-10, orgasmic dysfunction is an absence of, or markedly delayed, orgasm in which the individual has had no experience of an orgasm in any situation (similar to "lifelong" subtype in DSM-IV-TR) or developed the dysfunction after a period of relatively normal response (similar to "acquired" subtype), and must not be the result of prolonged abstinence from sexual activity. Other criteria include frequently occurring orgasm difficulties that keep the individual from participating in satisfactory sexual activity lasting for a period of at least 6 months.

The Prevalence of Female Orgasmic Disorder

Orgasm difficulties ranked as the second most frequently reported sexual problem after sexual desire difficulties based on the interviews of 1749 American women (aged 18–59) in the National Health and Social Life Survey [82]. Specifically, 25% reported a lack of orgasm in the past year for at least several months or more. This percentage is comparable to clinic-based data. Orgasmic problems were noted by 29% of women (aged 18–73) who attended an outpatient gynecologic clinic [16] and by 23% of women (aged 18–65+) attending a UK general practice clinic [18]. A recent study of attendees (aged 18–75) at several general practice clinics

revealed that 18% received an ICD-10 diagnosis of orgasmic dysfunction, 13% of which reported it was also a problem for them [13]. [82] found that the frequency of orgasm both with a partner and during masturbation was greater for older groups of women and lowest for women between 18 and 24 years of age. Age differences in orgasm frequency may be due to differences in sexual experience such that younger women tend to have less experience and fewer partners [19, 82]. As young women engage in more sexual experiences, they may become more familiar with their bodies and learn what is sexually pleasing for them, including how to achieve orgasm.

Evaluating the prevalence of orgasm dysfunction in cancer survivors is complicated by the diversity of psychological, medical, and social factors that contribute to sexual outcomes and by the fact that most studies report the impact on sexual functioning in general without specifically addressing orgasm dysfunction. Out of the population of women treated for breast and gynecologic cancers, one half experience long-term sexual dysfunction [20]. Breast cancer is the most common cancer diagnosed in women, but has a high patient survival rate – 75% live at least 5 years post-diagnosis [21]. In a study of breast cancer survivors 1–5 years after initial diagnosis, roughly half the survivors exhibited a decreased interest in sex while 30% reported a decrease in sexual activity overall [22]. Gynecological cancer is the third most common cancer diagnosed in women and inherently interferes with sexual functioning due to the location of the cancer [23]. Defined as cancer of the female reproductive tract, gynecological cancer can affect the cervix, endometrium, fallopian tubes, ovaries, uterus, and vagina [20]. Several studies have examined sexual dysfunction resulting from these cancers, but cross-study comparison has proved to be difficult as patients fall into different categories of diagnoses, stages, and treatments [22]. Despite this issue, sexual dysfunction is a serious issue for cancer survivors; in one study, 50% of women with gynecological cancer reported sexual problems as having a devastating impact on quality of life [24].

The Impact of Cancer on Women's Sexual Health

When a woman is diagnosed with cancer, the priority for medical professionals is to determine whether or not she will survive and what must be done to give her the best possible prognosis. When treating an oncological patient, the main focus is on the physical ailment; however, cancer is certainly more than skin deep. As they battle their ailments, patients often cope with a variety of side effects; many basic human processes are affected, and sexual functioning is particularly susceptible to complications.

In their book about sexuality and chronic illness, Schover and Jensen elucidate the relationship between the two by asserting that cancer and its associated treatments can affect all biological systems necessary for normal sexual function. Symptoms such as pain during intercourse can lead to an initial diagnosis, and concern about their sexual functioning can influence patients as they evaluate possible treatment options [25]. Although surgery, chemotherapy, and radiation eradicate cancer cells, patients must cope with side effects such as hair loss, nausea, vomiting, weight gain, and fatigue.

Sexual responses are also affected by treatment; for example, situations that would normally excite someone may not elicit the same effect because chemotherapy affects the chemicals of the brain for stimuli [26]. Other possible sexual side effects include genital pain, premature menopause, dyspareunia, vaginal dryness, and vaginal stenosis [22]. Patients may also face arousal problems due to decreased lubrication and reduced vaginal elasticity [27].

In addition to physical effects, patients may also suffer emotional trauma. Potentially losing one's life can induce feelings of anger, fear, anxiety, sadness, and guilt, while disfiguring surgeries can alter a patient's self-image as a sexual being and lead to a decrease in sexual interest and desire [28]. Patients recovering from cancer may face depression and adjustment disorder, which can negatively affect sexual functioning, and this can be further compounded through the administration of selective serotonin

reuptake inhibitors (SSRIs) as treatment. Studies have revealed that sexual dysfunction can be a side effect of SSRIs, so it may be difficult to determine what impacts the patient's sexuality: the cancer treatment or SSRI [29].

Relationship issues may also develop during a cancer diagnosis and therapy. Women may need to reduce their workload in order to fully recuperate, which can seriously strain a relationship as their domestic and wage-earning duties must be shouldered by their partners. High costs of medical care may also impose a financial burden on the couple, and decreased sexual activity as the woman recovers can create marital and sexual tension that further damages the couple's relationship [30]. Sexual rehabilitation may be required for the couple to return to their previous levels of intimacy.

Effects of Specific Cancer Treatments on Orgasm Function

Women with cancer often face issues with their sexual health as procedures designed to treat cancer, such as surgical procedures, radiation, chemotherapy, and hormone therapy, negatively impact sexual functioning and satisfaction. Combining two or more therapies can result in even greater sexual dysfunction via vaginal stenosis, known as the narrowing of the vagina accompanied with increased dryness, loss of elasticity, and scar tissue [31]. Undergoing pelvic surgery often results in changes to sexual functioning along with one's body image and self-esteem [32]. In one study, 66% of women treated with radical pelvic surgery continued to experience sexual problems more than 6 months after the surgery [33]. Although invasive surgeries such as hysterectomies may affect the autonomic nerves activated during sexual arousal, Thakar et al. [34] found that women receiving full hysterectomies did not differ from women who received partial hysterectomies on orgasm frequency, intercourse frequency, or sexual desire. When compared to healthy controls, women treated with radical pelvic surgery were found to have less sexual desire and decreased vaginal lubrication, but no differences in orgasmic function or dyspareunia at 12 months post-surgery [35].

Radiation therapy impacts orgasm function to a greater degree than does the pelvic surgery. Radiation can cause thickening and contraction of the skin in the vaginal canal, vaginal stenosis, and changes in texture leading to difficulties with vaginal penetration and genital sensitivity [32]. Radiation-induced injury to genital organs has been reported objectively [36] and subjectively by patients [37, 38] described in the cancer literature. Jensen et al. [39] noted that in a sample of 118 women with cervical or vaginal cancer, 67% reported never to occasionally experiencing orgasm 1 month after radiotherapy with little improvement at 1 year (62%). In addition, the relative risk of orgasm dysfunction was approximately 1.5 times greater for women with cancer compared to the control group.

Chemotherapy is particularly detrimental to orgasmic function. Head, face, or genital hair loss, a common side effect of chemotherapy, may impact the way a woman feels about her sexual attractiveness and self-esteem [32, 83]. Other side effects include fatigue and weight change [83]. Ovarian failure due to chemotherapy is considered to have a direct effect on sexual functioning; a decrease in estrogen levels, provided by the ovaries, is associated with decreased vaginal lubrication leading to difficulty with intercourse and other sexual activities [40, 83]. Young-McCaughan [41] reported that women who underwent chemotherapy were seven times more likely to report difficulty attaining orgasm than women not treated with chemotherapy. Results from an outpatient study of 50 Italian women emphasize the damaging effects of chemotherapy compared to other treatments [42]. Of the women who did not report sexual problems prior to breast cancer treatment, 26% reported sexual dysfunction after chemotherapy, much greater than the women treated with surgery or radiotherapy, 12 and 6% respectively [42].

Endocrine therapy is effective for several medical conditions (e.g., diabetes, hypothyroidism) and is commonly used for treating estrogen receptor positive breast cancer [32]. Selective

estrogen receptor modulators such as tamoxifen and raloxifene bind to the receptor sites within cancer cells not allowing the cell to divide. Other hormone treatments include aromatase inhibitors and GnRH agonists, which lower estrogen levels. One prospective study of women receiving different combinations of hormone therapy found that women reported minimal sexual side effects with the use of tomaxifen alone and significant sexual dysfunction with zoladex, a luteinizing hormone-releasing hormone agonist, compared to cancer patients not receiving endocrine therapy [43]. Generally, cancer patients tolerate endocrine treatment much better than other therapies, especially chemotherapy (e.g., [32]).

The Treatment of Female Orgasmic Disorder

Several therapeutic perspectives including psychoanalytic, cognitive-behavioral, pharmacological, and systems theories approaches have been applied to the treatment of anorgasmia. To our knowledge, there has been little research on the effectiveness of these interventions specifically among cancer survivors who experience orgasm difficulties. Cancer survivors face a number of psychological and physiological challenges that need to be considered when planning treatments for sexual concerns. Here we review the effectiveness of empirically validated treatments for orgasm difficulties. Where available, we include information on whether the treatment has been effective among cancer survivors.

Determining a course of treatment for sexual dysfunction in cancer patients requires additional research and investigation as sexuality issues are not frequently discussed during routine oncological care [84]. The addition of sexual health training for physicians and improved patient education detailing cancer's potential sexual side effects would ensure a more accurate prevalence assessment and hopefully break down communication barriers between patients and physicians.

Psychological Approaches (Table 11.1)

Directed Masturbation

For women with orgasm dysfunction, masturbation exercises may be beneficial in a number of ways. Focussing on nonsexual cues rather than sexually arousing cues has been shown to impair sexual response [44]. Masturbation can help guide a woman's attention toward pleasurable sexual sensations (i.e., erotic cues). In addition, solitary masturbation eliminates performance anxiety or discomfort with communicating with a partner, both of which may play role in a woman's orgasm difficulties. Moreover, having the ability to immediately adjust the type of stimulation and intensity according to what a woman prefers may be more effective than depending on her partner to touch her with appropriate stimulation.

For women with *primary* anorgasmia, directed masturbation is the most frequently prescribed treatment. This treatment program was initially developed by LoPiccolo and Lobitz [45] and other researchers have produced variations of directed masturbation such as bibliotherapy, individual, couples, and group therapy formats (e.g., [46]). The directed masturbation program consists of successive stages of guided masturbation to train a woman to locate and manually stimulate genital areas that bring her sexual pleasure. The first stages begin with a visual examination of her body, using a mirror and educational diagrams depicting female genital anatomy. After visual and manual identification of her genitals, she is instructed to explore those areas and note which genital areas are sensitive and elicit pleasure. Then she is instructed to apply targeted manual stimulation to these regions and to increase the intensity and duration until "something happens" or until discomfort arises. Aids such as topical lubricants, vibrators, and erotic materials can be incorporated into the exercises. Training on self-stimulation is directed toward the woman's achieving orgasm alone. Once she has accomplished this, her partner is included in the directed masturbation sessions. The addition of her partner's presence serves as desensitization to anxiety that she may have experienced up until this point. As the woman learns to experience sexual

Table 11.1 Studies for the psychological treatment of orgasm dysfunction

References	Design	*N*	Treatment	Conclusion	Level of evidence
Directed masturbation (DM) studies					
LoPiccolo and Lobitz [45]	Single group treatment study; 15 sessions	8 women with primary anorgasmia	Individual DM modeled after Masters and Johnson, combined with Kegel exercises	All subjects, orgasmic with masturbation, 75% coitally orgasmic; gains maintained at 6-month follow-up	Assessment method not specified
Barbach [49]	Single group treatment study; 10 sessions over 5 weeks	83 women with primary anorgasmia	DM in group therapy	92% of subjects orgasmic with masturbation	Anorgasmia defined as no orgasmic experience
Heinrich [50]	Randomized three-leg study with control condition; between 1 and 5 weeks in length	44 women with primary anorgasmia	DM in group therapy (10 sessions/5 weeks) vs. individual DM bibliotherapy (1 session) vs. wait list	Both DM treatments improve masturbatory and coital orgasmic function (with group therapy more effective); little to no improvement with wait list	Assessment method not specified
McMullen and Rosen [52]	Randomized three-leg study with control condition; 1 session weekly for 6 weeks	60 women with primary anorgasmia	DM with videotape modeling vs. DM with written instruction vs. wait list	No significant difference between DM conditions, but both more effective than wait list; gains maintained/improved at 1-year follow-up	Sexual function questionnaire, clinician interview, self-reports
Delehanty [51]	Randomized two-leg study with control condition; 10-week duration	28 preorgasmic women	DM and assertiveness training in group therapy for 10 weeks vs. wait list	82% of subjects achieved orgasmic success with treatment	Sexual function questionnaire, self-reports

Fitchen et al. [53]	Randomized three-leg study; 14 week duration	23 women with secondary anorgasmia	DM, sexual info, relaxation, Kegel exercises, sensate focus, sexual communication training; done with couples vs. groups vs. minimal contact bibliotherapy	No change in orgasm for all groups	Subjects orgasmic less than 25% of time
Hurlbert and Apt [54]	Randomized two-leg study; four treatment sessions and four phone sessions	36 women with secondary anorgasmia	Individual coital alignment technique (CAT) vs. individual DM	CAT subjects improved more substantially in coital orgasmic function than DM subjects	Self-reports and sex diaries
No control outcome studies					
Masters and Johnson [11]	Single group treatment study	342 women with primary and secondary anorgasmia	Couple's therapy that included sex education, sensate focus, sex communication training, and in vivo systematic desensitation	Varying levels of improvement for all subjects; 1–2% relapse rate at 1-year follow-up	Assessment method not specified
Brotto et al. [27]	Single group treatment study; three sessions/6 weeks	26 women seeking treatment for acquired sexual desire and/or arousal concerns	Mindfulness-based psychoeducation (PED) in small groups (4–6 women)	Improvement in subjective feelings of wetness post-PED compared to baseline; beneficial effect on sexual desire and distress	Clinician assessment

arousal and orgasm openly in the company of her partner, anxiety accompanying sexual encounters lessens. In addition, the partner is able to observe how to stimulate the woman effectively.

Directed masturbation is highly effective and evidence to support this treatment is presented in the link between masturbation and orgasm ability. Kinsey et al. [47] reported that the average woman reached orgasm more frequently during masturbation than with intercourse (95 vs. 73% of the time). More recently, Laumann et al. [48] reported a strong relation between frequency of masturbation and orgasmic ability during masturbation. Women who masturbated one to six times per year reported less frequent orgasms (67%) than women who masturbated once a week or more (81%).

A number of outcome studies and case series reported directed masturbation is highly successful for treating primary anorgasmia. High rates have been reported for orgasm attainment through group directed masturbation, ranging from 82 to 100% of anorgasmic women [49–51]. Self-directed masturbation via text and video yielded lower rates, 47–65% [50, 52].

Few controlled studies have examined the effects of directed masturbation for treating secondary anorgasmia. Fitchen et al. [53] compared minimal therapist contact bibliography with several established techniques, including directed masturbation, relaxation exercises, Kegel exercises, sensate focus, and sexual communication training. Surprisingly, the authors found no change in orgasmic ability among 23 women with secondary anorgasmia. These findings may indicate that factors other than orienting oneself to her body sexually and focussing on pleasurable physical sensations may be at play. Hurlbert and Apt [54] compared the effectiveness of directed masturbation with coital alignment technique in 36 women with secondary anorgasmia. Coital alignment is a technique in which the woman assumes the supine position and the man positions himself up and forward on the women. Thirty-seven percent of the women and their spouses receiving instructions on coital alignment technique vs. 18% of those receiving directed masturbation reported substantial improvements (>50% increase) in orgasmic ability during intercourse, orgasmic strength, and an increase in the number of orgasms during sexual activity with their spouse after four 30-min sessions. The benefits of this technique result from the fact that clitoral contact and possibly paraurethral stimulation are maximized. The effectiveness of directed masturbation for the treatment of anorgasmia among cancer survivors has yet to be examined.

Anxiety Reduction Techniques

Barlow [44] theorized that when faced with a sexual situation, individuals with sexual dysfunction shift their focus of attention away from erotic cues and re-direct their attention toward nonerotic cues (e.g., performance anxiety). This may be particularly relevant for cancer survivors as their bodies can be changed physically through the treatment of cancer. During sexual situations, these women may begin to focus on body image concerns stemming from altered breast [55] or genital tissues [56]. Healthy women with orgasm dysfunction may experience anxiety and negative emotions such as performance concerns, embarrassment, or guilt. It is very likely that cancer patients might also experience negative effect regarding important issues such as mortality and loss of reproductive capability [28] that could result in orgasmic difficulties along with other sexual problems. Focussing on these and other anxieties and concerns could result in "spectatoring" or self-monitoring during sexual activity [11]. Spectatoring is thought to impede sexual functioning through cognitive interference, with cognitions being directed away from the sexual experience and leaving less cognitive resources for processing erotic and physiological arousal cues.

Two commonly prescribed anxiety reduction techniques for the treatment of FOD include systematic desensitization and sensate focus. Wolpe [57] developed systematic desensitization for the treatment of specific phobias. When applied to orgasmic dysfunction, the woman and the therapist create a fear hierarchy of anxiety-provoking stimuli which successively increases in the amount of anxiety the activity produces. The deep relaxation exercise training aids in replacing fear responses with a calm, relaxed state. When anxiety is reduced and a relaxed state

is achieved, the woman can progress to the next, more fearful task in the hierarchy. The procedure is first completed by imagining all the items on the hierarchy. Afterward, she restarts the fear hierarchy by engaging in the actual activities.

Sensate focus is a skills-based couples' therapy developed by Masters and Johnson [11] that, like directed masturbation, increases awareness of sexually pleasurable regions for each partner and emphasizes communication of each other's preferences and pleasurable experiences via a sequence of body-touching exercises. The first stage of sensate focus is to explore their partner's nonsexual body areas without the goal of sexual activity. Once the couple increases the practice of sexual touching without the pressure of intercourse and the woman can maintain a relaxed state, she can move toward more sexually oriented touching such as female-guided genital stimulation or penile stimulation and eventually intercourse. Sensate focus combines the hierarchical nature of systematic desensitization with in vivo desensitization in order to reduce anxiety associated with orgasm performance.

Many of the treatment outcome studies that assess the effectiveness of anxiety reducing techniques for FOD combine these techniques with other modalities such as directed masturbation, skills and communication training, bibliotherapy, Kegel exercises, or sexual education. With the current literature, it is difficult to ascertain the extent to which these anxiety-focussed modalities impact treatment outcomes. In addition, the variation in sample characteristics, such as demographics, sexual dysfunction severity, diagnoses, primary vs. secondary anorgasmia, therapist characteristics, and treatment setting and duration, provides additional heterogeneity when systematically comparing anxiety reduction techniques. Meston et al. [58] reviewed controlled studies and found that anxiety appears to play a small role in FOD and these techniques are most effective when women experience concurrent sexual anxiety. Cancer patients use relaxation techniques to reduce general anxieties [59]; it may be possible that sexually anxious individuals could benefit from such techniques. Sexual anxiety was found to be a key factor in sexual relationships of women after breast reconstruction surgery [60].

Other Techniques

Sex education has been an important component of sex therapy since the publication of Masters and Johnson's *Human Sexual Inadequacy* (1970). Particularly, education about genital anatomy and learning techniques to enhance sexual pleasure aid in gaining orgasmic capability. Several studies provide evidence for the effectiveness of sexual education for primary and secondary anorgasmia [61]. [27] examined the effects of a brief sex education intervention on sexual arousal concerns among women with early-stage gynecologic cancer. The sexual education was conducted over three 1-h sessions and included education on masturbation and orgasm attainment, marital satisfaction, mindfulness, and relaxation techniques. Among improvements in sexual function, orgasm frequency and satisfaction increased significantly after the intervention.

Kegel [62] proposed that conducting exercises that strengthen the pubococcygeous muscle could facilitate orgasm by increasing vascularity to the genitals. Treatment studies comparing therapies with and without Kegel exercises have not produced significant differences in the alleviation of orgasmic dysfunction. However, Kegel exercises may act to boost orgasmic ability by enhancing physical arousal via increasing vascularity in the pubococcygeous muscle and may help women to identify and focus on pleasurable genital feelings much in the same way as other genital stimulation techniques.

Pharmacological Approaches

A small number of placebo-controlled studies have examined the effectiveness of pharmacologic agents for treating FOD not induced by antidepressant medication. Sustained release bupropion failed to improve orgasm in nondepressed, antidepressant-free women ($n=20$) with orgasmic dysfunction as compared to placebo [63]. However, a small percentage of women (20%) experienced facilitated and/or more intense orgasm during bupropion treatment. Zajecka et al. [64] reported improvement in orgasm among depressed women

reporting sexual dysfunction, including orgasm difficulties, compared to baseline after 12 weeks of treatment with nefazodone. Studies on sildenafil for FOD show mixed results. In one study, 53 premenopausal women diagnosed with sexual arousal disorder received a randomized combination of three 4-week periods consisting of either sildenafil, or washout, or placebo [65]. Women reported improvements in sexual arousal and orgasm and increased frequency of sexual fantasies and intercourse with sildenafil [65]. These findings were replicated in premenopausal women with sexual arousal disorder and type I diabetes [66]. An in-laboratory study by Basson and Brotto [67], however, found that the administration of sildenafil (Viagra) among 34 postmenopausal estrogenized women did not improve sexual arousal or orgasm. Meston et al. [68] examined the effects of *Ginkgo biloba* in 68 sexually dysfunctional women. Women were randomly assigned to 8 weeks of *Ginkgo biloba* extract, sex therapy, placebo, or *Ginkgo biloba* combined with sex therapy. Long-term use of *Ginkgo biloba* alone did not have a significant impact on sexual functioning, though when combined with sex therapy, significant increases were noted for sexual desire and satisfaction compared to placebo. Sex therapy alone significantly increased orgasmic function.

Several studies have examined potential pharmacotherapies for treating FOD induced by medications such as SSRIs, antipsychotic, and antiepilepsy drugs. Drugs tested as antidotes include antiserotonergic agents, such as cyproheptadine, buspirone, mirtazapine, and granisetron; dopaminergic agents, such as amantadine, dextroamphetamine, bupropion, methylphenidate, and pemoline; adrenergic agents, such as yohimbine and ephedrine; cholinergic agents, such as bethanechol; and the selective phosphodiesterase type 5 inhibitors. Numerous case reports and open-label studies examining SSRI-induced anorgasmia report success in alleviating reduced orgasmic function with some of these agents. However, placebo-controlled studies generally have not shown differential effects across these active treatments and placebo (for review, see Meston et al. [58]).

Hormone manipulation for the treatment of sexual dysfunction among cancer survivors has primarily consisted of either estrogen or androgen therapy [32, 69]. Cancer treatments such as chemotherapy and hysterectomies may lead to impaired ovary function [85]. Ovarian failure results in decreased levels of androgens and estrogen which, in turn, can impair sexual functioning, particularly sexual arousal [70]. Much of the hormone replacement research is dedicated to the alleviation of menopausal symptoms, natural and chemotherapy-induced, which include changes in one's sexual function (for a review, see Hickey et al. [71]).

A case series conducted by [84] found that oral esterified estrogen with methyl-testosterone (known commonly as the testosterone patch) improved sexual desire and arousal in three women with a history of recent breast cancer, one of which reported an increase in orgasmic function. Although hormone treatment has been shown to be effective and well tolerated (e.g., [72, 73]), certain risks have been identified. Findings from the Women's Health Initiative conducted across 40 US clinical sites conservatively suggest that hormone therapy may be linked to increased risk of heart disease and stroke and that beginning hormone therapy closer to menopause decreases the risk of heart disease [73–75].

Complementary and alternative treatments are used by cancer patients primarily to alleviate symptoms and side effects due to the disease itself and conventional treatment. Several survey studies have found that usage rates range from 9 to 91% across a variety of cancer diagnoses [76–80]. Therapies include (1) physical interventions such as yoga, acupuncture, massage, and therapeutic touch, (2) mind–body methods including relaxation techniques, music therapy, and meditation, (3) dietary remedies such as herbs, homeopathy, specific diets, and vitamins, and (4) alternative medical systems including Chinese medicine and ayurveda, a traditional Indian medicine [59, 81]. Studies assessing the efficacy of these treatments have found that there are benefits to the patients regarding subjective reports of relief of side effects and increased coping ability [81], although the known effects of alternative treatments on sexual difficulties among cancer patients are limited (Table 11.2).

Table 11.2 Studies for the pharmacological treatment of orgasm dysfunction

References	Design	*N*	Drugs	Conclusion	Level of evidence
Antidepressants					
Michelson (2000)	Randomized, placebo-controlled; 4 weeks	57 women with fluoxetine-induced sexual difficulty	Amantadine (50, 100 mg), buspirone (20, 30 mg); fluoxetine continued during tx	Improved orgasm with tx and placebo; no difference between tx vs. placebo	Daily diary and clinician interview
Modell et al. [63]	Single-blind, placebo-controlled; 12 weeks	20 nondepressed women reporting nonphysiological orgasmic difficulty	3-week bupropion-SR (150 mg), 3-week bupropion-SR (300 mg)	Significant improvement of satisfaction with orgasm intensity and overall sexual satisfaction beyond placebo	Sexual function questionnaire
Zajecka et al. [64]	Cognitive behavioral analysis system of psychotherapy, nefazodone, or combined for 12 weeks	431 women; 65% reported depression; 48% reported sexual dysfunction	Nefazodone (200–600 mg)	Nonsignificant improvement in orgasm with psychotherapy, nefazodone, and combination groups at 12 week compared to baseline	Sexual function questionnaire, physician-rated depression severity
Phosphodiesterase inhibitors					
Caruso et al. [65]	Double-blind, crossover; 12 weeks	51 premenopausal women with sexual arousal disorder	Sildenafil (25–50 mg)	25 and 50 mg sildenafil increased orgasm frequency, compared to placebo and baseline; placebo increased orgasm relative to baseline	Sexual function questionnaire at baseline and monthly
Basson et al. [17]	Randomized, double-blind, placebo-controlled; two sessions	34 oestrogenised postmenopausal women with acquired genital female sexual arousal disorder and impaired orgasm	Sildenafil (50 mg)	Reduced latency to orgasm for low vaginal pulse amplitude responders only	Genital arousal (vaginal pulse amplitude); orgasm latency (timed), and intensity (self-report)
Caruso et al. [66]	Double-blind, crossover, placebo-controlled; 16 weeks	32 premenopausal women with type I diabetes and seasonal affective disorder	Sildenafil (100 mg)	Increased clitoral blood flow and improved subjective sexual experience (arousal, orgasm, sexual enjoyment, dyspareunia) with sildenafil	Sexual function questionnaire

(continued)

Table 11.2 (continued)

References	Design	*N*	Drugs	Conclusion	Level of evidence
Alternative treatments					
Ito et al. [86]	Double-blind placebo-controlled; 4 weeks	77 women, 6 with previous sexual dysfunction	ArginMax herbal supplement (ginseng, gingko, damiana, L-arginine)	47% in ArginMax tx improved orgasm function at 4 weeks vs. 30% in placebo	Sexual function questionnaire
Michelson et al. [87]	Double-blind, randomized, parallel, placebo-controlled; 10 weeks	148 premenopausal women with fluoxetine-induced sexual dysfunction	Mirtazapine (15–30 mg), yohimbine (5.4–10.8 mg), olanzapine (2.5–5 mg)	No differences between tx and placebo in diary or self-report ratings of orgasm function	Daily diary, sexual function questionnaire, structured interview
Meston et al. [58]	Cross-over, double-blind, placebo-controlled; 8 weeks	19 women with SSRI-induced sexual dysfunction	Ephedrine (50 mg)	Significant increase in orgasmic ability compared to baseline, but not placebo	Sexual function questionnaire
Meston et al. [68]	Randomized, placebo-controlled; 8 weeks	167 sexually dysfunctional women	Gingko biloba extract (300 mg)	Short-term use increased genital arousal response; long-term sex therapy alone increased orgasm function	Genital arousal (vaginal pulse amplitude), clinical interview, sexual function questionnaire
Hormonal treatments					
Krychman et al. [84]	Open-label; case series	3 women with history of breast cancer	Testosterone, varied administration	Sexual satisfaction and desire improved for two of three women	Comprehensive sexual medicine evaluation

Conclusion

This chapter provided a summary of FOD, highlighting the prevalence of orgasm dysfunction among female cancer survivors. A cancer diagnosis can significantly impact a patient's sexuality as the cancer itself, and its treatment has a variety of physiological and psychological side effects. The array of therapies available to treat FOD offers women with cancer the opportunity to regain their sexual identities and capacity for response as they focus on achieving a high standard of health overall.

In order for female cancer survivors to gain access to these treatments, it is imperative that sexual oncology be incorporated into a patient's treatment regimen. In order to fully understand and effectively address orgasm concerns among this group, physicians must broaden their focus to all elements of their patients' well-being, which includes sexual fitness. Assessing sexual function at the time of diagnosis and throughout treatment will provide data that researchers can use to develop therapies more finely tailored to the patient's needs.

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Chapter 12
Sexual Pain Disorders

Corrie Goldfinger and Caroline F. Pukall

Keywords Adjuvant treatment • Anodyspareunia • Anxiety/fear • Biofeedback • Chemotherapy • Cognitive-behavioral therapy • DSM • Dyspareunia • Hormones • Hysterectomy • Injectable therapy • Menopause • Oopherectomy • Pain • Pelvic floor muscles • Physical therapy • Topical therapy • Tricyclic antidepressants • Vaginal atrophy • Vaginal dilation • Vaginismus • Vestibulectomy • Vulvodynia

Introduction

Sexual pain disorders encompass a broad array of conditions which lead to difficult or painful sexual intercourse. The term dyspareunia is used in this chapter to describe recurrent or persistent urogenital pain that interferes with sexual and/or nonsexual activities. Prevalence estimates of dyspareunia ranged from 0.4 to 61% in one recent systematic review [1], and there is considerable evidence to suggest that these varying rates reflect the inconsistency of dyspareunia definitions as well as differences in study design and measurement [1–3]. Women with dyspareunia, in general, suffer negative impacts in psychosocial and sexual areas of their lives [4]. Despite the common clinical complaint of dyspareunia, there is still limited knowledge regarding its etiology and effective treatment strategies. The lack of knowledge surrounding this multifaceted condition only serves to increase the difficulty inherent in its assessment and management.

This chapter focuses on conditions that cause dyspareunia in women and attempts to conceptualize them within a biopsychosocial framework. The majority of the chapter covers pain conditions considered to be idiopathic (i.e., with no known physical cause); however, organic pain conditions (i.e., those due to medical conditions) are also summarized. Sexual pain disorders in men are briefly outlined, and the chapter concludes with a discussion of sexual pain experienced by patients with cancer.

Classification of Sexual Pain Disorders

Two main challenges in reviewing the sexual pain disorders are: (1) the varying methods of classification and definitions by medical and psychiatric bodies, as well as various authors, and (2) the current discrepancy between the classification systems and empirical findings. The DSM-IV-TR [5] definition of sexual pain disorders within the sexual dysfunction category includes dyspareunia and vaginismus not solely due to medical conditions, while their organic counterparts are coded as sexual dysfunctions due to a general medical condition. Dyspareunia is defined as "recurrent or persistent genital pain associated with sexual intercourse," (p 556) while vaginismus is "recurrent or

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persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with intercourse" (p 558). Diagnostic criteria also require that pain specifiers be placed on the cause of the pain (due to psychological factors, or due to combined psychological and medical factors), and whether the condition is lifelong or acquired and global or situational.

As will be discussed in further detail later, there are a number of concerns related to the definition of vaginismus given findings from empirical studies. Additionally, the DSM-IV-TR makes a clear distinction between organic and idiopathic pain. Pukall et al. [6] have argued, however, that there is neither empirical nor theoretical support for this distinction. They further purport that this distinction may lead health professionals to assume a psychogenic cause of the pain if no medical cause can be found, which can often result in the woman being told that the pain is "all in her head," leading to a referral to a psychiatrist or other mental health professional. Furthermore, by classifying dyspareunia as a sexual dysfunction, the attention is placed on sexual aspects of the disorder, rather than on the major clinical symptom of the disorder, pain. This classification is therefore being challenged by a body of evidence that supports the conceptualization of dyspareunia as a pain disorder that interferes with sexual function rather than as a sexual dysfunction per se [7–9]. Classifying dyspareunia as a pain disorder may lead to different ways of investigating the causes of the pain and to more appropriate treatment modalities.

Another classification system is that of the International Society for the Study of Vulvovaginal Disease (ISSVD). This system is specific to vulvar pain conditions and is in line with viewing dyspareunia as a pain, rather than a sexual, disorder. This classification system (summarized in Table 12.1) organizes vulvar pain into two categories: (1) those related to a specific disorder, and (2) vulvodynia. Vulvodynia is defined as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable neurologic disorder" [11] (p 775). Vulvodynia is further classified into subtypes depending on (1) the location of the pain [i.e., localized (pain in a particular vulvar area) versus generalized (pain affecting the whole vulvar region)], and (2) the temporal characteristics of the pain [i.e., provoked (pain that only occurs when elicited by some form of pressure), unprovoked (pain that exists on a constant basis and needs no provocation), or mixed (a combination of provoked and unprovoked pain)]. The criteria also stipulate that provoked pain can be elicited in sexual and/or nonsexual situations. Although this system does not take into account all forms of dyspareunia (e.g., deep pelvic pain), it provides a model to classify sexual pain disorders such that the focus is on the primary presenting symptom of pain.

Table 12.1 Classification of female vulvar pain disorders and male sexual pain disorders

Classification of vulvar pain	Classification of sexual pain disorders in men
Type 1: Vulvar pain related to a specific disorder	*Type 1*: Isolated ejaculatory pain (pain during or after ejaculation)
(a) Infectious (e.g., candidiasis)	(a) Identifiable cause
(b) Inflammatory (e.g., lichen planus)	(b) Idiopathic
(c) Neoplastic (e.g., squamous cell carcinoma)	*Type 2*: Pain associated with sexual activity, as part of chronic pelvic pain syndrome (CPPS)
(d) Neurologic (e.g., herpes neuralgia)	*Type 3*: Painful genital conditions (e.g., chronic testicular pain) which interfere with sexual activity or are associated with sexual dysfunction
Type 2: Vulvodynia	*Type 4*: Other causes of sexual pain
(a) Generalized	(a) Penile causes (e.g., phimosis)
(i) Provoked	(b) Other types of sexual pain disorder (e.g., anodyspareunia)
(ii) Unprovoked	
(iii) Mixed	
(b) Localized	
(i) Provoked	
(ii) Unprovoked	
(iii) Mixed	

Adapted from Luzzi and Law [10] and Moyal-Barracco and Lynch [11]

Sexual Pain Disorders

Pain Related to a Specific Disorder

Table 12.2 summarizes a variety of conditions that can cause recurrent or persistent dyspareunia in women. As evidenced by this extensive, yet likely nonexhaustive, compilation of conditions, it is important that a thorough medical history interview and physical exam be conducted to rule out physical illness or abnormalities as the cause of the pain. Goldstein [13] delineates the broad array of issues that should be addressed in the medical history interview and encourages that the health professional obtaining the history be sensitive to the woman's concerns, validate her emotional responses to her pain, and allow the woman to tell her story while guiding them through the process to get as much detailed information as is required. The areas covered in the medical history interview for women presenting with sexual pain include: past and current urogynecological functioning and concerns, urogenital and other pain history, voiding habits, dermatological concerns, sexual functioning, and mental health. The ISSVD website (www.ISSVD.org) has an extensive questionnaire that women can fill out before seeing their doctor. The physical exams conducted will depend on the information obtained during the interview but may include the following: visual examination of the vulva, preferably with the use of vulvoscopy; sensory exam using a cotton swab (see Section "Assessment" under "Vulvodynia" below for further details); speculum exam of the vagina; manual exam with one finger to assess the urethra, bladder, and pelvic floor muscles (PFMs); bimanual exam to assess the uterus and adnexa; and a rectovaginal exam. A number of tests may also be conducted based on the physical exams and could include: wet mount and cultures of vaginal discharge, vulvar or vaginal biopsy, serum testing, medical imaging, diagnostic laparoscopy, cystoscopy, or colonoscopy. Although it is important to rule out specific medical causes for sexual pain in women, due to the painful nature of these women's concerns, exams and tests should only be performed when there is sufficient reason to believe that their outcome will be helpful in determining a diagnosis.

Vulvodynia

The two main subtypes of vulvodynia are provoked vestibulodynia (PVD; previously called vulvar vestibulitis syndrome), characterized as

Table 12.2 Causes of dyspareunia

Disorders of the vulva	Vaginal disorders	Disorders of the pelvic area	Disorders of the urinary and gastrointestinal tract
Infections (bacterial, viral, fungal)	Congenital factors (vaginal agenesis, duplication, septation)	Hysterectomy	Acute and chronic cystitis
Irritation (mechanical, chemical)	Structural abnormalities from surgery or radiation	Adenomyosis of uterus	Interstitial cystitis
Dermatoses	Pelvic organ prolapse (cystocele, rectocele, enterocele)	Ovarian pathology	Urethral lesions
Vulvar papillomatosis	Atrophic vaginitis	Prolapsed adnexa	Urethral diverticulum
Hymenal stenosis	Vaginitis	Leiomyoma or benign tumors of the uterus	Urethritis
Adhesions	Infections	Salpingitis	Fistulas
Trauma	Inflammatory or allergic reaction	Pelvic inflammatory disease	Inflammatory bowel disease
Episiotomy scars		Endometriosis	Diverticulitis
Decreased lubrication		Pelvic adhesions	Hemorrhoids
Peri/postmenopausal or lactation atrophy		Pelvic floor muscle dysfunction	Crohn's disease
Estrogen deficiency		Pelvic venous congestion	
Inflammatory or allergic reaction		Neuropathies (nerve entrapment)	
Cancer (radiation)			

Adapted from Glazer [12]

localized and provoked pain of the vulvar vestibule, and generalized vulvodynia (GVD), characterized as generalized and unprovoked pain. There is some controversy, however, over the distinction between the various subtypes of vulvodynia based on location and temporal pattern because many women have pain that is both localized and generalized [14, 15].

PVD is the most common form of vulvodynia. It is typically described as a sharp or burning pain at the entrance of the vagina in response to contact or pressure to the vulvar vestibule. Friedrich [16] outlined the three diagnostic criteria for PVD: (1) severe pain upon vestibular touch or attempted vaginal entry, (2) tenderness to pressure localized within the vulvar vestibule, and (3) physical findings limited to vestibular erythema (i.e., redness) of various degrees. Only the first two criteria have shown to be diagnostically valid and reliable [17]. The onset of pain may be at first intercourse attempt (i.e., primary PVD) or may develop after some period of pain-free intercourse (i.e., secondary PVD). Alternatively, women with GVD describe chronic vulvar discomfort that is not dependent on contact, characterized by a burning or stinging sensation covering the entire vulvar region (e.g., labia minor and majora, perineum). Some women with GVD may also meet the diagnostic criteria for PVD.

A diagnosis of vulvodynia is a diagnosis of exclusion, i.e., specific causes for the pain must be ruled out. It is based on the woman's self-report of vulvar pain (i.e., pain location, quality, and description), and in the case of PVD, the diagnosis is also dependent on the presence of pain during the cotton swab test (the standard gynecological method for diagnosing PVD [16]).

Epidemiology

A population-based study estimated the prevalence of vulvodynia in an ethnically diverse sample of almost 5,000 women between the ages of 18 and 64 in the United States [18] and found a lifetime prevalence rate of 15.6% for chronic vulvar pain. A majority of these women (12.4%) reported a pain pattern consistent with PVD (i.e., excessive pain on contact with attempted insertion or penetration), while fewer (3.3%) described pain consistent with GVD (i.e., chronic burning or knife-like pain). The authors found that although the prevalence of PVD-like symptoms decreased with age, GVD-like symptoms maintained the same prevalence across age groups. Furthermore, although Caucasian and African-American women had similar prevalence rates, Hispanic women were 80% more likely to have chronic vulvar pain [18].

Etiology

Research into the etiology of vulvodynia has been varied and sometimes inconsistent, leading to the conclusion that there are likely multiple etiological pathways for and numerous maintaining factors of the pain. Table 12.3 summarizes research findings supporting various etiological theories for PVD. Several studies investigating vestibular

Table 12.3 Etiological theories of provoked vestibulodynia

Vestibular tissue factors
Increased inflammatory mediators [19]
Increased nerve fiber innervation [19–22]
Increased subepithelial heparanase activity [23]
More pain receptors [24]
Increased blood flow [25]
Increased pain-related peptides [26]
Central nervous system dysfunction
Increased sensitivity to vestibular touch [27–30]
Increased sensitivity to touch in nonvestibular areas [30, 31]
More pain related complaints [30, 32, 33]
Increased neural response to vestibular touch and pain [34]
More grey matter in pain-related brain areas [35]
Genetic factors
Higher incidence of alleles associated with abnormal regulation of inflammation [36–38]
Higher incidence of alleles associated with immune defence against micro-organisms [36]
Hormonal factors
Higher risk of PVD in oral contraceptive users [39–41]
Higher risk of PVD in those with early menarche and painful menstruation [39, 42]
Decrease in estrogen receptor expression [43]
Oral contraceptive pills changes in hormonal reception and morphology of vestibule [44, 45]
Pelvic floor muscle dysfunction
Increased pelvic floor muscle tone [46–48]
Pelvic floor muscle instability, poor contractile strength, and poor recovery after contraction [49]

tissue differences between women with PVD and nonaffected women support that altered pain processing plays a role in PVD. It has been proposed that these vestibular factors could lead to a heightened sensitivity in response to pressure applied to the vestibular tissue, which has been previously demonstrated [27, 30]. Interestingly, the increased sensitivity exhibited by women with PVD is not restricted to the vestibule. Evidence from controlled quantitative sensory testing (QST) and brain imaging studies supports a central, in addition to a peripheral, pain modulatory dysfunction in women with PVD [28–30, 34]. This combination of findings supports a general view of PVD as a neuropathic pain condition.

Further implicating the role of systemic factors are findings of a higher incidence of several alleles in women with PVD, supporting a possible genetic contribution. One hypothesis for this contribution is that women with PVD who present with some of these alleles may be at increased risk for an inflammatory immune response following some trigger (e.g., yeast infection, vulvar injury) and may not have the ability to terminate this response. The prolonged inflammation may trigger other changes and lead to an increased sensitivity both within and outside the vestibule [37, 50]. Alternatively, the presence of some alleles might increase susceptibility to a lower genital tract infection by a micro-organism that may cause symptoms of PVD [36]. Other findings support a hormonal contribution to PVD, although the exact causal mechanism is not clear. One possibility is that alterations in the hormonal milieu may lead to increased sensitivity of the vestibule in affected women [44].

It has also been suggested that PVD may be associated with PFM dysfunction. This theory is based on the findings of PFM dysfunction in women with PVD as well as improvements in PVD symptoms following PFM treatments such as electromyographic biofeedback [46]. Reissing et al.'s [48] study on hypertonicity (i.e., increased tone) of the PFMs in women with PVD suggests that hypertonicity likely results from, rather than causes, PVD. The authors posit that the tension acts as a maintaining and exacerbating factor in PVD.

Research into the etiology of GVD has been scarcer and less clearly conceptualized as compared to PVD. The onset of GVD commonly follows some acute event, with highly reported triggers being local treatments such as vulvar cream application or laser surgery [51]. GVD has been conceptualized as a neuropathic pain condition for some time, with early research pointing toward changes in cutaneous perception as a cause for the pain [52], and more recent findings suggesting possible complex regional pain syndrome (CRPS) or pudendal neuralgia [53, 54]. Further support to this theory are the findings that women with GVD are more likely to have other CRPSs such as interstitial cystitis [55, 56]. Similar to PVD, PFM dysfunction, including hypertonicity and instability of the muscles, has been implicated in GVD [57].

Given the multitude of etiological theories for both PVD and GVD, it has been suggested that either subtype of vulvodynia may be caused by more than one factor and that the contributing factors likely differ for each woman [58].

Psychosocial Factors

Numerous psychological, sexual, and relational factors have been investigated in women with vulvodynia; however, due to the correlational design of the studies, psychosocial and sexual factors associated with vulvodynia can neither be attributed as causes nor as resulting from the pain. These factors, however, are more commonly conceptualized as consequences of pain. Knowledge of these issues helps to better understand the experiences of affected women and may guide treatment planning.

Research has shown that vulvodynia is associated with negative impacts such as reduced quality of life, including feeling out of control of one's life and body [59]. Numerous studies have also found significantly higher levels of psychological distress, including depression and state and trait anxiety, in women with vulvodynia as compared to nonaffected women [4, 60–63]. Moreover, affected women show differences in pain-related cognitions, including greater

degrees of hypervigilance and catastrophizing [30, 64, 65].

In addition to psychological impacts, vulvodynia also has consequences on sexual functioning, given the intimate connection between vaginal penetration and the experience of pain. Studies examining women with vulvodynia and those comparing affected and nonaffected women demonstrate negative effects on sexual desire and arousal, lower intercourse and orgasmic frequency, poorer vaginal lubrication, lower sexual self-concept, and lower sexual satisfaction scores [61, 66–70]. Not surprisingly, many women reduce the frequency of or completely stop sexual activity due to pain [59]. Furthermore, women with vulvodynia are less likely to make sexual advances, more likely to refuse a partner's sexual advances, and more likely to participate in partnered sexual activity despite the lack of desire to do so [61, 68–70]. Women also report negative impacts on self-esteem, self-confidence, and body image following the onset of their vulvar pain [69]. Although it would be intuitive to assume poorer relationship functioning among women with vulvodynia, the empirical findings in this area are mixed, with some studies finding no differences between affected and nonaffected women [4, 71, 72], and others finding poorer relationship functioning and satisfaction among affected women [70, 73].

This pattern of findings suggests that vulvodynia has a widespread negative impact on affected women's lives, and it supports conceptualizing vulvodynia from a biopsychosocial viewpoint. This perspective emphasizes that biological, psychological, and social factors are seen as fundamental to understanding and treating women with vulvodynia. Once vulvar pain has been present for some time, a vicious cycle of pain is put into motion (see Fig. 12.1) in which psychological factors (e.g., anxiety, catastrophizing), sexual and relationship difficulties (e.g., decreased desire and arousal), and pelvic floor muscle dysfunction (e.g., hypertonicity, heightened reactivity) – which initially result from the pain – lead to further increases in pain and distress. The continuous interaction of all of these factors explains pain maintenance and possible exacerbation despite the absence of physical findings for the pain.

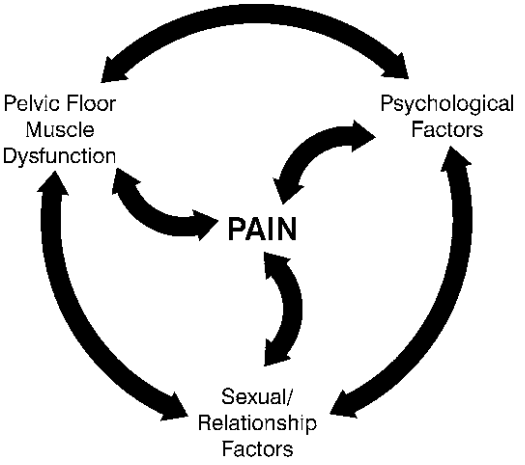

Fig. 12.1 The vicious cycle of pain

Assessment

It has been recommended that the assessment of vulvodynia takes a multidisciplinary approach where possible [74]. This assessment would include a mental health professional to conduct the clinical interview, and a gynecologist and physical therapist to conduct the physical exams. Thus far, the only vulvodynia diagnostic assessment is the cotton swab test, the standard gynecological test for diagnosing PVD [16]. The test consists of palpating vulvar sites with a cotton swab in a randomized fashion to control for sensitization [75] while recording the woman's pain ratings upon palpation. Although it has good clinical utility, measurement error due to inconsistency of pressure application is inherent in the test and, therefore, it may not be reliable for research use. Pukall and colleagues [76, 77] therefore developed the vulvalgesiometer, a tool that exerts standardized pressure to the vulva to measure pressure pain thresholds in a clinical research setting, and can be useful in detecting differences in pain sensitivity as a result of treatment. Given the role that PFM functioning plays in both PVD and GVD, a formal evaluation of the PFMs by a pelvic floor physical therapist is recommended for treatment planning because some treatment options may be less likely to result in complete pain relief if the muscle dysfunction is not addressed.

Other than the physical exams and tests used to rule out specific causes for sexual pain (see Section "Pain Related to a Specific Disorder" above), the clinical interview is the most important assessment tool with respect to diagnosing vulvodynia, as well as in treatment planning. The interview should provide the clinician with extensive information about the woman's history of pain (often best obtained through the natural history approach) as well as her current reasons for seeking treatment, pain mediators and the impact that pain has on various aspects of her life, comorbid disorders, and treatment history and outcomes. The use of standardized self-administered questionnaires to measure pain, sexual and psychological functioning, and relationship adjustment may prove useful to clinicians in obtaining more detailed information from the affected woman. Table 12.4 summarizes the information that should be obtained during the clinical interview.

Table 12.4 Clinical interview components for vulvodynia

Pain
Onset of pain (when did it start, antecedents)
Duration of pain
Location of pain
Perception of pain characteristics (e.g., quality, intensity)
Temporal pattern of pain (provoked vs. unprovoked vs. mixed)
Factors that trigger or exacerbate pain
Factors that reduce pain
Previous diagnoses and tests/assessments
Past treatments attempted and outcomes of those treatments
Perception of pelvic floor muscle tension
Medical history
Urogynecological functioning and concerns
Dermatological concerns and allergies
Comorbid disorders
Food and medication intake
Psychological functioning
Responses to pain (emotional, cognitive, and behavioral)
Impact of pain on mental health/well-being
Sexual and relationship history and functioning
Past sexual functioning
Impact of pain on sexual functioning (e.g., arousal, lubrication)
Sexual satisfaction
Past and current sexual practices
History of abuse
Relationship quality and interpersonal functioning
Partner's sexual or genital symptoms
Impact of pain on relationship functioning

Treatment

There are numerous treatment recommendations for both PVD and GVD; however, few treatment options have received empirical support from controlled studies or randomized controlled trials (RTCs). Treatment options can be categorized as: topical, injectable, systemic, surgical, psychological, PFM therapies, or alternative. Additionally, lifestyle changes are often recommended to these patients. Table 12.5 summarizes the various treatment options recommended for PVD and/or GVD. Although some of these recommendations are based on empirical findings, many are based on expert opinion and are yet to be empirically proven.

A recent review of various treatment options for PVD found success rates for medical treatments – including topical, injectable, and systemic medications – ranging from 13 to 67% [117]. In general, the studies investigating medical treatment options had numerous methodological limitations including the lack of control/comparison group(s), random assignment, blinded treatment evaluation, and definition of therapeutic success. In addition, some studies did not control for participants receiving additional treatments between the intervention and follow-up, leading to difficulties in assessing the outcome of the intervention under study. The authors of the review study conclude that, given the research conducted, lidocaine 5% applied daily and combined injections of both corticosteroid and lidocaine have the most promising outcomes in nonsurgical medical options.

This same review also investigated the extant literature investigating the effectiveness of surgical treatment options for PVD, yielding success rates ranging from 61 to 94% [117]. In one randomized trial, however, the surgery group had the highest

Table 12.5 Treatment options for vulvodynia

Medical/surgical treatment options	Behavioral, cognitive-behavioral, and alternative treatment options
Surgery [78–83]	*Psychological therapies* [78, 79, 99–102]
Vestibulectomy: (1) local excision, (2) total vestibulectomy, (3) perineoplasty (PVD[a], GVD[b])	Cognitive-behavioral therapy (group or individual format) (PVD[b], GVD[a])
Topical therapies [84–87]	*Pelvic floor therapies* [46, 57, 78, 79, 103–111]
Anesthetics (e.g., lidocaine) (PVD[c], GVD[a])	Electromyographic biofeedback (PVD, GVD)
Capsaicin (PVD)	Physical therapy (PVD[a], GVD[a])
Nitroglycerin (PVD, GVD)	Hypocontact vulvar therapy (PVD)
Estrogens (PVD[a], GVD[a])	Vaginal dilation (PVD, GVD)
Gabapentin (PVD, GVD)	Electrical stimulation (PVD, GVD)
Steroids (PVD[a], GVD[a])	*Alternative therapies* [112–116]
Injectable therapies [88–93]	Acupuncture (PVD)
Corticosteroids (e.g., betamethasone, methylprednisolone) (PVD[a], GVD[b])	Hypnotherapy (PVD)
Interferon (PVD[b], GVD[b])	Laser therapy (PVD)
Botulinum toxin type A (PVD, GVD)	*Lifestyle changes to reduce irritation in PVD and GVD*
Oral medication [94–97]	Cotton underwear
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, desipramine) (PVD[c], GVD[d])	Avoid fabric detergent and softeners on underwear
Anticonvulsants (e.g., gabapentin) (PVD[a], GVD[c])	Use of mild soap and not applying soap to the vulva
Other therapies [98]	Unscented and dye-free cotton menstrual pads
Local anesthetic nerve blockade (PVD)	Lubrication (without propylene glycol) during sexual activity

Note: Superscript letters refer to the percentage of clinicians who reported recommending the therapy for PVD or GVD based on Updike and Wiesenfeld's [123] survey

[a]25–49%

[b]0–24%

[c]50–74%

[d]75–100%

drop-out rate; in addition, a small percentage of participants who underwent this relatively invasive procedure reported worse outcomes following the treatment [78]. Therefore, although this procedure has shown to have the highest success rates of any treatment for PVD, it is not effective for all women and some women may choose to not undergo the procedure due to its invasiveness.

There is considerably less medically related treatment outcome research for women with GVD. In general, there is some limited empirical support for tricyclic antidepressants [95], gabapentin [94], and botulinum toxin type A [93]; however, these findings are based on small uncontrolled studies. Surgery is not generally recommended for women with GVD.

Cognitive-behavioral interventions for vulvodynia include pain management and sex therapy to target pain reduction and sexual functioning. Success rates ranging from 43 to 86% have been reported in three studies in which sex therapy and pain management were combined in a group format for women with PVD [99, 101, 102]. One recent study investigated individual cognitive-behavioral therapy (CBT) in women with various forms of vulvodynia, and found significantly greater improvements in pain and sexual outcomes compared to women who received supportive psychotherapy [100]. The effectiveness of group CBT in women with GVD has not yet been empirically tested, although the importance of treating the psychosexual and relationship functioning in women with all forms of vulvar pain is emphasized [118].

There have also been a number of empirical investigations of the use of treatments targeting the PFMs in women with vulvodynia. These studies have provided evidence for the effectiveness of surface electromyographic (sEMG) biofeedback [46, 47, 104, 108] as well as other single physical therapy modalities, such as

electrical stimulation [110] and vaginal dilation [107, 109, 111]. Some physical therapists, however, purport that certain therapies, such as biofeedback, should not be recommended as a solitary treatment modality [119]. Two studies have provided support for multimodal treatment of the PFMs (typically termed pelvic floor physical therapy) in women with PVD; these studies found evidence of improvements in both pain and psychosexual functioning [103, 106]. Regarding GVD, however, there is no empirical support for pelvic floor physical therapy despite its effectiveness in normalizing and facilitating normal muscle tone and in increasing PFM strength and desensitizing local tissues in women with PFM dysfunction [120].

Research on alternative treatment strategies including acupuncture [112, 115], hypnotherapy [113, 116], and laser therapy [114] is preliminary and has shown some success in treating women with PVD.

The most extensive treatment outcome study conducted to date has been a RCT comparing the short- and long-term effectiveness of vestibulectomy, group CBT, and sEMG biofeedback in the treatment of PVD [78, 79]. Success rates for the three groups were 68, 39, and 35%, respectively. Vestibulectomy resulted in significantly lower pain levels than the two other treatments at posttreatment, and this pattern was maintained when comparing vestibulectomy to biofeedback at 6 months posttreatment [78]. Both pain and psychosexual outcomes in all the three groups were maintained at a two and a half year follow-up [79].

Despite the importance placed on multidisciplinary treatment approaches for vulvodynia, only two published studies have assessed the effectiveness of multimodal treatment programs for PVD, and they only included nonmedical treatment modalities (physical and psychosocial therapies) [121, 122]. Although both studies resulted in positive outcomes, they did not include any control groups or standardized treatment protocols.

A recent survey including two scenarios, one of a woman presenting with PVD and another with GVD, was sent to American clinicians known to treat women with vulvar pain (e.g., gynecologists, dermatologists, family physicians) and asked them to identify what treatments they would use for the cases [123]. The most commonly reported treatments for PVD were tricyclic antidepressants, local anesthesia, and vestibulectomy. These treatments were used as first line therapy by 27, 35, and 3% of clinicians, respectively. The most commonly reported treatments for GVD were tricyclic antidepressants, gabapentin, and physical therapy, with these treatments being used as first line therapy by 55, 11, and 16% of clinicians. Results from this study indicated a broad array of variability in the treatment of vulvodynia across clinicians and support the need for more rigorous and controlled studies to aid in treatment planning.

In 2005, Haefner et al. [124] outlined a treatment algorithm for vulvodynia with the recommendation that treatment should follow the following progression: vulvar care measures, topical medications, oral medications, injections, biofeedback/physical therapy, low oxalate diet with calcium citrate supplementation, and CBT with sexual counseling. Surgery is recommended only in the case that this progression of treatment options does not provide adequate results. The algorithm may be helpful for some health care professionals as it offers a step-by-step approach to treatment; however, a number of authors support a more individualized treatment approach based on the interview and physical exams [125, 126]. Supporting a case-by-case treatment plan is the fact that there is no single treatment that has proven effective for all women; therefore, prognosis is never clear. Furthermore, it is important that women with vulvodynia develop realistic treatment goals and expectations as successful treatment may take time and a complete "cure" may not be achievable.

Dyspareunia in Postmenopausal Women

Dyspareunia is a commonly reported problem by postmenopausal women. Kao et al. [127] found point prevalence rates of postmenopausal dyspareunia ranging between 2 and 29% among population-based studies and much higher rates among clinical samples (11–45%). As compared

to the multiple etiological theories for vulvodynia in premenopausal women, postmenopausal dyspareunia has consistently been attributed to the cascade of events following declining levels of endogenously produced estrogens. These events include tissue aging, and cytological and chemical changes in the vagina, urethra, and bladder. These changes can result in vulvovaginal and urogenital atrophy, vaginal dryness [128–130], narrowing, and shortening [131, 132].

One recently published literature review investigating dyspareunia in postmenopausal women offers novel insight into the theoretical and methodological limitations of research in this area [127]. This review critically examined the five extant studies investigating the relationship between postmenopausal dyspareunia and either estrogen levels or vaginal atrophy and found inconsistent relationships between the presence of dyspareunia and estrogen levels. It also concluded that not one single study evidenced a significant relationship between the presence of dyspareunia and vaginal atrophy. These findings suggest that factors other than hormone-related changes may be involved in the development of postmenopausal dyspareunia.

Several authors have pointed to the importance of psychosocial factors in contributing to or maintaining sexual dysfunction in postmenopausal women including negative perceptions of menopause, poor body image, negative attitudes towards postreproductive sexuality, relationship difficulties, partner sexual dysfunction, and loss of social support [133, 134]. Pukall et al. [6] therefore point out the importance of assessing for possible nonbiomedical factors that may play a role in postmenopausal dyspareunia in addition to the physical exam, the collection of hormonal assays, and cytological evaluations.

There are currently mixed findings with respect to the effectiveness of various hormonal regimes in treating postmenopausal dyspareunia with concurrent vaginal atrophy [135–138]; however, hormone replacement therapy (HRT) is currently considered the primary intervention for postmenopausal dyspareunia [139]. Findings from a randomized, open-label study resulted in a recommendation that nonhormonal moisturizers such as Replens® (Lil' Drug Store Products, Cedar Rapids, IA) be offered to those women who wish to avoid HRT [139]. Although there are no empirical studies evaluating their effectiveness, sex therapy, couples therapy, and physical therapy have also been recommended as treatment avenues in postmenopausal women with dyspareunia [131, 140]. In line with the inclusion of nonhormonal treatments for this population, Kao et al. [127] encourage the empirical study of the role of psychosocial factors in these women.

Vaginismus

Vaginismus has received much criticism from both researchers and clinicians, mainly surroundings its definition and its classification as a sexual pain disorder. The main argument against its current definition is that there is no empirical basis for including vaginal spasm as a diagnostic criterion given that muscle spasms are neither exclusive nor specific to vaginismus [47]. As with dyspareunia, the classification of vaginismus as a sexual pain disorder and the wording of its definition focus on the sexual nature of the condition to the exclusion of its more central behavioral and cognitive components, and disregard the interference that the condition has on nonsexual activities such as tampon insertion and gynecological exams. Another major concern related to the classification and definition of vaginismus is the role of pain. Pain is not currently a diagnostic criterion in the DSM-IV-TR and no information is provided on the pain characteristics (e.g., location, quality) of vaginismus.

There are also a number of researchers who purport that dyspareunia and vaginismus cannot be differentiated from one another given that: (1) vaginal penetration problems often present as a symptom of dyspareunia (e.g., in women with PVD) [141, 142] and are therefore not unique to vaginismus [143, 144], and (2) the PFM dysfunction that interferes with penetration is a

symptom in almost all women with vulvovaginal pain [48, 126]. Given the problems with the definition, and therefore the assessment, of vaginismus, accurate prevalence rates do not exist; however, in clinical settings, rates range from 12 to 17% [145, 146]. A consensus committee has recommended the following revised definition of vaginismus: "persistent difficulties to allow vaginal entry of a penis, a finger, and/or any object, despite the woman's expressed wish to do so. There is variable involuntary pelvic muscle contraction, (phobic) avoidance and anticipation/fear/experience of pain. Structural or other physical abnormalities must be ruled out/addressed" [147] (p 226).

A number of etiological theories exist for vaginismus. Some of the proposed theories include vaginismus as a result of PVD [141–143], PFM dysfunction (i.e., increased tone, poorer strength) [47], negative sexual attitudes [148–150], and a specific penetration phobia. The latter theory is supported by findings that fear of pain is the primary reason that women with vaginismus report for their avoidance of vaginal penetration [150]; in addition, affected women demonstrate strong emotional and behavioral reactions to attempted penetration and engage in active avoidance of penetration [47]. Although initially thought to play a role in the etiology of vaginismus, sexual abuse prevalence rates are not higher in women with versus without vaginismus [151, 152].

Like dyspareunia, the experience of vaginismus has been proposed to act cyclically (see Fig. 12.2), with either an initial negative or painful experience – or even a negative expectation about penetration – leading to symptoms of anxiety, including catastrophizing and fear of pain or penetration. These negative cognitions result in a woman either avoiding penetration or being hypervigilant to pain during attempts, which in turn, leads to pelvic floor reactivity and heightened tone during an attempt. This failed and likely painful event leads to confirm the woman's negative expectations of penetration [153].

Treatment outcome studies for vaginismus have investigated various treatment options

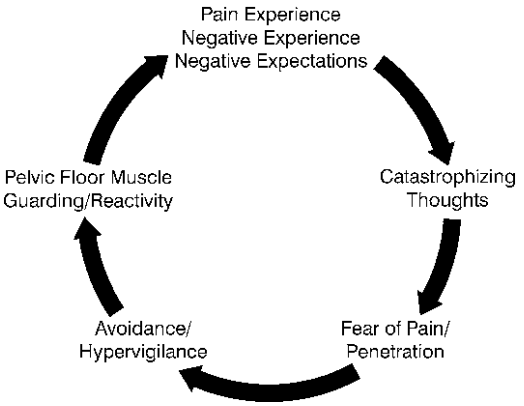

Fig. 12.2 The vicious cycle of vaginismus. Adapted from Reissing [153]

including anxiolytic medication [154], combined physical therapy modalities and cognitive-behavior therapy [155], surgery to widen the introitus [156], botulinum toxin injections [157], and topical anesthetic creams [158]. The standard treatment for vaginismus, however, includes vaginal dilation combined with progressive desensitization and relaxation techniques [153]. These techniques are often accompanied by education to improve sexual knowledge and attitudes, psychotherapy to reduce related psychological issues such as fear of pain or poor body image, and couple intervention to improve communication and understanding as well as sensate focus to aid in working toward penetration. A recent review of vaginismus treatment studies concluded that although uncontrolled studies indicate very positive outcomes, the same encouraging results are not found in the few controlled trials that exist [159]. A recent RCT resulted in modest effectiveness of the standard treatment for vaginismus with only 14% of women being able to have penetration at completion of the treatment [160]. When the same researchers conducted another study on the effectiveness of therapist-aided exposure to reduce fear and avoidance, much higher success rates were found, with 90% of women being able to achieve penetration [161]. As with vulvodynia, researchers support an individualized treatment approach for women with vaginismus [126].

Sexual Pain Disorders in Men

There is much less research available with respect to pain associated with sexual activity in men. Luzzi and Law [10] developed a definition and classification system for sexual pain disorders in men (summarized in Table 12.1). They proposed four broad categories which can be diagnosed in men over the age of 18 with a history of persistent or recurrent genital or pelvic pain during sexual activity. They also outline specific causes of ejaculatory pain which have been noted in the literature including seminal vesicle disorders (e.g., calculi, metastatic cancer), other pelvic causes (e.g., chronic pelvic pain syndrome (CPPS), urethral stricture), psychotropic medications (e.g., antidepressants, neuroleptics), mercury poisoning, and psychogenic factors. Like the ISSVD classification system of vulvar pain, this system distinguishes between organic and idiopathic pain. Also similar to sexual pain in women, prevalence rates vary considerably due to different definitions of male sexual pain. Lifetime prevalence rates range from 0.2 to 3%, with factors such as duration of pain and geographic region affecting rates [162–165].

One common cause of sexual pain in men is ejaculatory pain due to CPPS. The prevalence rate of CPPS is approximately 2–3% [166], and one study of men with CPPS indicated that 24% experienced persistent painful ejaculation [167]. Assessment strategies with men follow similar steps to that of women and include a thorough history taking; genital, abdominal, and pelvic examination; and various medical tests (e.g., urine sampling, diagnostic imaging) to rule out medical conditions. Management of idiopathic pain conditions follows the recommended approach to CPPS and include symptom assessment and control, role function and psychological factors, and sexual functioning [168].

One recent direction in research has been the study of anodyspareunia or the "recurrent or persistent pain experienced by the receptive partner during anal intercourse" [169] (p 289). This pain experience has been studied in men who have sex with men (MSM) and has been found to mirror female dyspareunia in a number of ways. For instance, prevalence rates were 12 [169] and 14% [170] in two studies of MSM. Furthermore, the pain during anal intercourse was reported to cause significant distress and/or interpersonal difficulty in a large percentage of the men studied. In addition to factors such as penis size, lack of lubrication, and lack of anal foreplay, a commonly reported hypothesized cause of the pain was psychological factors (e.g., degree of relaxation) [169, 170]. The authors propose that anodyspareunia should be added to future revisions of the DSM under the sexual pain disorders category, and they make recommendations for pain reduction including anal foreplay, deep breathing, and focused anal sphincter relaxation [170].

Dyspareunia and the Cancer Patient

Sexual dysfunction in cancer survivors, including dyspareunia, is considered to be multifactorial in that it can be a consequence of the cancer itself, a side effect of treatment, and/or due to psychological issues related to diagnosis, treatment, or other life issues. Relative contributions of cancer compared to the treatment effects are often unclear [171]; however, cancers that affect the pelvis (e.g., colorectal cancer) and sexual organs (e.g., cervical, ovarian, and vulvovaginal cancers in women, and penile, testicular, and prostate cancers in men) can all lead to dyspareunia even before diagnosis or treatment. The majority of empirical studies examining cancer survivors, nonetheless, have focused on sexual side effects of cancer treatments.

Treatment-Related Side Effects

The majority of research in the area of sexual side effects of cancer treatment has been conducted among women treated for breast or gynecological cancers. Although breast cancer and its surgical treatment do not cause dyspareunia, a

number of studies have focused on the systemic effects of adjuvant treatment. Dyspareunia has been documented in women following the use of chemotherapy, tamoxifen, anastrozole, and aromatase inhibitors and is attributed to vaginal dryness associated with reduced estrogen levels following treatment [172–174].

Although the use of chemotherapy and other adjuvant therapies for gynecological cancers can also lead to dyspareunia, research has focused on the impact of local therapies including surgery and radiation therapy (RT). The sexual side effects can be due to both local effects, such as scarring, and systemic effects, such as hormonal changes following removal of the uterus or ovaries. Treatment for cervical cancer with hysterectomy, trachelectomy, or RT can result in decreased vaginal lubrication, vaginal swelling upon stimulation, destruction of the vaginal epithelium, scarring, and perception of a shortened and/or inelastic vagina, all of which can lead to pain during intercourse [175–181]. Jenkins [182] also provided anecdotal reports of other consequences of RT for cervical cancer, including extreme sensitivity to touch at the vaginal introitus and local burning with exposure to semen. In studies investigating only cancer survivors, there have been contradictory findings with respect to which treatment for cervical cancer results in more frequent dyspareunia. One study comparing cervical cancer survivors to women in the general population, however, found that compared to control women, dyspareunia was only more frequent in women who had received RT [183]. Dyspareunia is also a commonly reported symptom following risk-reducing oophorectomy in women with ovarian cancer [184]. In the rare cases of vulvar cancer, vulvectomy can result in painful penetration due to scarring at the vaginal introitus. In addition to dyspareunia resulting from treatment of cancers affecting the sexual organs, studies have found high rates of painful intercourse in women following bone marrow transplantation [185], graft-versus-host disease after bone marrow transplantation [186], and surgery for colorectal cancers [187–189].

As with the general literature on sexual pain, little empirical work has been done with men. One study investigating men after surgery for penile cancer found that a small percentage experienced preoperative painful intercourse which resolved after treatment, while an even smaller percentage experienced newly acquired painful intercourse following surgery [190]. There have also been reports of pain with orgasm following radiation therapy for prostate cancer [191]. One methodological concern that may explain the limited amounts of information about sexual pain in male cancer patients is that studies report on general ejaculatory problems rather than specific symptoms, such as painful ejaculation.

Treatment of Cancer-Related Sexual Pain

There has been a growing literature base with respect to treatment strategies for dyspareunia among female cancer survivors with the focus placed on topical therapies. Local estrogen cream or pessaries, vaginal moisturizers such as Replens®, or water- and silicone-based lubricants are generally the first-line treatment for women with dyspareunia following cancer treatment; however, hormonal-based topical therapies are not recommended for women with hormone-receptive-positive breast cancer [192, 193]. Currently, there is no consensus on the safety of hormone therapy for women with breast cancer, especially if it is estrogen receptor positive [194, 195]; therefore nonhormonal lubricants should be attempted first. Empirically, this line of treatment has support from one study in which polycarbophil moisturizers showed significant reductions in dyspareunia following treatment for breast cancer [196].

Women who have undergone radiation therapy for gynecological cancers are required to perform graduated vaginal dilation [197], starting within the first few weeks following therapy, to maintain a certain degree of vaginal opening.

The use of dilators is recommended over several years in this population of women, although their use can be replaced with regular sexual intercourse if a woman is partnered and interested. Dilators can also be helpful in women following surgery for colorectal cancer or bone marrow transplantation for hematological cancer [198]. The use of vaginal dilators may also be helpful in reducing fear of pain during penetration and may help to prevent a cascade of events that can lead to long-term genital pain (e.g., PVD) or vaginismus. The regular use of Kegel exercises may also provide these benefits.

Amsterdam and Krychman [199] recommend a multimodal approach to the treatment of sexual pain following cancer including pharmacotherapy, sex therapy, and suggestions for specific problems. Sexual counseling among cancer survivors may include discussing alternative sexual positions to reduce pain, or building acceptance of sexual activities other than penetrative intercourse (e.g., oral sex, mutual masturbation, sensual massage) in the context of a supportive intimate relationship.

In general, cancer patients have reported that their physicians do not inform them of the sexual side effects of cancer treatment, and that at follow-up, they are not asked about sexual concerns [185, 200]. Although there is evidence to indicate that these discussions are important to patients [200], physicians may lack appropriate training or experience in discussing sexual issues, and furthermore, patients themselves may feel uncomfortable or embarrassed in bringing up these issues [201].

Summary

The classification of dyspareunia and vaginismus as sexual dysfunctions has been met with much criticism; further research into these conditions is required to better understand their etiology and pathophysiology such that appropriate definitions and classification, possibly as pain disorders, can be made. Dyspareunia is a common condition among both pre- and postmenopausal women and has significant and negative impacts on psychological and sexual functioning. It is likely that the causes of dyspareunia are multifactorial and unique to each woman; therefore, individualized and multidisciplinary assessment and treatment should be implemented. Dyspareunia is also a common complaint among cancer survivors following both local and systemic treatments. In patients with cancer, it is recommended that sexual side effects of treatment be discussed as part of the decision-making process and that follow-up related to sexual functioning be addressed.

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Chapter 13
Erectile Dysfunction: Prevalence and Pathophysiology

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Keywords Erectile dysfunction • Prevalence • Pathophysiology • NO • ET-1 • Testosterone • Rho kinase

Introduction

It was roughly 20 years ago when, in 1993, the US National Institutes of Health panel on impotence developed the rigorous definition for erectile dysfunction (ED), which was then described as the persistent inability to attain and/or maintain a penile erection sufficient to complete a satisfactory sexual intercourse [1]. In this context, a 3-month duration has been considered the minimum length of time necessary for actual establishment of the diagnosis, except in some instances of traumatic or surgically induced ED.

The launch on the market of oral phosphodiesterase type 5 inhibitor (PDE5-I) therapy in 1998 was associated with a surge in resource use for ED, as demonstrated by a 50% increase in physician office visits for ED throughout the subsequent years [2]. Likewise, as the mean life expectancy is progressively increasing, we should expect a steady increase in the number of men reporting ED and eventually seeking medical help. However, ED becomes a matter of sufficient medical interest to lead to a search for an appropriate therapy only when it causes personal distress either to the patient himself or to the couple. This definition is critical when evaluations of the prevalence of ED are considered, especially for ageing men. Indeed, even if it has been demonstrated that erectile function deteriorates progressively with ageing, only a scarce minority of patients who report some form of ED will finally request treatment when questioned [3].

Taking these aspects in mind, the aim of this chapter is to briefly review the data currently available on the epidemiology and pathophysiology of ED, mainly addressing the important concept of the ageing man.

Epidemiology of Erectile Dysfunction

In 1948, Kinsley et al. provided the first description of the association between ageing as a biologic factor and ED [4], showing a decline in overall sexual activity and erectile function quality coupled with the male ageing process. In that report, the incidence of ED was 25% in 65-year-old men and 75% in men aged >80 year [4]. These "historical" findings have been confirmed in a number of recent studies. Of major importance in the field is the original report from the longitudinal Massachusetts Male Aging Study, published in 1994, which detailed an overall ED incidence of 52% within a cohort of 1,290 men

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aged 40–70 years, with 10% of the study population experiencing severe ED [5]. Interestingly, within the same cohort of men, the probability of complete ED tripled with ageing from 5.1 to 15%, the probability of moderate ED doubled from 17 to 34%, and the probability of minimal ED remained constant at approximately 17%. An estimated 40% of the men included in the study were impotent at age 40 year, with an increase to 67% impotent men when they were aged 70 year. Likewise, in multivariate analyses, age reached the status of an independent predictor of ED even after adjusting for different clinical variables [5]. Similarly, the National Health and Social Life Survey, which assessed prevalence and predictors of various types of sexual dysfunction in both men and women, documented an incidence of ED of 18% in men 50–59 years old [6].

More recently, in a large population-based study, Saigal et al. found that in men aged 20 year and older, self-reported ED affected almost 1 out of 5 responders [7]. This prevalence dramatically increased in advanced age; 77.5% of men aged 75 years or older reported some form of ED [7]. In their multivariable analyses addressing the presence of ED, the authors found several associated medical conditions; however, across all prevalence studies, after having been adjusted for other factors, increasing age was the strongest predictor of ED [8]. In 13 studies that reported ED prevalence by decades of life, ED was reported between 2 and 15.9% for men in their 30s, between 9 and 39% for men in their 40s, between 16 and 67% for men in their 50s, between 27 and 76% for men in their 60s, and between 37 and 83% for men in their 70s [5, 6, 8–19] (Table 13.1).

Diabetes mellitus resulted in the greatest increase in ED risk of all medical comorbidities included in the models. In addition, risk factors such as obesity, hypertension, and cigarette smoking were also independently associated with ED [5, 6, 8–19]. In the National Health and Nutrition Examination Survey database, the overall prevalence of ED was 51.3% among people with diabetes [20].

Similar results were reported by Grover et al. [21], who analysed a cross-sectional sample of 3,921 men aged 40–88 year referring to primary care physicians. Using the International Index of Erectile Function (IIEF) [22], they recorded an overall prevalence of ED of 49%, defined as a score lower than 26 at the IIEF erectile function domain. Moreover, they demonstrated that cardiovascular disease, along with coronary artery disease, diabetes, either undiagnosed hyperglycemia or impaired fasting glucose levels, and a

Table 13.1 Prevalence of erectile dysfunction by decade of life [8]

				Decade of life				
References		Country	*n*	30–39 years (%)	40–49 years (%)	50–59 years (%)	60–69 years (%)	70–79 years (%)
Feldman et al. [5]	1998	USA	1.790	–	39	48	57	67
Laumann [4]	1999	USA	1.249	9	11	18	N/A	–
Braun [8]	2000	Germany	4.489	2.3	9.5	15.7	34.4	53.4
Chew [9]	2000	Australia	1.240	8.4	13.1	33.5	51.5	69.2
Kadiri [13]	2000	Morocco	646	5	–	–	56.7	–
Mahmoud [11]	2000	Egypt	594	15.9	–	–	35.7	–
Koskimaki [12]	2000	Finland	2.178	–	–	67	76	83
Glina [18]	2000	Brazil	825	2	9	16	27	49
Meuleman [10]	2000	Netherlands	1.779	10	–	–	–	78
Martin-Morales [14]	2001	Spain	2.476	1	1.7	4.5	11.7	–
Rosen [15]	2004	Multinational	27.839	11	15	22	30	37
De Boer [16]	2004	Netherlands	2.117	5.6	13.7	23.7	40	41.9
Ponholzer [17]	2005	Austria	2.869	–	28.9	37.5	–	71.2

N/A not applicable

formally diagnosed metabolic syndrome were independently associated with ED.

Currently, ED represents an important health problem both from the clinical and from the public health perspective. Based on the projected ageing of the population [23], it may be anticipated that it will affect an even larger proportion of men in the twenty-first century [24].

Pathophysiology of Erectile Dysfunction

Overview

Penile erection is a complex neurovascular phenomenon under psychological control. Erections are usually classified as *central*, *reflexogenic*, and *nocturnal* erections. In central erections, an initial stimulus arising from supraspinal centres travels through the spinal cord and reaches the corpora cavernosa, travelling finally along the cavernous nerves. Briefly, terminal branches of the cavernous nerves release several neurotransmitters involved in the erectile process [25].

In addition, endothelial cells lining the walls of the cavernous sinusoids release active mediators. Nitric oxide (NO), vasoactive intestinal polypeptide, acetylcholine, and a number of prostaglandins are considered the most important erectogenic neurotransmitters that ultimately lead to relaxation of the smooth muscle cells within the walls of the penile arteries and sinusoids. Relaxation of the intracavernosal sinusoids leads to blood filling the corpora cavernosa, with the subsequent compression of the subalbugineal venular plexus against the inner surface of the tunica albuginea, thus promoting the veno-occlusive mechanism of the corpora cavernosa. When this mechanism is activated, blood is actually entrapped within the corpora cavernosa, which become an isovolumetric reservoir. Further arterial inflow then leads to an increase in intracorporeal pressure and to penile rigidity. When ejaculation and orgasm are achieved, norepinephrine is released by neural adrenergic fibres within the corpora cavernosa and smooth muscle contraction is stimulated with subsequent penile detumescence.

The same cascade of events is also seen with reflexogenic erections, in which the triggering event is produced by mechanical stimulation of the dorsal nerve of the penis, which sends signals to the lumbosacral cord, where synapses with parasympathetic fibres travelling back to the corpora cavernosa occur. The continuous stimulation of the penis occurring naturally during sexual intercourse contributes to maintain activation of the descending neural pathways to the corpora cavernosa, sustaining penile rigidity until ejaculation or cessation of stimulation [26]. Nocturnal erections occur during rapid eye movement sleep from intrauterine life to late senescence and are still poorly understood [27, 28]. They are believed to represent a spontaneous mechanism for oxygenating the corpora cavernosa and maintaining the viability of cavernosal tissue [29, 30].

Abnormalities of erectile function have been traditionally classified as *neurogenic* (failure to initiate), *arteriogenic* (failure to fill), and *venogenic* (failure to store) [31]. However, the term *venogenic ED* should be viewed as affecting the anatomy and histology of the corpus cavernosum, leading to alteration of the cavernous veno-occlusive mechanism. In addition, abnormalities of the sex hormone milieu may significantly affect the quality of penile erections, and this aspect has attracted much interest with regard to its role in the ageing population [32].

Ageing

The process of ageing may affect all the pillars of the erectile process, including nerves, arteries, veins, cavernous tissue, and hormones. However, evidence in the literature of ageing-induced damage to these structures has certainly been influenced by the availability of techniques for identifying certain types of damage, and this is why vascular and endocrine abnormalities affecting the male erectile system seem to play a leading role in this regard. The process of ageing is multifactorial

in nature and depends on several factors, including but not limited to metabolic rate, genetics, lifestyle, and environmental conditions [33].

Independent of the initiating factor, the ultimate common pathologic process is damage to smooth muscle cells and an increase in the accumulation of fibrosis, which decrease the vasodilator response. Age-related smooth muscle dysfunction has long been recognised in the respiratory [34], gastrointestinal [35], and cardiovascular [36] systems. Ageing also affects the genitourinary tract and is associated with lower urinary tract symptoms [37] and sexual dysfunction [4–7, 21–24, 26, 29] in both men and women.

The exact mechanism that links ageing to smooth muscle dysfunction is not completely understood. Normal erectile function is a delicate balance between vasoconstrictor and vasorelaxant mediators on corporal smooth muscle tone [38]. Endothelium-derived NO (Fig. 13.1) and endothelin-1 (ET-1) have been individuated as modulators of erectile function. NO is a key regulator of cavernosal smooth muscle relaxation, whereas ET-1, being a potent vasoconstrictor agent, is believed to maintain penile flaccidity [39, 40]. Evidence suggests that there are age-related alterations in the levels of the latter modulators of erectile functioning when ED occurs [41–44]. Garban et al. demonstrated that decreased nitric oxide synthase (NOS) activity and a reduction in NOS-containing nerve fibres within the corpus cavernosum occur in the penis of ageing male rats [41]. Rajasekaran et al., in 2002, recorded age-related impairments in the expression of NO and ET-1 as well as in the production of growth factors, such as transforming growth factor-beta1 (TGF-β1) [44]. Defects in the production or release of neurotransmitters or the presence of antagonists could cause inhibition of cavernosal smooth muscle relaxation, resulting in inhibition of erection. However, another mechanism has been suggested by Chitaley et al. [45], who examined the role of the molecules involved in maintaining penile flaccidity.

Besides the well-established noradrenergic contraction mechanisms in the penis, an additional mechanism involving increased sensitivity to ionic calcium has been proposed [45, 46]. This pathway involves RhoA, a small monomeric G-protein that activates Rho-kinase. Activated Rho-kinase phosphorylates the regulatory subunit of smooth muscle myosin phosphatase

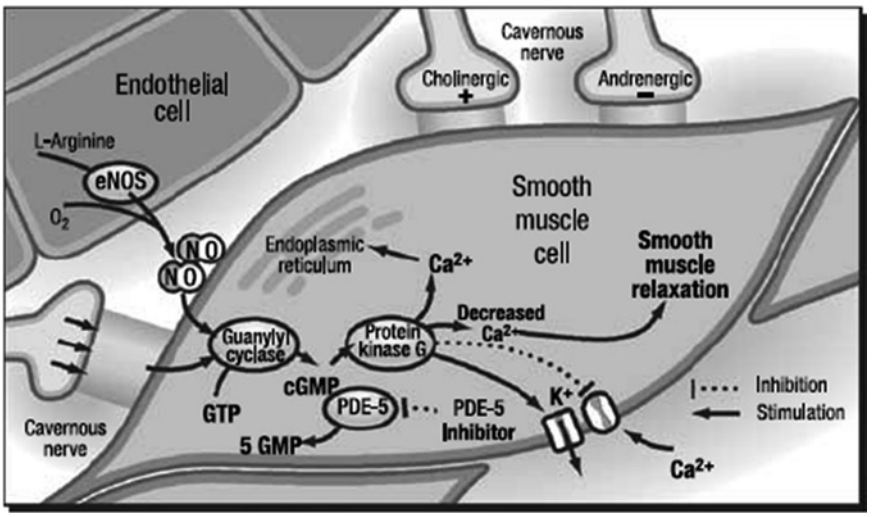

Fig. 13.1 Nitric oxide (NO) pathway of erectile function [112]. NO derived from the endothelium or cavernosal nerves signals guanylate cyclase, which then converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP), inducing a substantial increase in intracellular cGMP, causing smooth muscle relaxation via sequestration of intracellular calcium (Ca^{2+}) in the endoplasmic reticulum and inhibition of Ca^{2+} ion channels. Phosphodiesterase type 5 breaks down cGMP

(SMPP-IM). Inhibitory phosphorylation of SMPP-IM leads to the sensitisation of myofilaments to Ca^{2+} [47], which translates into smooth muscle contraction. An age-related increase in RhoA expression has been documented in rat vascular tissues, and this over-expression has been suggested as being responsible for age-associated vascular disorders [48]. Chitaley et al. showed that a specific inhibitor of Rho-kinase is able to relax vascular and non-vascular smooth muscle, and intracavernosal injection of this inhibitor in rats has been shown to induce penile erection [45]. Moreover, hypertension, which has been recognised as a well-known vascular risk factor for ED [49, 50], is associated with elevated penile RhoA levels [51]. In turn, inhibition of Rho-kinase activity has been demonstrated to be beneficial in attenuating the decline in erectile function in hypertensive rats [52]. In addition, Rho-kinase appears to be effective in reversing ED in castrated hypogonadic rats [53]. In summary, the net result of the impairment of erection regulators, such as NO, ET-1, and Rho-kinase, would be an increased penile smooth muscle tone, which may be responsible for the impaired erectile response seen in the ageing rats.

Vascular Disease

A further significant mechanism suggested as a potential cause of ED is pelvic atherosclerosis. Atherosclerosis-induced arterial insufficiency is a common clinical problem in the elderly and remains the leading cause of death in the adult population [54, 55]. The abdominal aorta and its branches, especially the bifurcation of the iliac arteries, are early and severely involved by atherosclerotic lesions [56]. According to the artery size theory proposed in 2003 by Montorsi et al., the atherosclerosis involvement of the penile district begins earlier because of the small size of the penile vessels and can anticipate severe vascular and coronary symptoms: ED can be considered the "tip of the iceberg" [57].

In animal models mimicking pelvic ischemia and hypercholesterolemia, Azadzoi et al. demonstrated an evident similarity in the smooth muscle alterations of the detrusor and of the corpora. In their report, chronic ischemia resulted in fibrosis, smooth muscle atrophy, and noncompliance of the bladder [58]. Chronic ischemia is also involved in the deterioration of cavernosal smooth muscle and in the development of corporeal fibrosis, which in turn may lead to ED [30, 59, 60]. Moreover, pelvic atherosclerosis may damage the pudendal-cavernous-helicine arterial tree [61]. In the early stages of atherosclerosis, this process results in decreased arterial blood flow to the corpora cavernosal and, as a consequence, leads to ED [60]. However, in more advanced stages, the erectile tissue loses its capability to produce the quantity of NO needed for smooth muscle relaxation, because of the down-regulation of the expression of the constitutive NOS [62]. In addition, elderly men are subjected to a decrease in smooth muscle content in the corpus cavernosum, which is associated with an impairment of the corpora expandability. This phenomenon is mostly responsible for the veno-occlusive dysfunction observed in the ageing male [63].

Chronic ischemia is also responsible of the over-expression of TGF-β1. This protein is a pleotropic cytokine demonstrated to be an essential mediator of tissue fibrosis [49]. Overproduction of TGF-β1 decreases the smooth muscle-connective tissue ratio by inducing the expression of collagen, fibronectin, and proteoglycans, while inhibiting the growth of smooth muscle cells and the activity of collagenase [64]. In this context, Azadzoi et al. [58] demonstrated that – at least in the rabbit – the level of TGF-β1 correlates with the severity of the fibrosis.

Oxidative stress is another important mechanism recently suggested as a potential factor in the pathogenesis of ED in the elderly. Oxidative damage to the vasculature caused by reactive oxygen species (ROS) plays a fundamental role in the natural ageing process [65–67]. The interaction between ROS and NO has been indicated as crucial to the development of ED [68]. Specifically, NO interacts with superoxide to form peroxynitrite, which has been reported to play a central role in atherogenesis [69]. In the

presence of peroxynitrite, the enzyme responsible for inactivating superoxide is inhibited, which in turn results in a further increase of peroxynitrite and may drive a reduction in the concentration of the available NO [70]. Moreover, peroxynitrite and superoxide increase the incidence of apoptosis in the endothelium, leading to a further decrease in available NO. Finally, the reduction in NO concentration increases the adhesion of platelets and leukocytes to the endothelial cells, which react with a vasoconstriction stimulus mediated by thromboxane A2 and leukotrienes [71]. Because the reduced availability of NO and long-term endothelial damage are the two most important causes of ED, the role of oxidative stress in the corpora cavernosa is a critical determinant in the pathophysiology of ED. Endothelial dysfunction represents the first step in the pathophysiology of ED and can anticipate a major peripheral vascular problem [72, 73].

FM/AS: *a paragraph or two on endothelial dysfunction?*

Endocrine Factors

The endocrine status plays a significant role in the regulation of erectile function/dysfunction. Several authors showed that a proper endocrine milieu is necessary for penile function: An alteration of one or more hormones can be the cause of ED [74–76]. Hypogonadism has been defined as a state of deficiency in gonadal function made manifest by deficient secretion of gonadal hormones and/or gametogenesis [77]. In ageing men, an alteration of the androgen production – and, consequently of the circulating levels of sex steroids – has been extensively described; when clearly symptomatic, such a deficiency has recently been renamed *symptomatic late-onset hypogonadism* [78–80].

Several hormones are affected by constant decrease throughout the ageing process, including testosterone, dehydroepiandrosterone (DHT), thyroxine, melatonin, and growth hormone [81]. Symptomatic hypogonadism is associated with numerous symptoms and signs, among them are decreased libido and erectile quality, decreased intellectual capacity (along with depression, fatigue, depressed memory, and impaired cognitive function), decreased lean body mass, decreased mineral bone density, decreased body hair and skin, and increased insomnia. Moreover, it is characterised by a gradual decline in serum total and bioavailable testosterone owing to a decrease in testicular Leydig cell number and in their releasing capacity as well as an age-related decrease in episodic and stimulated gonadotropin secretion [81–83]. The prevalence of hypogonadism has been addressed in several longitudinal studies and has been recorded in 2% of men younger than 50 years of age, while it ranges from 34 to 70% in patients aged 70–79 years [78, 81, 84, 85]. Briefly, the hypothalamic-pituitary-gonadal system is a closed loop of feedback control mechanism modulating and maintaining reproductive function; in this context, the gonadal hormones have inhibitory effects on the secretion of luteinising hormone (LH) and follicle-stimulating hormone. Testosterone represents the major secretory product of the testis and is the primary inhibitor of LH secretion in men [86]. However, other hormones are involved in LH suppression, such as estrogens and DHT.

In normal, healthy males, 2% of testosterone is free in the blood, 30% is bound to the sex-hormone-binding globulin (SHBG), and the other fraction is transported by albumin and other plasma proteins [87]. Bioavailable testosterone, which is the fraction of testosterone not bound to the above reported proteins, represents the cornerstone of androgen function; in turn, changes in SHBG concentration are responsible for androgen function regulation. In healthy subjects, the normal testosterone range is 300–1,000 ng/dL, corresponding to 10.4–34.7 nmol/L in most assays of serum total testosterone [88]. However, as previously mentioned, the levels of total and free testosterone decrease with age [89]. Therefore, it is still questionable and unclear whether the reference range of serum androgens derived from younger men is also appropriate for the elderly population. Mohr et al. [89] have thus suggested age-specific thresholds for defining hypotestosteronemia: 251, 215, 196, and 156 ng/dL for men in their 40s, 50s, 60s, and 70s, respectively.

Testosterone is therefore a key factor in sexual function and is necessary for libido, ejaculation, and spontaneous erections. Animal data suggest that testosterone may play a role in the mechanism of NO-mediated vasodilatation in the penis and in other organs [90–93]. In castrated rats, Chamness et al. [90] demonstrated that the activity of NOS is reduced by 45% and that testosterone replacement can recover its production. Moreover, testosterone is implicated in the modulation of alpha-adrenergic vasoconstrictor activity [94, 95] and, in turn, can enhance erections by attenuation of vasoconstriction and by contributing to the venous occlusion mechanism responsible for the maintenance of erection [96].

Furthermore, testosterone is involved in central nervous system (CNS) control of the erectile pathway. Indeed, animal studies demonstrate that testosterone may facilitate erection in the dopaminergic mesolimbic cortex, responsible for sexual arousal [96]. In human subjects with pharmacologically induced hypogonadism, both the libido and the frequency of spontaneous erections decreased. These alterations have been demonstrated to be reversible after restoration of normal blood levels of testosterone [97–101]. In this context, recent studies highlighted the interaction between testosterone and PDE5-Is [102–106]. Aversa et al., for instance, were probably the first to clearly show that in a small group of patients with arteriogenic ED and low to normal androgen levels, defined as non-responders to sildenafil alone, short-term testosterone administration was able to increase serum levels of both T and free T, these results being coupled with a significant improvement in the erectile response to sildenafil, likely by increasing arterial inflow to the penis during sexual stimulation [107].

Neurological Factors

Also of importance from the pathophysiology standpoint is the role of the dopaminergic system, which seems to be closely involved in sexual function and positively correlated to that [108]. Patients treated with l-DOPA for Parkinson's disease demonstrate an increase in sexual activity, and this can anticipate improvements in neurologic activities and symptoms [109]. Again, the use of dopaminergic agonists in the treatment of hyperprolactinemia showed a rapid increase in sexual activities [110]. In contrast, dopamine-blocking agents often reduce sexual response.

Prolactin is another neurotransmitter that plays a key role in the CNS regulation of the erectile pathway. Prolactin, indeed, is part of the hypothalamic-testicular-pituitary axis implicated in ED. Patients suffering from hyperprolactinemia may primarily complain of ED [111].

Conclusions

It seems reasonable to hypothesise that the age link in ED may be mostly considered as the result of atherosclerosis-induced cavernosal ischemia, which ultimately leads to both severe cavernosal fibrosis and eventual veno-occlusive dysfunction. Abnormalities in circulating levels of hormones controlling sexual organs – mainly testosterone – most probably play a significant role at least in some patients. As the ED of ageing appears to be a slowly progressive disorder, it seems wise for the patient to seek medical intervention earlier rather than later to minimise the development of veno-occlusive dysfunction.

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Chapter 14
Androgen Deficiency

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Keywords Hypogonadism • Testosterone • Deficiency • Bone density • Supplementation

Definition

In men, the term hypogonadism generally refers to decreased levels of circulating testosterone. In reality, hypogonadism is much more difficult to define, given the myriad of end-organ responses to circulating androgens. The standard clinical diagnosis of hypogonadism relies on a combination of laboratory measurements of androgens and an assessment of signs and symptoms related to low androgens. For example, a man may have a low-normal testosterone level but suffer symptoms suggestive of hypogonadism, such as fatigue, depression, and erectile dysfunction (ED). On the other hand, a man may have normal libido, sexual function, and energy levels but have low testosterone levels. In these scenarios, it would be difficult to assign a diagnosis of hypogonadism in the second patient without symptoms. In addition, treatment with supplemental testosterone would not be indicated. This simplified patient scenario demonstrates the difficulty in defining such a complex condition and perhaps underscores the concept of individual thresholds of testosterone actions in different target organs.

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In practice, clinicians must utilize the laboratory data in conjunction with symptoms to determine a probable cause and effect. Additionally, validated questionnaires have been developed to provide some objective measurement of symptoms associated with hypogonadism (Androgen Deficiency in the Aging Male questionnaire, International Index of Erectile Function) [1, 2].

Physiology of Hypothalamus-Pituitary-Gonadal Axis

The male reproductive axis involves the secretion of multiple signaling proteins from various levels that alter downstream hormonal release (Fig. 14.1). Neurons located in the preoptic area of the hypothalamus release gonadotropin-releasing hormone (GnRH) into the portal circulation surrounding the pituitary gland. GnRH is released from the hypothalamus in a pulsatile fashion and can also vary based on the season and time of day. Secretion tends to be highest in the spring season. Also, levels tend to be highest in the morning and can vary throughout the day with a peak in secretion every 90–120 min. GnRH release directly stimulates production of leutinizing hormone (LH) and follicle stimulating hormone (FSH) in the anterior pituitary. Changes in the pulse frequency of GnRH secretion can alter gonadotropin secretion from the pituitary. For instance, an increase in GnRH secretion interval (longer interval) results in an increase in the response amplitude for LH secretion.

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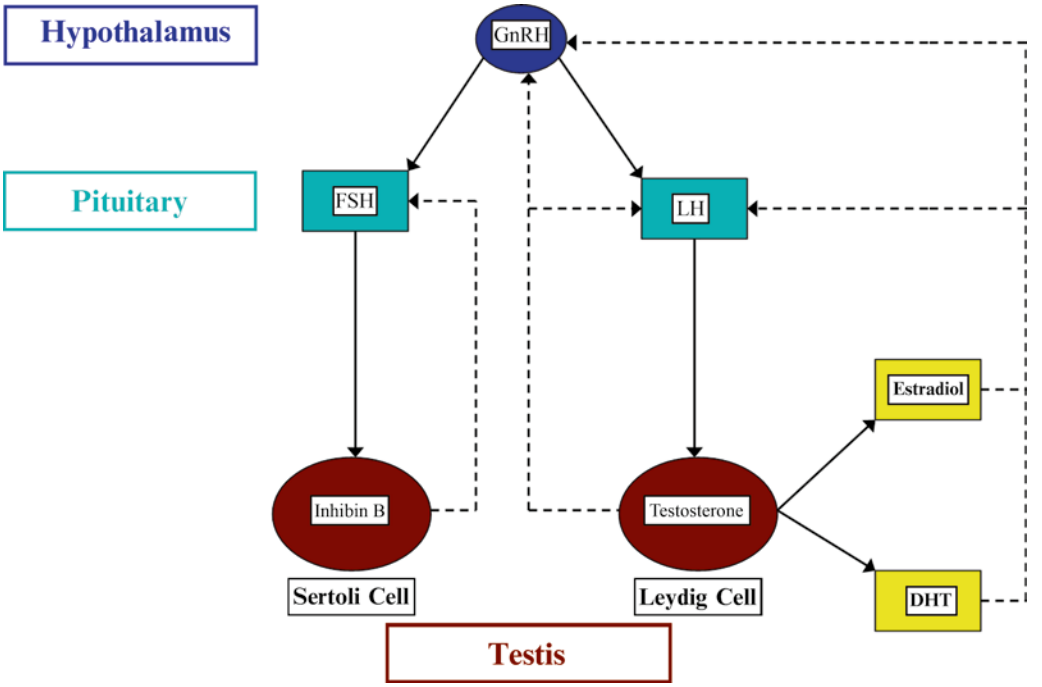

Fig. 14.1 Hypothalamic-pituitary-gonadal axis in the male. *Solid lines* represent stimulation, *dashed lines* represent negative feedback inhibition. Testosterone is converted to estradiol and dihydrotestosterone (DHT) by aromatase and 5-α reductase, respectively, in target organs

Alternatively, a decrease in GnRH secretion (shorter interval) results in a profound decrease in LH release, thus serving as the basis for androgen ablation with GnRH analogs.

The pituitary gland is divided into two segments, the anterior and posterior pituitary. The posterior pituitary gland is directly innervated by hypothalamic neurons that function to control the release of arginine-vasopressin (AVP, or antidiuretic hormone) and oxytocin. The anterior pituitary is a collection of cells involved in the tightly regulated release of stimulating hormones, including prolactin, thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone (GH), LH, and FSH. This review of physiology will concentrate on the sex-steroid hormone axis involving LH and FSH. However, alterations in the secretion of the any of the pituitary hormones can have dramatic effects on the release of others.

Release of LH and FSH relies on a tightly regulated system of stimulatory and inhibitory signals. Pulsatile GnRH release from the hypothalamus causes periodic release of gonadotropins from the pituitary gland. Both LH and FSH exert their endocrine effects in the male testis. LH stimulates Leydig cells in the testes to produce testosterone. FSH exerts its effects on Sertoli cells lining the seminiferous tubules to promote and maintain spermatogenesis.

Feedback mechanisms are primarily responsible for the tightly regulated control of gonadotropin release and hormone production. Testosterone acts mainly at the level of the hypothalamus and the pituitary by binding to androgen receptors to inhibit GnRH release and subsequent LH release. Metabolites of testosterone also act to regulate gonadotropin release. Testosterone is converted to estradiol in the periphery by the enzyme aromatase. Estradiol binds to estrogen receptors at the level of the pituitary to inhibit gonadotropin release. Even dihydrotestosterone (DHT) regulates gonadotropin release. Men with genetic 5-α reductase deficiency have been shown to have higher circulating levels of LH. In addition to steroids and their metabolites regulating gonadotropin release, other molecules are also involved in the regulatory process. Inhibin B is secreted by

Sertoli cells and acts at the level of the pituitary to block transcription and release of FSH. In fact, evidence suggests that Inhibin B is the predominant negative regulator of FSH release [3]. Additionally, activins are secreted by Sertoli cells and locally by the pituitary gland to stimulate production of FSH. It is intuitive that alterations in any of these feedback loops can have dramatic effects on gonadotropin release and circulating hormone levels.

Causes of Hypogonadism

Etiologies of hypogonadism, or low levels of circulating androgens, can be subdivided based on gonadotropin secretion (Table 14.1). Hypogonadotropic hypogonadism generally encompasses conditions resulting in decreased release of LH and/or FSH. The primary defect may be in the hypothalamus or the pituitary. The classic example of hypogonadotropic hypogonadism is Kallman's syndrome. This congenital syndrome is characterized clinically by anosmia, hypogonadism resulting from decreased or absent GnRH secretion, and other midline defects (cleft lip/palate, color blindness, seizures, etc.). The syndrome is thought to result from impaired migration of GnRH-releasing neurons to the hypothalamus during the embryonic period. These patients typically present with delayed puberty. Idiopathic hypogonadotropic hypogonadism (IHH) results in a similar clinical picture as Kallman's syndrome. Any damage to the hypothalamus or pituitary before puberty can result in low gonadotropin levels. Infection, tumor, radiation, surgery, and infarction of the hypothalamus or pituitary gland can lead to low levels of gonadotropins and resultant hypogonadism. For example, pituitary prolactinomas and elevated prolactin secretion result in decreased gonadotropin secretion and subsequent hypogonadism.

Hypergonadotropic hypogonadism (also classified as testicular failure) is associated with low levels of circulating androgens despite high levels of pituitary gonadotropins. Testicular failure can be further classified as primary or secondary. Primary causes of testicular failure result from congenital defects leading to low levels of androgen production. Klinefelter's syndrome is the classic example of primary hypergonadotropic hypogonadism in the male. These patients may demonstrate a 47,XXY karyotype or a mosaic pattern 46,XY/47,XXY karyotype. Interestingly, some patients may have normal testosterone levels but have low bioavailable testosterone levels due to elevated estrogen and sex-hormone binding globulin (SHBG) levels. However, LH is usually elevated and FSH is markedly elevated in these patients. Other rare primary causes of testicular failure include XX male syndrome and

Table 14.1 Causes of male hypogonadism

Hypogonadotropic hypogonadism	*Decreased gonadotropin secretion*
Congenital	Kallman's syndrome
Tumor	Craniopharyngioma, metastatic lesions, Hand–Schuller–Christian syndrome, glioma, pituitary adenoma (prolactinoma)
Inflammatory/infectious diseases	Sarcoidosis, tuberculosis
Hemorrhage/ischemia	Simmond's disease
Radiation therapy	
Surgery	
Medications	LHRH agonists
Aging	
Hypergonadotropic hypogonadism	*Testicular failure* (*primary or secondary*)
Congenital	Klinefelter's syndrome, male XX syndrome, congenital anorchia
Tumor	
Inflammatory/infectious diseases	Mumps orchitis, tuberculosis
Trauma	Testicular torsion, traumatic anorchia
Chemotherapy	
Radiation	
Drug use	
Aging	

Hypogonadotropic hypogonadism can result from any interruption in normal hypothalamic or pituitary cellular function, thus decreasing gonadotropin release. Hypergonadotropic hypogonadism refers to any cause of testicular failure and resultant decreased testosterone synthesis, despite normal hypothalamic and pituitary function

congenital anorchia. Both of these conditions result in the absence of functional testicular tissue and display low serum testosterone levels with elevated gonadotropins.

Secondary causes of testicular failure can range from infection and trauma to drug use and exposure to chemotherapeutic agents or radiation. Severe cases of mumps orchitis can irreversibly impair testicular function, including Leydig cell production of testosterone. Testicular torsion or trauma resulting in anorchia can lead to hypogonadism.

Another often unrecognized secondary cause of hypogonadism is due to aging. Several clinical descriptors have been used to characterize this phenomenon – androgen deficiency in the aging male, late-onset hypogonadism, testosterone deficiency syndrome, and andropause. Symptoms of this condition resemble those of "normal" aging and include decreased cognitive function, changing body composition, decreased libido, and ED. Approximately 30% of men aged 70–79 have low serum levels of total testosterone. In addition, SHBG levels tend to rise with age, resulting in an even lower level of bioavailable testosterone [4]. Some men may exhibit an increase in LH secretion resulting from the low serum testosterone levels while others may have low or inappropriately normal LH levels. These findings indicate not only a primary testicular failure but also alterations in the hypothalamus-pituitary axis.

Chemotherapy and radiation have been widely studied in their effects on gonadal function. Chemotherapy is well known to cause azoospermia. Many cases of azoospermia are temporary and reproductive function can show recovery over time. However, certain chemotherapeutic agents, such as alkylating agents, result in much lower rates of subsequent fertility. In addition, male children with Hodgkin's lymphoma suffer a very high incidence of infertility (in some studies, up to 100%) when treated with certain protocols, such as MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) [5]. Newer chemotherapeutic protocols appear to preserve reproductive function in male patients. Even though past research centered on reproductive function, overall gonadal function has only recently been studied. The majority of studies have shown that, despite retained reproductive function, hypogonadism persists after treatment. For example, Eberhard et al. studied over 140 men with testicular cancer who received either chemotherapy or radiation as adjuvant treatment [6]. Their study found that hypogonadism, defined as low serum testosterone, was prevalent. Furthermore, those men with hypogonadism prior to adjuvant therapy with chemotherapy or radiation were at very high risk for persistent hypogonadism up to 3 years after adjuvant treatment [6]. Greenfield et al. studied 176 cancer survivors where 97% had received chemotherapy and 40% had received radiation [7]. The authors measured total testosterone levels as well as calculated free testosterone levels and compared these results to 213 control patients. Cancer survivors were found to have significantly lower levels of testosterone, greater fat mass, higher insulin and glucose levels, and decreased sexual function [7]. Previous evidence implied that Leydig cells were generally radioresistant and androgen production was not impaired by radiation therapy. However, more recent studies have challenged that assumption. Schmiegelow et al. studied 30 male patients with childhood cranial tumors. These patients were treated with radiation and/or chemotherapy. Mean follow-up was 18 years. Although the sample size was small, the results demonstrated that both patients receiving radiation only and those receiving radiation plus chemotherapy had persistently low levels of testosterone. Cranial radiation also produced lower levels of LH, indicating direct damage to the hypothalamus-pituitary axis. In addition, inhibin B levels were significantly lower in patients receiving radiation and chemotherapy, also pointing to a component of primary gonadal failure [8].

One of the most studied anticancer therapies known to cause hypogonadism is hormonal therapy for prostate cancer. Since the days of Charles Huggins and the Nobel Prize-winning work demonstrating the hormonal response to prostate cancer and potential targets of therapy, initial strategies in the treatment of advanced prostate

cancer centered on surgical castration. Significant clinical improvements in symptoms were noted after castration. However, prominent side effects of androgen ablation were also evident, such as decreased libido, hot flashes, and ED. Knowledge of the physiology of the hypothalamus-pituitary-gonadal axis led to the development and use of several agents to reduce androgen levels. Estrogens, mainly diethylstilbestrol (DES), were used to block release of LH at the level of the pituitary gland. Identification and purification of GnRH led to the production of GnRH agonists and antagonists. GnRH agonists exert their effect by overriding the normal pulsatile release of LH and, following an initial surge in testosterone levels, eventually lead to subsequent downregulation of LH release and medical castration. Blockade of the androgen receptor has also been extensively studied. Both steroidal and nonsteroidal antiandrogens have been used clinically. Cyproterone acetate, a steroidal antiandrogen, has both antiandrogen effects by blocking the androgen receptor and estrogen-like effects. This molecule is a derivative of 17-hydroxyprogesterone and exerts a central estrogen-like effect by blocking release of LH at the level of the pituitary gland. Therefore, it causes typical hypogonadal symptoms in addition to direct androgen blockade. On the other hand, nonsteroidal antiandrogens exert their effect only by competitive inhibition of the androgen receptor. These molecules lead to a rise in circulating LH and testosterone levels, theoretically ameliorating some of the clinical symptoms of hypogonadism. The elevated levels of circulating testosterone can lead to increased peripheral conversion to estradiol, leading to painful gynecomastia or breast tenderness in some men.

Table 14.2 Effects of testosterone on body systems

Organ/function	Effect
Bone	Decreased bone resorption Increased bone mineral density Accelerated linear bone growth Closure of epiphyses
Body composition	Increased muscle mass Decreased fat mass via decreased lipoprotein lipase activity
Cognition/mood	Possible improvement in memory and visuospatial learning Possible decreased risk of Alzheimer's disease Possible improvement in depressive symptoms Improvement in libido
Metabolic	Improved insulin sensitivity Decreased LDL levels Decreased triglyceride levels
Cardiovascular	Possible improvement in endothelial function (increased vasodilation) Decreased pro-inflammatory cytokines (IL-1, TNF-α) Possible decreased risk of atherosclerosis
Sexual function	Improvement in libido Short-term improvement in erectile function
Male sexual organs	Prostate growth and function Penile growth Spermatogenesis
Skin	Sebum production Hair growth Balding
Kidney	Stimulation of erythropoietin

Effects of Hypogonadism

Bone

Androgens have a direct impact on bone mineral density (Table 14.2). It is clear from studies involving androgen deprivation in men with advanced prostate cancer that low androgen levels significantly decreased bone mineral density and increased the fracture risk, particularly in the hip and spine [9]. One recent study showed a fracture risk of 19.4% of men receiving androgen deprivation therapy for prostate cancer vs. 12.6% of men in the control group [10]. Clinical and molecular evidence suggest that both testosterone and estrogens play an important role in bone health. estrogens may play a more important role than testosterone [11]. Several population-based studies have shown that bone mineral density in elderly men was more directly related to lower estrogen levels [12]. The effect of estrogens

appears to be centered on osteoblastic activity that augments bone deposition, whereas testosterone appears to have a direct effect by inhibiting osteoclastic activity [13]. Estrogens appear to activate osteoblasts and enhance production of osteoprotegerin which, in turn, inhibits osteoclastic bone resorption. Circulating estrogen levels in men depend on aromatization of both testosterone and androstenedione to estradiol and estrone, respectively. Therefore, low testosterone levels can cause an increase in osteoclast-induced bone resorption and secondarily lead to low levels of estrogens, leading to further decline in bone mineral density.

Body Composition

There is a clear association with aging and a change in body shape and composition. There is a decline in muscle mass and a subsequent increase in adipose tissue. The effect of testosterone on muscle mass appears to be due to an increase in muscle protein synthesis [14] and muscle fiber hypertrophy. Cross-sectional volumes of muscle fibers have been shown to increase in a dose-dependent manner in healthy men supplemented with testosterone injections [15].

Studies of hypogonadal men and patients undergoing androgen deprivation therapy for prostate cancer have shown there are increases in weight and overall body fat mass as well as a decrease in lean body mass with declining androgen levels [16–18]. In addition, androgens appear to play an important role in adipose tissue distribution. Again, men treated with androgen deprivation therapy show an increase in visceral and subcutaneous adiposity. There is also noted to be an increase in fat tissue in the buttocks and thighs. Testosterone replacement therapy in hypogonadal men has been shown to decrease the amount of adiposity, thus increasing lean body mass, as well as to alter its distribution [19]. The effect of testosterone on declining adipose tissue results from the inhibition of lipoprotein lipase and resultant lipolysis [20].

Cognition and Mood

There is some evidence suggesting a role of androgens in cognition, especially in elderly men. One study examining cognition in elderly men found a relationship between low testosterone levels and significant declines in memory and visuospatial performance [21]. Several theories have been postulated regarding the role of androgens and cognition. Animal studies have demonstrated that areas of the brain involved in spatial learning, such as the hippocampus, are targets of androgens. Testosterone has been shown to upregulate the expression of nerve growth factors and induces an increase in acetylcholine release and an upregulation of nicotinic receptors in these areas [22].

Recent prospective studies have identified a link between low androgen levels in aging men and an increased risk of Alzheimer's disease [23, 24]. In vitro animal studies suggest that low levels of testosterone may increase β-amyloid deposition and decrease neuronal survival in response to toxic insult [25, 26]. Still, there is no direct evidence that low androgen levels lead to Alzheimer's disease.

The effect of hypogonadism on mood is also difficult to establish. Studies examining the role of testosterone replacement therapy on depressive symptoms have shown conflicting results, mainly due to relatively small subject numbers and heterogenous patient populations [27, 28].

Metabolic Effects

While previous studies have clearly documented the clinical symptoms of hypogonadism, recent evidence has examined the extensive metabolic effects of low androgens, such as insulin resistance, type 2 diabetes, lipid alterations, and the metabolic syndrome. Several studies have demonstrated that men with low levels of androgens have higher glucose and insulin levels, higher rates of obesity, and an increased incidence of type 2 diabetes [29, 30].

Furthermore, men undergoing androgen deprivation therapy with preexisting diabetes were found to have increased levels of glycosylated hemoglobin (HbA1C) [31] and required higher doses of self-administered insulin to maintain glycemic control [32]. There is some evidence to suggest that testosterone replacement therapy can reverse some of these metabolic effects caused by hypogonadism. Page et al. studied 70 hypogonadal men treated with testosterone replacement therapy and found improvements in body composition and lipid profiles. Increases in lean body mass and decreases in total body fat were seen in treated patients. There were also decreases in LDL (low-density lipoprotein) and triglyceride levels. Interestingly, there was no improvement in HDL (high-density lipoprotein) levels [33].

There is significant interplay between components of the "metabolic syndrome." These components include dyslipidemia, obesity, hypertension, hyperglycemia, and insulin resistance. There is significant evidence demonstrating that androgens play an important role in the regulation of these components. Testosterone replacement therapy in hypogonadal men has been shown to improve both lipid profiles and body fat composition. In addition, studies have also demonstrated a significant improvement in insulin sensitivity in diabetic men treated with supplemental testosterone [34, 35]. Based on current evidence, it is difficult to discern if there is a direct causal relationship between androgen deficiency and metabolic syndrome. It is unclear if insulin resistance and the development of obesity lead to increased peripheral conversion of testosterone to estradiol and resultant hypogonadal symptoms. This, in turn, could exacerbate the effect by negatively altering body fat mass and lipid profiles, further worsening glucose homeostasis. Alternatively, low androgen levels could primarily lead to increased body fat mass and insulin resistance. Even though there is no direct evidence to establish a causal relationship between hypogonadism and metabolic syndrome, the two entities are clearly interconnected.

Cardiovascular Effects

Given the emerging body of evidence regarding the link between hypogonadism and metabolic syndrome, it stands to reason there would be cardiovascular implications with androgen deficiency because metabolic syndrome is a risk factor for cardiovascular disease. Several studies have suggested a link between hypogonadism and cardiovascular disease [36–38]. Hak et al. showed there was a direct correlation between low testosterone levels and increased risk of aortic atherosclerosis. This correlation was independent of age, BMI, total cholesterol, smoking status, or diabetes. This finding suggests not only a correlation of hypogonadism and cardiovascular disease, but perhaps a direct causal relationship [39]. D'Amico et al. found that 6 months of androgen deprivation therapy for prostate cancer led to an earlier onset of fatal myocardial infarction [40]. Additionally, Keating et al. performed an observational study of over 70,000 men undergoing androgen deprivation therapy for prostate cancer. They identified an increased risk of diabetes, coronary artery disease, myocardial infarction, and sudden cardiac death in men treated with GnRH agonists. Interestingly, men undergoing orchiectomy were at increased risk for developing diabetes, but were not at increased risk for coronary artery disease or myocardial infarction [41].

Several preclinical and clinical studies have suggested possible mechanisms of action of androgens regarding endothelial function. Microscopic evaluation of endothelial tissue from castrated rats demonstrated significant damage to the endothelial lining. This damage was partially reversed with androgen supplementation [42]. In addition, pro-inflammatory cytokines, such as TNFα (tumor necrosis factor-alpha) and IL-1 (interleukin-1), were decreased in hypogonadal men after treatment with testosterone [43]. An increase in pro-inflammatory cytokines is thought to increase the risk of atherosclerotic disease.

In addition to the association of hypogonadism and metabolic syndrome, the risk of endothelial dysfunction appears to be associated with low androgen levels, further increasing the risks

of cardiovascular disease in these patients. The question of whether early identification and treatment of hypogonadism can halt, or perhaps reverse, any endothelial damage has yet to be determined. There does appear to be significant interrelationships between obesity, lipid profiles, insulin resistance, and endothelial dysfunction leading to increased cardiovascular risk.

Sexual Function

Androgens are known to play a significant role in sexual function. However, erectile function may not be directly dependent on androgens. Studies offer differing conclusions regarding the effect of androgen supplementation and erectile function. These studies are plagued by heterogenous populations and inclusion criteria [44, 45]. Testosterone supplementation appears to have a lasting improvement in libido, but improvement in erectile function based on a validated questionnaire is short-lived [46]. Hypogonadal men with ED were found to have improvement in erectile function for a limited time based on validated questionnaire after treatment with both testosterone supplementation and phosphodiesterase type 5 inhibitors [47]. These studies demonstrate the difficulty in identifying a direct relationship between androgens and erectile function.

Preclinical and clinical studies may offer some connection between erectile function and androgen levels. There is a clear association between endothelial dysfunction and hypogonadism. Also, there is evidence of a link between ED and endothelial dysfunction. In fact, some suggest that men presenting with significant ED should undergo a cardiac evaluation as ED may be a harbinger of concomitant coronary artery disease [48]. Testosterone supplementation has been shown to improve endothelial function by demonstrating an improvement in brachial artery flow-mediated dilation [49]. In vitro studies offer possible mechanisms of action of androgens in endothelial function. Androgens, including testosterone and dehydroepiandrosterone (DHEA), may act via activation of endothelial nitric oxide synthase (eNOS) in the endothelial lining of the vascular wall [50]. However, testosterone-dependent vasodilation has also been demonstrated in denuded endothelium, suggesting vasodilation is not dependent on an endothelial mechanism [51]. Further in vitro evidence suggests testosterone-mediated vasodilation may be due to inhibition of calcium entry into endothelial smooth muscle cells [52].

Diagnosis of Hypogonadism

As noted, the diagnosis of hypogonadism can be challenging for the clinician. Routine reliance on laboratory testing can sometimes lead to a missed diagnosis of hypogonadism. The presence of significant clinical symptoms often influences the diagnostic algorithm. An objective evaluation of subjective symptoms can be difficult as well. Fortunately, validated questionnaires assessing symptoms related to androgen deficiency can help with diagnosis and can be used as screening tools. Unfortunately, prospective evaluations of these questionnaires have demonstrated less than perfect symptom assessment. These questionnaires include the Androgen Deficiency in the Aging Male questionnaire [1], the Aging Male Survey [53], and the International Index of Erectile Function [2]. The results of these questionnaires should be used in conjunction with laboratory measurements of androgen levels to diagnose hypogonadism.

Laboratory diagnosis of testosterone levels also has its own drawbacks and pitfalls. Testosterone circulates in three fractions. The majority (~60%) of circulating testosterone is bound to SHBG. Testosterone bound to SHBG is tightly bound and not active. Approximately one-third of circulating testosterone is bound to albumin and only 1–2% of testosterone is free and available for cellular penetration and activity. The portion bound to albumin is easily released and, in addition to free testosterone, is referred to as bioavailable testosterone. As such, measurements of total testosterone can vary greatly since circulating levels of SHBG can change. In addition, total testosterone levels may not accurately reflect the level of bioavailable testosterone.

Laboratory measurement of serum testosterone can be accomplished by multiple methodologies. Most laboratories use either chemiluminescence assays or radioimmunoassay to measure total testosterone. In addition, testosterone can be measured by high performance liquid chromatography-mass spectrometry or gas chromatography-mass spectrometry. There can be wide variability in testosterone measurements using any of these techniques and standard reference values for testosterone levels can vary among different laboratories and different assay manufacturers, thus making accurate diagnosis of hypogonadism difficult [54]. Measurement of free testosterone would be the most accurate method of determining true hypogonadal levels. However, this measurement is difficult to obtain and costly. Ultrafiltration and equilibrium dialysis methods are historically the most accurate. These procedures are only available in select centers. Isotope dilution mass spectrometry has also been advocated but results vary significantly [55]. Free testosterone and bioavailable testosterone levels can be calculated, but this calculation relies on accurate measurements of total testosterone and SHBG. This calculator tool is available online (http://www.issam.ch). Measurement of bioavailable testosterone can be accurately accomplished using ammonium sulfate precipitation techniques. This technique works by precipitating the SHBG-bound fraction of testosterone and then measuring testosterone in the supernatant. As with free testosterone assays, this test may not be readily available. Newer methods to measure testosterone levels are being researched, such as salivary testosterone, but these methods still require further investigation and standardization [56].

At present, there is no standard reference laboratory value for the diagnosis of hypogonadism. Clinical symptoms, along with laboratory measurements, guide the clinician toward a diagnosis. While reference values for total testosterone vary significantly, most authors would agree that a morning serum total testosterone measurement of 200–300 ng/dL would be classified as low-normal. However, given the variability in testing for total and bioavailable testosterone, a patient with low-normal testosterone levels and clinical symptoms of hypogonadism would be a candidate for a trial of testosterone replacement.

Treatment

Treatment of male hypogonadism varies depending on the underlying cause. In general, treatment involves replacement of either pituitary gonadotropins to stimulate endogenous androgen production or simply replacement of androgens, usually testosterone. The treatment for men with hypogonadotropic hypogonadism depends on the desire for future fertility. Testosterone replacement therapy is the easiest and most cost-effective form of treatment, but results in suppression of the endogenous hypothalamic-pituitary-gonadal axis leading to infertility. If fertility is desired, treatment can be given by supplementation with GnRh, human chorionic gonadotropin (hCG – an analog of LH), or human menopausal gonadotropin (hMG – mimics both LH and FSH). Both pulsatile supplementation of GnRH and supplementation of LH and FSH can result in sperm production in hypogonadotropic hypogonadal men. The use of a GnRH infusion pump can be used to provide pulsatile delivery of GnRH. Use of this treatment protocol requires the patient to have an intact and functional pituitary gland. Therefore, patients with previous pituitary surgery, trauma, or possibly radiation may not be candidates for GnRH therapy. Gonadotropin supplementation can be administered by subcutaneous injection 2–3 times weekly (2,000–2,500 IU of hCG). This therapy is sufficient to initiate sperm production but FSH supplementation is also necessary for sperm maturation. Therefore, FSH can be supplemented either by administering recombinant FSH 2–3 times weekly (75 IU) or by administering hMG, which contains both FSH and LH [57]. Testosterone levels are usually normalized with supplementation of gonadotropins, assuming functional testicular tissue.

If fertility is not an issue, then supplementation with testosterone is provided. Testosterone supplementation is discussed in detail in other sections

(see Testosterone Supplementation in the Male Cancer Patient). In general, testosterone can be supplemented using intramuscular injections of testosterone preparations (testosterone enanthate, testosterone cypionate, testosterone undecanoate), testosterone gels (Androgel, Testim) and patches (Androderm, Testoderm), and buccal testosterone tablets. Long-acting subcutaneous pellets of testosterone are making a resurgence (Testopel, Slate Pharmaceuticals). Long-acting depot testosterone injections (Nebido, Bayer) are available in most countries in the world.

Each method of supplementation carries different risks and benefits. Injectable forms are the most cost-effective, but typically cause significant variations in testosterone levels. Transdermal forms of testosterone replacement offer more physiologic levels of testosterone, but these are more costly and carry the risk of person-to-person transfer of androgen. Risks of testosterone replacement therapy are discussed in further detail elsewhere. In general, blood counts should be periodically monitored, especially with injectable forms of testosterone. With any form of testosterone replacement therapy, routine digital rectal exam (DRE) and prostate-specific antigen (PSA) monitoring should be performed, given the hormonal responsiveness of prostate cancer. Patients with abnormal DRE or elevated PSA should undergo further evaluation prior to proceeding with testosterone replacement therapy. Treatment of hypogonadal men with a history of prostate cancer is more controversial, but recent evidence suggests the practice is safe [58, 59]. Evaluation of urinary symptoms in males on testosterone replacement therapy is optional, as it appears testosterone replacement has no significant impact on lower urinary tract symptoms in the short term [60].

Androgen Deficiency in the Female Patient

Female hypogonadism refers to an abnormality, either congenital or acquired, in the function of the hypothalamic-pituitary-ovarian (HPO) axis resulting in estrogen deficiency and which presents clinically with menstrual cycle disturbances [61]. Female hypogonadism is classified into three categories based on circulating hormone levels: hypogonadotropic hypogonadism, eugonadotropic hypogonadism, and hypergonadotropic hypogonadism. Patients suffering from hypogonadotropic hypogonadism have a defect of the hypothalamic-pituitary axis, low levels of LH and FSH, and resultant decreased serum estrogen levels. Eugonadotropic hypogonadism presents with normal levels of LH and FSH, as well as normal estrogen levels. Elevated levels of LH and FSH with low levels of estrogen characterize the patient with hypergonadotropic hypogonadism, whose primary defect is at the level of the ovary. Hypogonadism leads to a broad range of menstrual cycle disturbances, though most commonly women with hypogonadism present with either primary or secondary amenorrhea.

As defined by the Association of Professors of Gynecology and Obstetrics (APGO), primary amenorrhea is the absence of menses by age 14 in a patient without growth or development of secondary sexual characteristics, or the absence of menses by age 16, regardless of normal growth and development. Secondary amenorrhea is the absence of menstruation for at least three cycles in a woman who has been menstruating previously, or 6 months of amenorrhea. Hypogonadism of varying etiologies underlies the majority of anovulatory women; therefore, women presenting with amenorrhea must be evaluated for a wide differential diagnosis of female hypogonadism.

Physiology of Hypothalamic-Pituitary-Ovarian (HPO) Axis

The physiology of the HPO axis and of pulsatile GnRH release is identical to that previously discussed for males, except for action at the level of the ovaries (Fig. 14.2). LH stimulates *desmolase* in the theca cells of the ovary to convert cholesterol into androstenedione, which is then converted to estrogen by aromatization in ovarian granulosa cells. FSH facilitates this conversion

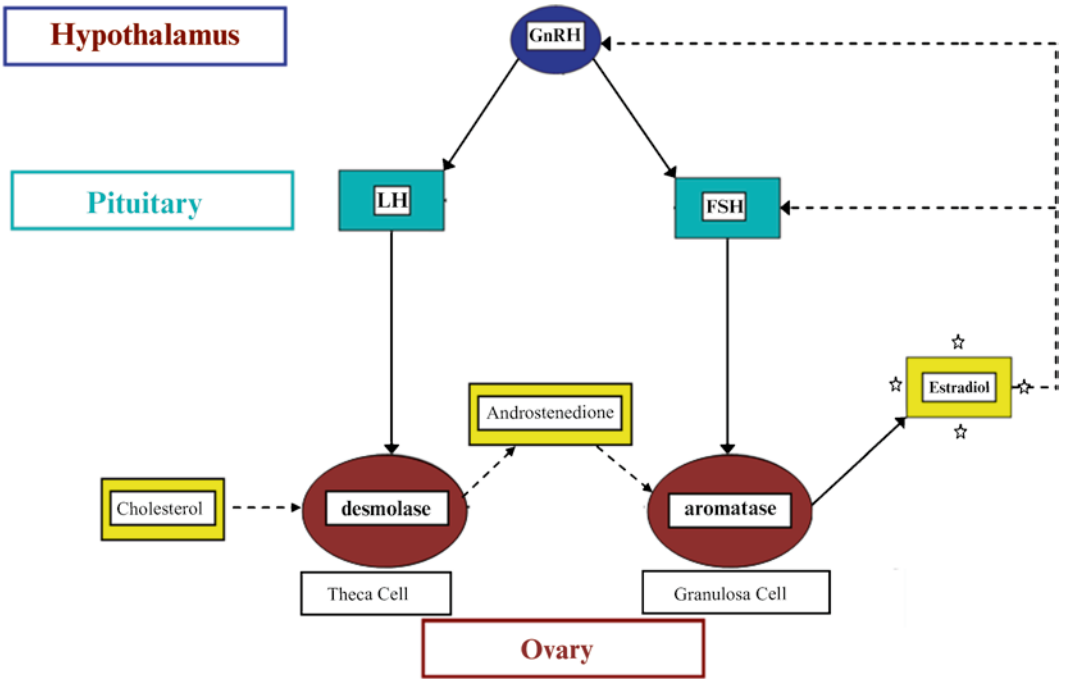

Fig. 14.2 Hypothalamic-pituitary-gonadal axis in the female. LH stimulates conversion of cholesterol to androgens in the theca cells of the ovary, and FH stimulates conversion of those androgens to estrogens in the granulosa cells of the ovary by stimulating aromatase

by stimulating *aromatase* in granulosa cells [61]. Estrogen produced by the ovary provides negative feedback at the level of the pituitary to downregulate LH and FSH production when estrogen levels are adequate. Congenital and acquired anomalies at the level at the hypothalamus or pituitary that diminish the release of LH and FSH from the anterior pituitary cause decreased serum estrogen levels because of a lack of ovarian stimulation.

Causes of Hypogonadism

Hypogonadotropic Hypogonadism

Any deficiency at the level of the hypothalamus or the pituitary gland can lead to female hypogonadotropic hypogonadism. IHH disrupts the HPO axis by affecting GnRH release at the level of the hypothalamus (Table 14.3). A subset of these patients with anosmia are known to have Kallman's syndrome, an inherited mutation in the *KAL* gene (Xp 22-3) which encodes for the protein responsible for migration of GnRH-releasing neurons from the olfactory placode to the hypothalamus. Since the neurons fail to migrate to their correct location, secreted GnRH fails to stimulate the anterior pituitary to produce both LH and FSH [62, 63]. Acquired causes of CNS-hypothalamic dysfunction include extreme exercise, weight loss, anorexia nervosa, and stress. Amenorrhea is most often seen in athletic women whose exercise regimen is associated with significant fat loss (long-distance runners, gymnasts, ballerinas), and if significant training occurs before menarche, puberty may be delayed [62]. Exercise increases catechol estrogens and reduces catecholamine degradation, which in turn increase levels of dopamine (a potent inhibitor of GnRH release) by competition for catechol-methyl-transferase. Strenuous exercise also increases endorphins, which positively affect dopamine secretion and further diminish GnRH

Table 14.3 Causes of female hypogonadism

Hypogonadotropic hypogonadism	*Decreased gonadotropin secretion*
Congenital	IHH, Kallman's syndrome
Tumor	Craniopharyngioma, metastatic lesions, Hand–Schuller–Christian syndrome (eosinophilic granuloma), glioma, pituitary adenoma (prolactinoma), germinoma, enodermal sinus tumor
Inflammatory/infectious diseases	Sarcoidosis, tuberculosis
Hemorrhage/ischemia	Sheehan's syndrome, Simmond's disease
Radiation therapy	
Surgery	
Medications	LHRH agonists
Exercise, stress, weight loss, anorexia	
Eugonadotropic hypogonadism	
Tumor	Steroid-producing ovarian tumors
Adult-onset congenital adrenal hyperplasia (CAH)	
Polycystic Ovarian syndrome (PCOS)	
Hypergonadotropic hypogonadism	*Ovarian failure* (*primary or secondary*)
Congenital/inherited	Gonadal dysgenesis, Turner's syndrome, female abnormal X syndrome, 17α-OH deficiency
Premature ovarian failure (POF)	
Ovarian resistance (savage) syndrome	
Chemotherapy/radiation	
Drug use	
Aging	

Hypogonadotropic hypogonadism can result from any interruption in normal hypothalamic or pituitary cellular function, thus decreasing gonadotropin release. Eugonadotropic hypogonadism results from steroid disruption of the HPO axis. Hypergonadotropic hypogonadism refers to any cause of ovarian failure and resultant decreased estrogen synthesis, despite normal hypothalamic and pituitary function

secretion [64]. Significant weight loss places stress on the body and increases cortisol and cortisol releasing hormone (CRH), which decreases GnRH pulsatile activity. Insulin sensitivity is increased with significant weight loss, which ultimately leads to low fasting serum levels of glucose and insulin [65]. Weight loss that is significant enough to yield amenorrheic changes may be caused by simple weight loss or to anorexia nervosa. While weight loss is a stressor on the body, other forms of stress, such as those associated with traumatic events, deaths in the family, or marital problems, can also produce amenorrhea by increasing cortisol levels.

Hypothalamic injury, infiltrative diseases (tuberculosis, sarcoidosis), and lesions/tumors such as craniopharyngioma, germinoma, endodermal sinus tumor, eosinophilic granuloma (Hand–Schüller–Christian syndrome), glioma, and metastasis are also associated with hypogonadotropic hypogonadism [62, 65]. Trauma and radiation to the hypothalamus destroys its ability to maintain normal GnRH pulsatile activity. Radiation therapy can also have effects on GnRH secretion, as the hypothalamic releasing factor neurons are more radiosensitive than pituitary cells [66]. Pituitary adenomas (more specifically, prolactinomas) are the most common cause of acquired pituitary dysfunction causing amenorrhea, though any alteration in pituitary hormone secretion can produce amenorrhea. Prolactin is a potent stimulator of dopamine production, and elevated dopamine affects GnRH secretion. Anoxia, thrombosis, or hemorrhage commonly damages pituitary cells and compromises hormone secretion. When hypotension occurs with pregnancy, this disorder is referred to as Sheehan's syndrome (postpartum hemorrhagic necrosis) and if the hemorrhagic event is unrelated to pregnancy, it is called Simmond's disease [64, 65, 67]. For patients who have elevated prolactin levels or evidence of galactorrhea, headaches, or visual disturbances on history and physical examination, an MRI study of the pituitary gland is indicated to rule out a pituitary tumor [68]. In the case of nonneoplastic lesions of the pituitary, low LH, FSH, and estradiol levels can cause an absence of withdrawal uterine bleeding following IM administration of progesterone.

Eugonadotropic Hypogonadism

Eugonadism is caused by chronic steroid secretion that interferes with the normal feedback cycle between the ovary and the hypothalamic-pituitary axis. As a result, oocyte maturation fails to occur, and amenorrhea results. Because these patients maintain normal gonadotropin levels, they will secrete estrogen normally. Hence, they may suffer from chronic anovulation despite the presence of estrogen [67]. Three main disorders underlie eugonadal hypogonadism: polcystic ovarian syndrome (PCOS), late-onset/adult-onset congenital adrenal hyperplasia (CAH), and steroid-producing ovarian tumors. PCOS, defined as the presence of oligomenorrhea/amenorrhea and hyperandrogenism in the absence of other pathologic hyperandrogenic disorders, has a prevalence of 5% in women of reproductive age, and approximately 70% of women with ovulatory dysfunction [69]. Aside from elevated levels of testosterone, DHEA, and androstenedione, higher than normal LH levels are measured, with an LH:FSH ratio greater than 3:1. Visualization by ultrasound reveals enlarged ovaries, dense stroma, and little to no cystic activity [70]. Late-onset CAH can present with similar symptoms as PCOS, namely hyperandrogenism and irregular menstrual cycles [67]. CAH is caused by a mutation in the CYP21 gene that encodes for *21-hydroxylase*. As a result, these women cannot convert progesterone to cortisol and aldosterone, thereby increasing the production of androgens. Similar to PCOS, the increasing amounts of androgens inhibit oocyte maturation and cause anovulation and amenorrhea. Androgen-producing ovarian tumors can also cause elevated levels of testosterone and cause chronic anovulation despite estrogen being present [67, 70].

Hypergonadotropic Hypogonadism

Hypergonadotropic hypogonadism refers to hypogonadotropic disorders that originate at the level of the ovary. Decreased estrogen levels, as a result of decreased ovarian stimulation, are insufficient to provide negative feedback on LH and FSH, thus the levels of these pituitary hormones remain high [67]. Though there are acquired causes of hypergonadotropic hypogonadism, inherited/genetic etiologies underlie the majority of cases, and it has been suggested all women presenting with hypergonadotropic amenorrhea undergo karyotyping to identify individuals with gonadal dysgenesis [63, 66]. Gonadal failure due to genetic abnormalities, which presents as hypergonadotropic hypogonadism, includes the following disorders: Turner's syndrome (45,XO), pure gonadal dysgenesis (46,XX and 46,XY), 46,X with abnormal X, genetic mosaicism, and *17-alpha-hydroxylase* deficiency. In all of these disorders, except for *17-alpha-hydroxylase* deficiency, women do not have primordial follicles and thus cannot make ovarian steroids. Women with *17-alpha-hydroxylase* deficiency do have primordial follicles, but cannot make sex steroids regardless [64]. Patients with Turner syndrome will exhibit gonadal dysgenesis along with a variety of physical abnormalities including short stature, webbed neck, low hairline, shield-chest, cardiovascular defects, streak gonads, and sexual infantilism [71]. The streak gonads in these patients are incapable of producing ovarian steroids, which underlies the elevated LH and FSH levels due to lack of negative feedback inhibition by estrogen. Invariably, almost all women with Turner's syndrome are sterile and therefore need estrogen replacement therapy. The etiology of gonadal failure in patients with pure gonadal dysgenesis who are either 46,XX or 46,XY is poorly understood, but it is thought to be caused by single gene defects or by destruction of gonadal tissue in utero by infection or toxins [67]. 46,XY patients are phenotypically female because testosterone and Mullerian inhibiting substance are not secreted by the testes [67]. Patients with pure gonadal dysgenesis have normal stature and will not have the somatic abnormalities associated with Turner's syndrome, but will often have primary amenorrhea and absent secondary sex characteristics [71]. 46,X individuals with an abnormal X have a 46,XX karyotype, though genetic material

from one of the X chromosomes is missing. The phenotype of these individuals will depend on the magnitude of the deletion, and whether it is located on the short or long arm of the respective X chromosome. Those with deletions in the long arm usually present with normal stature, streak gonads, and sexual infantilism, but do not have somatic abnormalities. However, if the deletion is on the short arm, the individual's phenotype resembles that of a Turner's syndrome patient [67, 71]. Many different mosaic states are associated with primary amenorrhea with normal female external genitalia, but the most common form is 45,X/46,XX [65, 67, 71]. These patients are generally taller with fewer anomalies than a Turner's syndrome individual who is pure 45,XO. *17-alpha-hydroxylase* deficiency (in a 46,XX patient) is a rare genetic disorder that causes primary amenorrhea with normal internal female genitalia and absence of breast development. *17α-hydroxylase* is normally involved in the production of glucocorticoids and sex steroids and so a deficiency in this enzyme will cause a decrease in the synthesis of cortisol and sex steroid synthesis, as well as an increase in the synthesis of mineralocorticoid precursors. The lack of sex steroids leads to sexual infantilism, manifested as the lack of breast development, lack of pubic and axillary hair, and small uterus in genetic females. The increased levels of ACTH result in sodium retention and hypokalemia. This disease is suspected when a patient presents with delayed puberty, absent secondary sexual characteristics, or primary amenorrhea [67, 71]. These patients have elevated serum progesterone values (>3 ng/mL), low *17α-hydroxylase* levels (0.2 ng/mL), and elevated serum deoxycorticosterone values.

Premature ovarian failure (POF), the loss of oocytes and their surrounding support cells prior to age 40, is a major cause of acquired hypergonadotropic hypogonadism. As a result of this oocyte loss, the ovaries fail to produce enough estrogen to stimulate endometrial growth prior to the onset of physiological menopause [65]. POF can present as infertility, estrogen deficiency (hot flashes, night sweats, etc.), irregular menses, or primary amenorrhea [66]. POF affects roughly 0.1% of women before age 30, and 1% of women before age 40 [68]. Most often, POF has an idiopathic etiology, though various medical conditions can lead to POF. POF is often seen in women with autoimmune endocrine disorders, such as Addison's disease, as well as in women with diabetes mellitus and hypothyroidism. Additionally, 20–40% of women with POF will develop another autoimmune disorder in the future; therefore, periodic testing is recommended [68]. POF can also be caused by irradiation or chemotherapeutic agents used in the treatment of other disorders, especially alkylating agents. As a result, the number of women presenting with transient or permanent ovarian failure has increased with increasing use of such agents [66, 68]. In general, the likelihood of developing ovarian failure is correlated with increasing amounts of radiation. Permanent failure almost always occurs when the ovaries are subjected to a radiation of more than 8 gy (or 800 rad) [67]. Additionally, the patient's age plays a significant role, as a younger patient undergoing radiation is less susceptible to ovarian failure than her older counterpart. In general, ovulation cannot be induced pharmacologically in these patients, and they are therefore considered to be sterile [64, 66, 68]. Ovarian resistance syndrome, or Savage syndrome, is a rare cause of hypergonadotropic hypogonadism. Women affected with this disorder present early with amenorrhea, elevated gonadotropins, and normal karyotypes. The etiologies are varied, and include defective or absent LH/FSH receptors in the ovary or follicles, postreceptor defects, mutated LH/FSH molecules, a defective secondary messenger system, or an autoimmune disorder with antibodies to the LH/FSH molecules or receptors. Three criteria need to be met in order to diagnose an ovarian resistance syndrome; hypersecretion of gonadotropins, presence of histologically normal ovarian follicles on ovarian biopsy specimens, and hyporeceptivity of ovaries to exogenous stimulation with hMG or pituitary gonadotropin [72]. The lack of ovarian stimulation leads to an arrest of ovarian maturation, loss of negative feedback, and resultant increased levels of FSH and LH.

Effects of Androgen Deficiency in Women

The hypoestrogenic state in hypogonadal women can cause osteoporosis, infertility, and delayed sexual maturation. Estrogen deficiency is a leading risk factor for osteopenia and osteoporosis, as women lose approximately 2% of cortical bone and 5% of trabecular bone per year for the first 5–8 years after menopause in addition to the 0.4% bone loss per year after reaching peak bone density [69]. Therefore hypogonadal women, who are often estrogen deficient at ages far younger than a typical menopausal woman, are particularly affected. Though rapid and significant cancellous bone loss occurs whether the cause is hypogonadotropic or hypergonadotropic, prospective quantitative CT measurement of spinal cancellous bone mineral density in women with hypothalamic amenorrhea demonstrated loss of bone mineral density averaging 10.7 mg/cm^3 per year compared to no loss in normal menstruating controls [73]. It has also been speculated that high levels of FSH play a role in hypogonadal bone loss, as studies performed with FSH-receptor knock-out mice were found to be resistant to bone loss despite severe estrogen deficiency [74].

Amenorrhea as a primary manifestation of hypogonadal states has been discussed at length, and will be important in the discussion of establishing a diagnosis of hypogonadal etiologies. The hypoestrogenic state of hypogonadal women also leads to physical changes, such as vaginal mucosal atrophy, that have adverse effects on female sexual function (inadequate lubrication, dyspareunia, etc.). Furthermore, many of the chronic conditions that underlie hypogondal states, as with many chronic disease states, have associated hypoactive sexual desire disorder (HSDD). Sex steroid insufficiency is associated with urogenital atrophy and may also adversely affect central sexual thought processes. Systemic estrogen and estrogen + progestin therapy alleviates climacteric symptoms, but there is no evidence that this therapy specifically improves HSDD [75]. Hypogonadal women may also experience overall loss of well-being, energy and drive with chronic tiredness, some of which at least may be due to accompanying deficiency of testosterone [76]. Exogenous testosterone has been shown in small randomized controlled trials to improve energy, sexual desire, arousal, and sexual satisfaction in women, whether pre- or postmenopausal, though there are no biochemical measures that clearly identify who to treat [75].

Patients with untreated PCOS exhibit large amounts of unopposed circulating estrogens associated with a theoretical risk for development of endometrial cancer. Associated with the insulin resistance in PCOS is a three to sevenfold risk for developing diabetes mellitus. There have been no prospective studies to document a definitive increased risk for coronary artery disease in patients who have PCOS despite abnormal serum lipid profiles, presence of diabetes, and surrogate endpoints showing an increased risk for heart disease [68]. In other hypogonadal women, cardiovascular risk comes into play with regard to hormone replacement therapy. While initial observational studies demonstrated estrogen replacement in postmenopausal women to be cardioprotective, the Women's Health Initiative (WHI) reported a hazard ratio for coronary heart disease of 0.95 (95% CI: 0.70–1.16) in a trial of conjugated equine estrogens (CEE) and of 1.24 (95% CI: 1.00–1.54) in a trial of CEE plus medroxyprogesterone acetate (CEE + MPA). These study discrepancies can be attributed to age differences, as nonsignificant risk reductions were found in women only 10 years out from menopause or less. However, opposite trends were noticed in regard to risk of stroke while on hormone therapy. Stroke risk was elevated by 77% in women within 10 years since menopause, but by a nonsignificant 13% in women beyond this range [77]. Though these studies were performed in postmenopausal women, their findings can be generalized to estrogen deficient hypogonadal women, in whom caution should be exercised when using CEE therapy.

Diagnosis of Androgen Deficiency in Women

Amenorrhea can be a symptom of many different pathological states, and thus needs to be worked up extensively since it is often a result of one of the many causes of hypogonadism. Certain disorders, such as *17α-hydroxylase* deficiency can be fatal, and it is therefore important to determine the etiology of the patient's amenorrhea and correct the illness before other problems develop. First, it is important to obtain a detailed history and physical examination with questions regarding birth, developmental history, course of puberty, growth curve, family history, age of menarche, menstrual cycle patterns, medication, drug and alcohol use, weight changes, stress levels, and diet and exercise patterns. Pregnancy should be considered and ruled out in every woman presenting with amenorrhea. The physician should also note the presence of symptoms indicating dysfunction in other pituitary hormones, such as galactorrhea, headaches, thyromegaly, other evidence of hypo/hyperthyroidism, and signs of cortisol excess [69]. Presence of acne, hirsutism, acanthosis nigricans, or indications of virilization should be noted. During the physical exam, the assessment of puberty and maturation of secondary sexual features need to be included. A pelvic exam is performed to detect the presence of a uterus and ovaries, and to assess for clitoromegaly and adequacy of estrogenization. The patient's BMI should be calculated, because if BMI is less than 20, it may indicate hypothalamic ovulatory dysfunction [64, 66, 69]. Abnormalities on physical exam will prompt diagnostic testing. Timed measurements of LH, FSH, estradiol, testosterone, DHEA-sulfate, and 17-hydroxyprogesterone levels help determine the correct diagnosis as described previously. The algorithm for the evaluation of amenorrhea provides a systematic approach of combining physical findings with laboratory testing to determine the etiology of a woman's amenorrhea (Fig. 14.3).

Specifically, when distinguishing between simple weight loss and anorexia in the workup of hypogonadal hypogonadism, measurements of serum triiodothyronine (T3) levels by radioimmunoassay prove helpful. T3 levels will be low in anorexia nervosa patients [64]. In amenorrhea related to weight loss, administration of GnRH has been used in an effort to differentiate between hypothalamic and pituitary etiologies. Patients who are severely underweight (including those with anorexia nervosa) have blunted LH responses and lower-than-normal increases in FSH following GnRH stimulation. As these women regain their body weight, the FSH and LH responses to administration of GnRH return to normal [64].

Treatment of Androgen Deficiency in Women

Since amenorrhea is a symptom of many different pathological states, treatment is directed by the etiology. In general, all women with low estrogen are given estrogen/progestin replacement to maintain normal bone density if the hypoestrogenic state cannot be promptly reversed. In women with primary amenorrhea, such as ovarian resistance syndrome, the initial goal is to facilitate normal sexual development. Secondly, the physician addresses issues of fertility. Young girls with estrogen deficiency who therefore fail to undergo puberty are started on estrogen therapy around age 12 [76]. The initiation of puberty, menses, and normal growth, as well as prevention of osteoporosis is achieved by low doses of estrogen, followed by estrogen and progesterone, or a combination oral contraceptive pill. The progestin therapy is used to prevent unopposed estrogen stimulation of the endometrium and breast tissue to circumvent negative oncologic outcomes. Peak bone density can be achieved with proper hormonal therapy. In these women, fertility rarely returns. If these patients wish to conceive, they are treated by ova donation and in vitro fertilization [66, 68].

The treatment of secondary amenorrhea is slightly different. The main focus is on the patient's fertility as well as prevention of complications associated with abnormal hormonal levels. The possibility of future conception is dictated by the reversibility of the cause of amenorrhea. Similar to primary amenorrhea, the treatment of secondary amenorrhea is tailored to its cause. Often, treating the source of the amenorrhea will

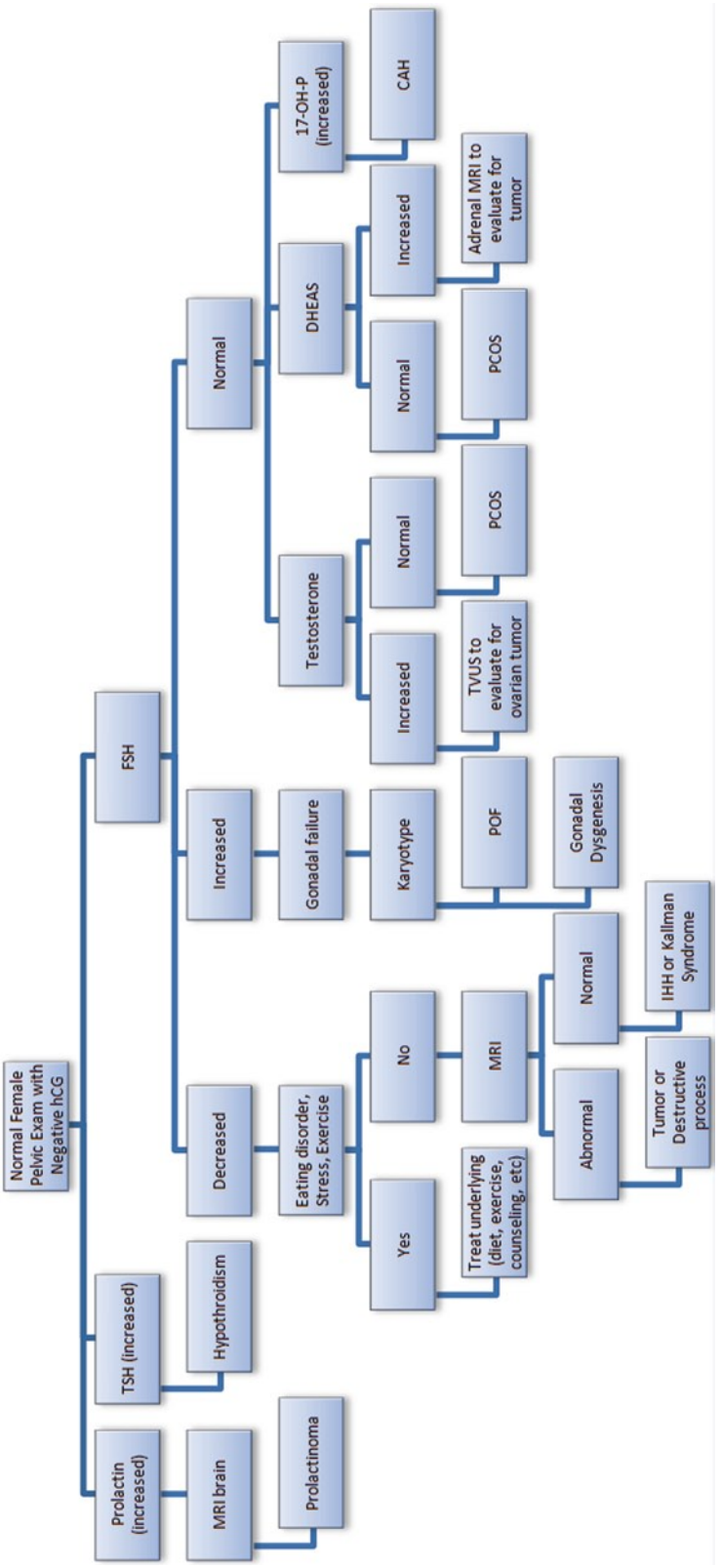

Fig. 14.3 Evaluating amenorrhea in patients with normal female genitalia and negative hCG. With normal exam, amenorrheic women must first be evaluated for pregnancy with hCG. If negative, their amenorrhea warrants further workup as described here to diagnose underlying etiology

reverse the symptoms. For example, women with secondary amenorrhea due to excessive exercise or weight loss can often regain menses when they reduce the amount of exercise or regain lost body weight. Psychiatric counseling may be advised for patients with anorexia nervosa. Those with tumors will often regain menstruation when the tumor is removed. Patients suffering from prolactinemia will regain normal function of the HPO axis when the prolactin levels return to normal ranges. If the patient is taking a medication that causes hyperprolactinemia which cannot be discontinued, sex hormone replacement is recommended. In general, these women are placed on hormonal therapy if their hypoestrogenic state cannot be reversed immediately [66, 68].

PCOS, as a eugonadal state, needs a different approach to treatment. Pharmacotherapy to suppress androgen excess using dexamethasone, oral contraceptives, or spironolactone is used in treatment. Cyclic progestin therapy can also be used to induce uterine bleeding and prevent the unopposed estrogen effect on the endometrium. When a patient desires pregnancy, clomiphene citrate is used to induce ovulation [64]. The primary treatment strategy for PCOS involves weight loss in conjunction with diet and exercise. A decrease in body weight by as little as 5% can make significant differences in lowering androgen levels and improving hirsutism, resumption of normal menses, and decreasing insulin resistance. Insulin-sensitizing agents, such as metformin and thiazolidinediones, can also be added to reduce insulin resistance [68].

There are also some special considerations in the treatment of hypergonadal hypogonadism states. For very short statured patients with Turner's syndrome, it has been recommended that low-dose androgens be used either preceding, or in conjunction with, estrogen replacement in an effort to maximize height gain [64]. Patients with ovarian resistance syndromes desiring fertility can be treated with high doses of conjugated estrogen in an effort to lower serum FSH and LH values into normal ranges, after which medroxyprogesterone acetate is added at days 16–25 of the woman's menstrual cycle. Once the drugs are stopped, the patient seen by a physician to obtain basal body temperature and see if ovulation has occurred [64]. As mentioned previously, these patients need to be monitored for cardiovascular risk.

Conclusions

Androgen deficiency can result from a multitude of factors, ranging from congenital, idiopathic, iatrogenic, infectious, inflammatory, malignancy, medication induced, or as a consequence of aging. The diagnosis of hypogonadism can be challenging for the clinician. Reliance on subjective clinical symptoms suggestive of hypogonadism in conjunction with laboratory measures is paramount for a correct diagnosis. Treatment depends on the underlying cause but generally involves supplementation. In men, either gonadotropin administration to stimulate endogenous androgen production or testosterone supplementation is used in one of many forms. The goal of therapy in the hypogonadal male is centered on restoring physiologic androgen levels and alleviation of clinical symptoms of hypogonadism. In women, estrogen replacement therapy is central to treatment with the goal of restoring estrogen levels, alleviating clinical symptoms, and preventing osteoporosis. Testosterone therapy may also be used in women to increase energy and sexual desire. Caution should be exercised in all patients when providing hormone replacement therapy, and all treatments should be tailored to individual patient's needs and risk factors.

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Chapter 15
Peyronie's Disease

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Keywords Peyronie's disease • Curvature • Deformity • Plaque • Scar • Cytokines • Plication • Plaque incision

Definition

Peyronie's disease (PD) is a psychologically and physically devastating disorder that is manifest by a fibrous inelastic scar of the tunica albuginea, resulting in palpable penile lesion in the flaccid condition and causing penile deformity including penile curvature, hinging, narrowing, shortening, and painful erections. In spite of multiple treatment options offered since Francois de la Peyronie described PD in 1743 [1]. PD remains a considerable therapeutic dilemma even to today's practicing physicians.

History

Francois de la Peyronie was a French Barber Surgeon who practiced from 1693 until his death in 1747 [2]. His career was prolific; he acted as the commander of the medical corps under Louis XV, founded the Royal Academy of Surgery in 1737, and became a very famous surgeon in Paris, caring for prominent Parisians as well as the kings of Poland and Prussia [2]. Today, his most famous contribution to medical history is his classic paper on induratio penis plastica (IPP) [1], describing "disfiguring knobs" [1] and "indurations" causing a bending of the penis. Other investigators throughout history have reported on PD, including Fallopius in the sixteenth century, going as far back as Theoderic of Bologna in 1265 [3].

Etiology and Molecular Mechanisms

The etiology of PD remains the subject of much scientific research. Historically described etiologies included the patient's sexual history, or a history of "deviant behavior" [4, 5]. Forceful penetration and penile trauma have long been thought to be causative factors [6], and although other investigators have questioned their role [7] it is likely that they remain an important triggering event in the development of the disease. More contemporary thinking would consider PD as a disorder of wound healing, and as such may be considered similar to the formation of hypertrophic scars. Recent investigations have focused on the mechanisms of wound healing, fibrosis, and scar formation, and have correlated their findings to the Peyronie's population.

Tissue injury is inherent in the creation of wounds, and the body's response to blood vessel disruption is the central feature of the acute phase. Exposure of sub-endothelial collagen to platelets from broken blood vessels leads to platelet aggregation and activation of the coagulation cascade,

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the end result of which is fibrin deposition and clot formation. The clot functions not only to provide hemostasis, but also as a physical scaffold for the movement of acute cellular response elements into the damaged area.

Macrophages and neutrophils arrive by approximately 48 h after injury. They function in a similar fashion to phagocytose dead or injurious material, and by destroying bacteria or other foreign cells via oxygen free radical reactions. In addition, macrophages strongly recruit other cellular elements by releasing TGF-β [8] and stimulate local tissue repair through the release of vascular endothelial growth factor (VEGF), insulin like growth factor (IGF), and endothelial growth factor (EGF).

The proliferative phase spans days 4 through 12 after injury, and it is during this phase that scar initially forms. Fibroblasts migrate to the site of injury, particularly via the action of platelet derived growth factor (PDGF). Their role is the production of collagen and the re-creation of the extracellular matrix lost during injury. Although there are many types of collagen in the body, types I and III dominate wound healing. Type I collagen is the primary collagen of skin, while type III becomes more important in wound healing. Fibroblasts also produce glycosaminoglycans (GAG), the principle elements of which in wound healing are chondroitin sulfate and dermatan. The interaction of collagen and GAGs remains an active area of research in the science of wound healing.The remodeling phase of wound healing begins during the proliferative phase and results in the final production of a smaller, potentially contracted scar. This phase is marked by a balance between matrix metalloproteinases (MMPs), which break down collagen, and the formation of collagen by fibroblasts. MMPs are induced by IL-1, and are inhibited by tissue inhibitors of metalloproteinases (TIMP), of which there are two identified molecules (TIMP 1 and TIMP 2), and by fibrinolytic inhibitors such as fibrin/plasminogen activator inhibitor 1 (PAI 1) [9].

Further study of the molecular etiology of PD has unearthed several important growth factors, which may be divided into profibrotic and antifibrotic groups. Profibrotic factors include TGF-β1, which is an activator of collagen I synthesis [10], and which is released by neutrophils and macrophages during the acute and proliferative phases of wound healing. A second group of profibrotic enzymes include the fibrin/PAI-1 system. Plasmin breaks down the extracellular matrix both directly and by activating MMPs to break down collagen. PAI-1 in turn inhibits MMPs as well as plasminogen activator (t-PA), which is an activator of plasmin [11]. Fibrin itself has been studied as an inducer of PD [12, 13], and has been used as an inducer of PD in an animal model [14]. It has also been found that levels of TGF-β1 and PAI-1 levels are increased in fibrin-induced PD plaques [13].

The major identified antifibrotic enzymes are the MMPs. Although many different MMPs have been discovered, there are a few that appear more relevant in PD research. Collagen I breakdown is mediated by MMPs 1 and 13, while for collagen III MMPs 1, 3, 10, and 13 appear most active. In addition, exciting studies are currently underway examining the possibility of fibrosis regression, particularly through the induction of the nitric-oxide synthase pathway.

It is possible that a genetic predisposition toward impaired wound healing and PD exists. Qian et al. [15] compared gene expression profiles in samples taken from PD tunica albuginea plaques, Dupuytren's contractures, and normal palmar fascia, and found several gene family similarities between the PD and Dupuytren's groups including MMP-2, MMP-9, and thymosins TMb10 and TMb4.

Evaluation of the PD Patient

Thorough evaluation of the PD patient is essential not only to diagnose the disease correctly, but also to guide treatment. Currently, no universally accepted standardized evaluation for the PD patient exists, nor has a validated questionnaire been developed. A suggested guideline for initial evaluation of the PD patient, including history, physical exam, and imaging analysis has been published [16] and is outlined below. Subjective and objective data gathering remains discordant among investigators, making the interpretation of

clinical trial data confusing at best. Currently, it appears that the most efficacious mechanism for the evaluation of the PD patient is via subjective and objective assessments specifically geared toward the application of known PD etiologies discussed earlier in this chapter.

The subjective assessment begins with the patient interview. History should be focused on the onset and duration of symptoms, the patient's presenting signs and symptoms, and the presence or absence of pain. It is particularly useful to elucidate whether the patient continues to experience pain at the time of the initial evaluation, as this may represent a man in the acute phase of the disease. Pain may be present with palpation, erection, or during coitus, and should be differentiated as this may indicate a different degree of acute inflammation. The patient's subjective curvature deformity should be noted; it also deserves to mention that up to 90% of men may report ED associated with PD, and ED may be their most bothersome symptom. It is important to know what if any prior PD therapies the patient has undergone, as they may help guide future treatment.

A detailed past medical and sexual history should be part of the initial evaluation of every man with PD. Medical history should focus on personal or family history of wound-healing disorders, including Dupuytren's contracture, which is reported in up to 20% of patients with PD. Any risk factors for ED such as dyslipidemia, atherosclerotic disease, history of tobacco use, and diabetes should be queried. Patient's baseline erectile function should be assessed using a validated questionnaire. Although a validated PD questionnaire is still in development, the IIEF may be used to gauge the patient's baseline sexual function, understanding its potential limitations in this population.

The objective evaluation begins with the physical exam. Although the focus should be on the genital exam, an examination of the hands or feet is appropriate to define the presence of Dupuytren' contracture or Ledderhose disease (of the plantar fascia). Measurement of penile length is critical, as the loss of penile length is not only a known complication of PD, but is also a source of great concern among patients. The penis should be measured in the stretched flaccid state, dorsally from pubis to corona or meatus. Note that the suprapubic fat pad should be compressed during measurement. Objective evaluation of curvature is best performed using penile duplex Doppler ultrasound after pharmacologic stimulation to produce a full erection equal to or better than the patient's at home. Simple erection induction in the office will allow objective assessment of deformity. Duplex ultrasound will allow assessment of vascular flow rates, the degree of curvature as measured with a protractor, the presence, and location of Peyronie's plaque(s), and the presence of any hinge effect. In addition, the degree of plaque calcification can be assessed. Autophotography should not be used as the sole means for curvature measurement, as this modality can be inconsistent and inaccurate.

The final portion of the PD evaluation is objective assessment of the patient's erectile capacity and penile sensation. During duplex Doppler ultrasound the patient should be asked to grade their pharmacologic erection as compared to home erections. In addition, biothesiometry may be performed to assess penile virbratory sensation, in particular in men being considered for penile reconstructive surgery. Using the distal phalanx of the index fingers as positive control and the ventral surface of bilateral thighs as negative control, the point at which vibratory sensation is achieved should be measured on the mid shaft bilaterally and on the glans. Please see Figs. 15.1–15.3 for abbreviated PD evaluation and treatment algorithms.

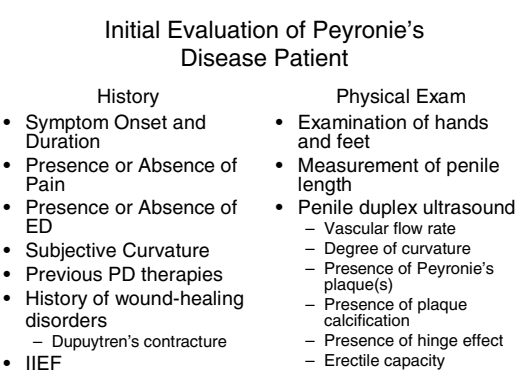

Fig. 15.1 PD – surgical algorithm

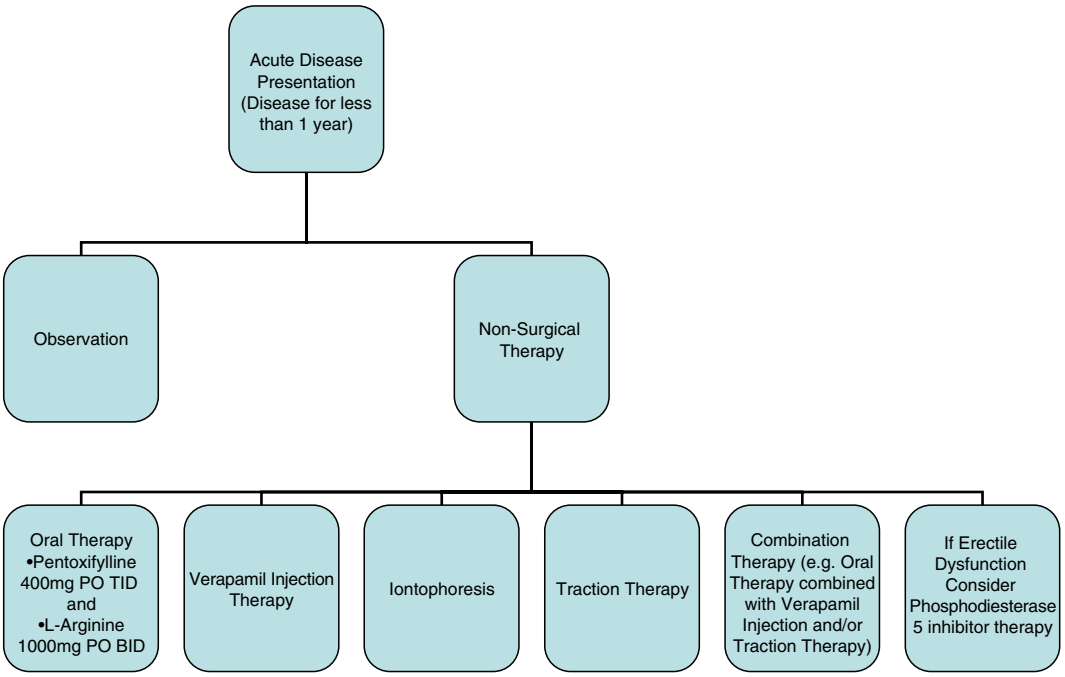

Fig. 15.2 Management of acute Peyronie's disease

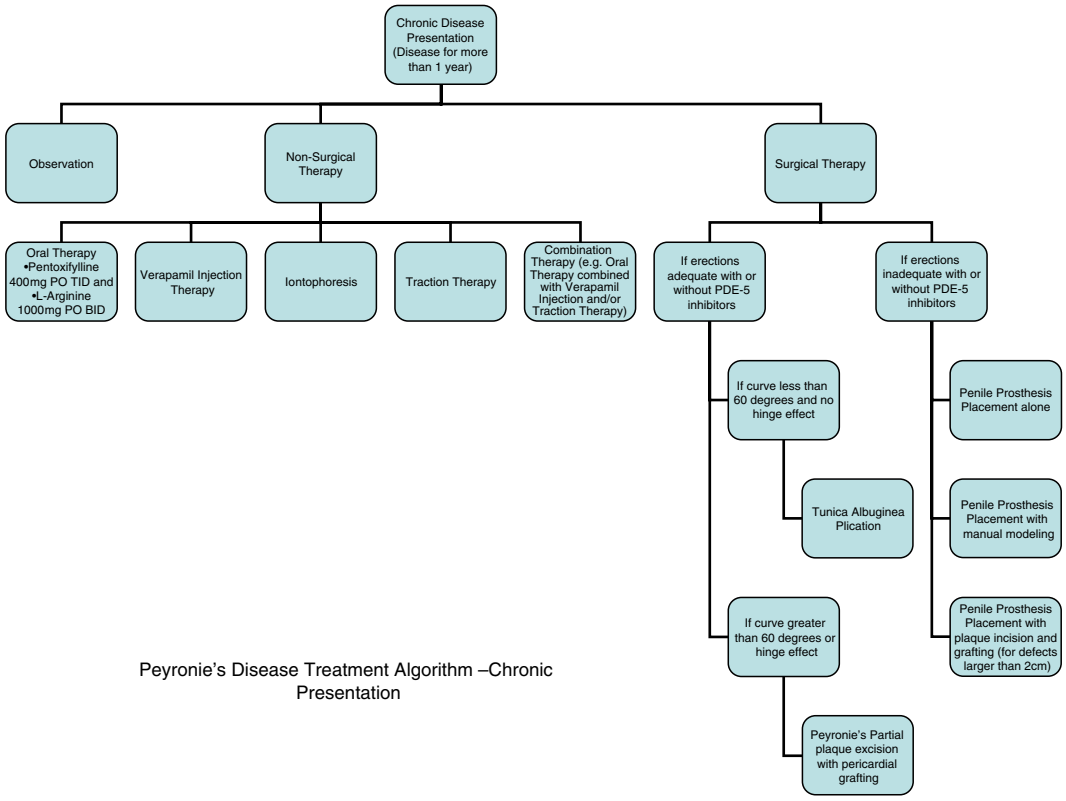

Fig. 15.3 Management of stable Peyronie's disease

Peyronie's Disease Following Radical Prostatectomy

Penile shortening has been noted in up to 71% of patients undergoing radical prostatectomy (RP) for prostate cancer [17]. The etiology of post-RP penile shortening is likely multifactorial, but recent work has begun to illuminate possible mechanisms for this occurrence. In addition, as PD is a disease of wound healing and fibrosis, it follows that PD has also been identified following RP surgery.

The etiology of post-RP penile fibrosis likely involves a combination of factors including changes in penile blood flow and penile tissue atrophy. It has been demonstrated in a rat model that the flaccid penis after RP is in a state of relative hypoxia in comparison to the pre-RP state [18]. In human corpora cavernosal tissue, Moreland et al. found that TGF-β1 was a key factor in the production of collagen and resultant fibrosis [19]. In a correlative study, Leungwattanakij et al. found that TGF-β1 and types I and III collagen were over-expressed in rat corporal tissue after bilateral cavernosal nerve injury [20]. These changes may also occur in the tunica albuginea.

Research in men post-RP support the basic science rat model research. Ciancio and Kim evaluated 110 men who underwent RP between 1996 and 1998 and who presented with post-RP erectile dysfunction (ED) [21]. The investigators found that 41% of men presenting with ED after RP had penile fibrotic changes, which represented 11% of the overall cohort of men undergoing RP during the specified time period. Interestingly, 93% of the men with fibrotic changes had curvatures as significant as 90°. In addition, 24% of the men had hinge effect narrowing deformities as well. Tal et al. [22] evaluated over 1,000 men who underwent RP for PD at a single institution. All men underwent preoperative examination by a sexual medicine specialist and were evaluated within 3 years of their surgery for the development of PD signs; all men who complained of penile curvature or had palpable Peyronie's plaques underwent curvature measurement after erection induction. The authors also performed a multivariate analysis to elucidate predictors of PD occurrence after RP. Several factors were evaluated including age, race (white vs. nonwhite), hypertension, hypercholesterolemia, ischemic heart disease, peripheral vascular disease, diabetes, and the quality of nerve sparing at the time of RP. Overall 15.9% of men developed PD after RP, with a mean time to the development of 13.9 months. The average curve was 31°. Multivariate analysis demonstrated that younger age (OR 1.3 for 5 year decrease in age) and white race (OR 4.1 vs. nonwhite) were independent predictors of PD after RP development. The incidence of PD after RP does appear to be significantly higher than in the general population, although no alterable preoperative or intraoperative factors have yet been identified as causative or associative. Further research is needed to elucidate the mechanism in order to offer patients preventative measures in the future.

Nonsurgical Therapy for Peyronie's Disease

Since the first description of PD in the literature, physicians have been searching for medical therapy options with little confirmed success. Consistent successful medical therapies continue to evade the practicing urologist, although current research into the molecular pathophysiology of PD may one day lead to medical cure. Several nonsurgical options, however, are currently available and may stabilize or reduce deformity and improve sexual function. The evaluation of their efficacy has been compromised by small clinical trials and without, in most cases, any placebo control. Several oral, topical, intralesional, external energy, and combination therapies have been proposed to date. Below is a brief summary of the most promising therapies currently in use. Table 15.1 provides a more comprehensive outline of the nonsurgical options for treatment of the pain and curvature of PD.

Table 15.1 Nonsurgical therapies for Peyronie's disease

Treatment	Mechanism of action	Comments
Oral		
Vitamin E	Antioxidant that theoretically reverses or stabilizes pathologic changes in the tunica albuginea	Limited side effects, low cost. Efficacy not proven
Colchicine	Inhibits fibrosis and collagen deposition	Mixed reports of efficacy in noncontrolled trials. Single randomized controlled trial failed to show benefit. May cause GI disturbances including severe diarrhea
Potassium aminobenzoate	Member of the Vitamin B complex, thought to increase the activity of monoamine oxidase, thereby decreasing local serotonin levels, which may contribute to fibrogenesis	Significant reduction in plaque size, but not curvature. Expensive, and difficult to tolerate due to GI side effects
Tamoxifen	May reduce TGF-β release from fibroblasts and may block TGF-β receptors, resulting in diminished fibrogenesis	Efficacy not proven. Side effects may include alopecia
Carnitine	Believed to inhibit acetyl coenzyme-A	Efficacy not proven, and more investigation is needed.
L-Arginine	Amino acid substrate in the formation of nitric oxide, which is thought to be lacking in PD tissue	Improvement in plaque size and collagen/fibroblast ratio in a rat model. Well tolerated
Pentoxifylline	Nonspecific phosphodiesterase inhibitor that may reduce collagen levels in PD plaques	Improvement in plaque size and collagen/fibroblast ratio in a rat model
Topical		
Verapamil	Increases extracellular matrix collagenase secretion through fibroblast inhibition and decreases collagen and fibronectin synthesis and secretion. Decreases fibroblast proliferation	When administered topically the drug does not appear to penetrate into the tunica albuginea
Intralesional		
Steroids	Antiinflammatory and cause reduction in collagen synthesis	Treatment with steroids is discouraged by the authors. Effects are unpredictable, and may cause atrophy and distortion of tissue planes
Collagenase	Breakdown of collagen	Statistically significant improvement in curvature has been noted in men with mild to moderate disease
Verapamil	Same as topical verapamil	Controlled and noncontrolled trials show promise as improvements in plaque volume, pain, and curvature have been reported
Interferons	Decrease the rate of proliferation of fibroblasts in Peyronie's plaques in vitro and reduced production of extracellular collagen and increased production of collagenase	Recent encouraging results with reports of improvement in curvature and pain. Dosing regimens and side effect profiles yet to be determined
External energy		
Penile ESWT	ESWT-induced inflammatory response with resultant plaque lysis, improved vascularity, and the creation of contralateral scarring	No statistically significant improvement noted in curvature, plaque size, or pain

(continued)

Table 15.1 (continued)

Treatment	Mechanism of action	Comments
Electromotively administered verapamil with/without dexamethasone	Effect of verapamil and steroids discussed previously. Electric current itself may have some beneficial effect on wound healing	Objective improvements of plaque size and curvature have been noted. Adverse effects include erythema at electrode site
Combination therapy		
Vitamin E and Colchicine	Discussed previously. Synergistic effect possible	Improvements in curvature and plaque size have been noted
ESWT with intralesional verapamil injection	Discussed previously. Synergistic effect possible	Significant improvement in plaque size compared with placebo
Intralesional verapamil with oral carnitine or tamoxifen	Discussed previously. Synergistic effect possible	Statistically significant subjective improvement in curvature, plaque size, and erectile function in patients treated with carnitine and intralesional verapamil
Penile traction devices		
fsPhysioMed penile extender	Expansion of contracted tissue may result in the formation of new connective tissue	Early results demonstrate improvement in curvature, increase in length, and improvement in hinge effect. Side effects were limited to mild discomfort with the device

Oral Therapies

L-Arginine

L-Arginine is an amino acid that, when catalyzed by nitric oxide synthase (NOS), combines with oxygen to ultimately form nitric oxide (NO). It is known that inducible NOS (iNOS) is expressed in the fibrotic plaques of PD, and that long-term suppression of iNOS exacerbates tissue fibrosis [23]. In 2003, Valente et al. reported that L-arginine, given daily in the drinking water of a rat model with TGF-β1-induced PD plaques resulted in an 80–95% reduction in plaque size and in the collagen/fibroblast ratio [23]. In addition, L-arginine was found to be antifibrotic in vitro. This suggests that L-arginine, as a biochemical precursor of NO, may be effective in reducing PD plaque size. Human trials are awaited.

Pentoxifylline

Pentoxifylline is a nonspecific PDE inhibitor. Valente et al. [23] found that normal human and rat tunica albuginea, as well as PD plaque tissue express PDE5A-3 and PDE4A, B, and D. In their in vitro study, PD fibroblasts were cultured with pentoxifylline and were found to have increased cAMP levels and reduced collagen I levels as compared to controls. In addition, pentoxifilline given orally to a TGF-β1-induced PD rat model resulted in a decrease in PD plaque size and collagen/fibroblast ratio. Brant et al. reported on a single case of successful PD treatment using pentoxifylline alone [24]. Further studies are required to definitively examine pentoxifylline for the treatment of PD; however, its known biochemical effect and early animal-model success make it an attractive option for oral therapy.

Colchicine

Colchicine is an antigout medication that inhibits fibrosis and collagen deposition primarily through its inhibition of the inflammatory response through inhibition of neutrophil microtubules [25]. Colchicine has been used as primary oral therapy for PD as well as in combination with other modalities. Akkus et al. [25] administered an escalating dose of colchicine in a nonrandomized,

nonplacebo controlled fashion to 19 patients with PD over a 3–5 month period. Thirty-six percent of patients noted a reduction in curvature, and 63% noted an improvement in the palpable plaque. Seventy-eight percent of the patients that were experiencing painful erections at the time of treatment initiation had resolution of this symptom. Kadioglu et al. [26] treated 60 patients with PD using 1 mg of colchicine twice daily, with a mean follow-up of 11 months. They found significant improvement of pain in 95% of men; however, 30% of patients reported improved curvature while 22% of patients reported worsened curvature. Safarinejad performed a randomized, placebo controlled trial of Colchicine in 2004 with 84 men [27]. It was found that Colchicine is no better than placebo at improvement of pain, curvature angle, or plaque size as measured by ultrasound. Colchicine is not recommended by the authors due to its lack of demonstrated efficacy in placebo controlled trials. The agent is also associated with gastrointestinal distress including diarrhea, and with rare aplastic anemia.

Potassium Para-Aminobenzoate

Potassium aminobenzoate (Potaba, Glenwood) is a member of the vitamin B complex that is believed to increase the activity of monoamine oxidase in tissues, thereby decreasing local levels of serotonin and thus possibly decrease fibrogenesis. Potassium aminobenzoate is used for other conditions including scleroderma, dermatomyositis, and pemphigus. Zarafonatis and Horrax [28] first described the use of potassium aminobenzoate for the treatment of PD, and a subsequent European study published in 1978 reported a 57% improvement rate with 9% complete resolution in a pooled cohort of 2,653 patients [29]. This study, however, did not include a control or placebo group. In 1999, Weidner et al. [30] published a randomized, placebo controlled trial of potassium aminobenzoate given 3 g orally 4 times per day for 1 year in 103 men. The only significant difference found between the two groups was plaque size, which was not and has not been shown to correlate with a decrease in penile curvature. A 2005 follow-up study also by Weidner et al. [31] suggested that the use of potassium aminobenzoate may protect against progression of PD plaques. Potassium aminobenzoate is expensive, and has low tolerability due to gastrointestinal side effects. It is also not recommended by the authors due to a lack of evidence regarding its efficacy in the treatment of PD.

Transdermal Agents

Interest in topical verapamil for the treatment of PD has followed its success as an intralesional agent (see below). However, one study demonstrated that tunica albuginea tissue concentrations of verapamil are not achievable through topical application [32]. A recent 3-arm trial without a known placebo demonstrated benefit with topical verapamil [33], but this study was significantly compromised [34]. Thus the use of verapamil as a topical agent for PD is not recommended.

Iontophoresis involves the transport of ions through tissue by means of an electric current. Several studies have investigated the efficacy of topically applied verapamil with or without dexamethasone with enhanced penetration using iontophoresis [35–38]. In 2002, Levine et al. confirmed that verapamil was found within the exposed tunica albuginea by examining surgically retrieved tunica albuginea from patients after a single intraoperative exposure during plaque incision and grafting surgery [39]. Di Stasi et al. recently reported on a prospective, randomized study of 96 patients treated with 5 mg verapamil plus 8 mg dexamethasone using iontophoresis vs. 2% lidocaine delivered electromotively [38]. Forty-three percent of patients in the verapamil/dexamethasone group noted objective improvement in plaque size and curvature; no changes were noted in the lidocaine group. In 2005, Greenfield et al. [40] reported on the use of 10 mg verapamil vs. saline iontophoresis. Patients were assessed using papaverine-induced erections prior to and 1 month after treatment. Sixty-five percent of patients in the verapamil group demonstrated improvement in curvature,

vs. 58% in the saline group. Mean curvature improvement was 9.1° in the treatment group vs. 7.6° in the saline group, which is not as robust as intralesional verapamil injections. In addition, the electric current itself may have some beneficial effect on wound healing, which is known and supported in the dermatologic literature [41]. Further investigation into iontophoresis remains ongoing.

Intralesional Therapies

Steroids

The powerful antiinflammatory effect of steroids leads to them being investigated early for intralesional therapy of PD. In 1954, Bodner et al. [42] reported improvement in 17 patients treated with intralesional hydrocortisone and cortisone. In 1975, Winter and Khanna [43] showed no difference between patients treated with dexamethasone injections and the natural history of the disease. In 1980, Williams and Green [44] published a prospective study using intralesional triamcinolone. All patients were observed for 1 year after study enrollment; during that time only 3% of patients reported improvement. Triamcinolone was administered every 6 weeks for 36 weeks; 33% of patients reported improvement, particularly in pain and plaque size. Currently, the use of intralesional steroids is discouraged due to the side effects of local tissue atrophy, fibrosis, immune suppression, and lack of objective measures of benefit.

Collagenase

Collagenase was first studied in vitro by Gelbard et al. [45]. A subsequent clinical trial by that group [46] demonstrated subjective improvement in 64% of patients within 4 weeks of treatment. A decade after their initial study, they published their findings of a double-blind trial in 49 men [47]. Statistically significant improvement in curvature was noted in the collagenase treated group; however, improvement was only seen in patients with less than 30° curvatures and plaques of less than 2 cm. Larger scale controlled trials of collagenase are currently ongoing.

Verapamil

Verapamil is a calcium channel blocker that has been shown in in vitro studies to inhibit local extracellular matrix production by fibroblasts, reduce fibroblast proliferation, increase local collagenase activity, and affect the cytokine milieu of fibroblasts [48, 49]. In 1994, Levine et al. [50] reported on 14 men who underwent biweekly intralesional injections of verapamil for 6 months. Significant improvement in plaque associated narrowing was noted in all patients, and curvature was improved in 42%. The first randomized single-blind trial of intralesional verapamil was published in 1998 [51]. Significant differences were noted in terms of erection quality and plaque volume. A trend toward improvement in curvature was also noted. As a follow-up, Levine and Estrada reported on 156 men enrolled in a prospective nonrandomized trial of PD men with a mean follow-up of 30.4 months [52].

A local penile block was performed with 10–20 mL 0.5% bupivicaine, followed by injection of 10 mg verapamil diluted in 6 mL sterile normal saline (total volume 10 mL) into the Peyronie's plaque using 1–5 skin punctures, but with multiple passes through the plaque. The goal is to leave the drug in the needle tracks, not to tear or disrupt the plaque. Injections were administered every 2 weeks for 12 total injections. Eighty-four percent of patients with pain achieved complete resolution, 62% were found on objective measurement to have improved curvature ranging from 5 to 75° (mean 30°), and only 8% of patients had measured worsening of curvature. More recently, Bennett et al. [53] administered six intralesional injections (10 mg in 5 mL) every 2 weeks to 94 consecutive patients with PD. Follow-up was at 5.2 months after completion of the sixth injection. Eighteen percent of patients ($n=17$) were found to have improved curvatures (average improvement 12°), 60% ($n=56$) had stable curvature, and 22% ($n=21$) had increased curvature (average increase 22°). All patients

with pretreatment penile pain had improvement at follow-up. It may be that six injections provide stabilization but is insufficient to accomplish reduction of curvature. Currently, we recommend a trial of six injections with each injection occurring every 2 weeks. If no improvement is noted, the therapy may be terminated, the verapamil dose can be increased to 20 mg, or interferon (IFN) injections may be offered. We consider verapamil contraindicated in patients with ventral plaques or extensive plaque calcification.

Interferon

Duncan et al. [54] reported in 1991 that IFNs decrease the rate of proliferation of fibroblasts in Peyronie's plaques in vitro, reduce the production of extracellular collagen, and increase the activity of collagenase. Initial studies performed by Wegner et al. [55, 56] demonstrated low rates of improvement, but a high incidence of side effects including myalgias and fever. In 1999, Ahuja et al. [57] reported on 20 men who received 1×10^6 units of IFN-α-2b biweekly for 6 months. Hundred percent of patients reported softening of plaque, 90% of men presenting with pain had improvement, and 55% had a subjective reduction in plaque size. Dang et al. [58] administered 2×10^6 units to 21 men biweekly for 6 weeks, and found objective curvature improvements in 67%, and improvement in pain in 80%. Seventy-one percent of patients reported improvement in ED symptoms. In 2006, Hellstrom et al. [59] reported on a placebo controlled, multicenter trial of 117 patients who underwent biweekly injections of 5×10^6 units for a total of 12 weeks. Average curvature in the treatment group improved 13° vs. 4° in the placebo arm, and 27% of patients in the treatment group had measured improvement vs. 9% of saline group. Pain resolution was noted in 67% of the treatment patients vs. 28% for placebo. IFN therapy requires further investigation to adequately determine efficacy, dosing regimens, and side effect profiles before its routine use in PD patients.

Penile Traction Devices

The use of tissue expanders has long been a mainstay of treatment in the orthopedic, oral–maxillofacial, and plastic surgery fields. It is well documented that gradual expansion of tissue results in the formation of new bone and connective tissue. Recently, initial work has been done to evaluate the efficacy of a penile extender device (fsPhysioMed® (FastSize LLC, Aliso Viejo, CA)) for the treatment of PD. An initial pilot study at our institution of 10 patients found that daily use of the fsPhysioMed® device resulted in a 33% improvement in curvature (from an average baseline curvature of 51–34° after treatment), an increase in penile length ranging from 0.5 to 2.0 cm, and an improvement in hinge effect in all those with advanced narrowing or indentation. No patients noted recurrence or worsening of curvature, and there was no incidence of local skin changes, ulceration, loss of sensation, or worsening of curvature. Long term and larger studies are needed before penile extender devices can be recommended for all patients with PD; however, these encouraging early results are met at our institution with excitement.

We currently favor a multimodal approach to nonsurgical therapy for PD. All patients are given Pentoxifylline 400 mg orally three times a day, with L-Arginine 1,000 mg twice a day. Patients are encouraged to use the fsPhysioMed® device 2–8 h per day for 6 months, and in appropriate patients are offered Verapamil injections as a means to improve curvature and, if present, pain.

Surgical Treatment of Peyronie's Disease

Surgery remains the gold-standard treatment for PD. Surgery should only be performed when the disease is stable enough to ensure long-term efficacy. In general, surgery should be considered only when disease duration is 9 months–1 year, and when the disease has remained stable for at least 6 months.

Preoperative history, physical examination, and duplex ultrasonography are essential to formulat a treatment plan. A treatment algorithm was developed at Rush University Medical Center in Chicago, IL, based on the patient's erectile function, degree of curvature, and the presence of hinge effect [60] (Fig. 15.1). In brief, if rigidity is adequate for intromission with or without the use of pharmacotherapy and the patient has a simple curve less than 60° and no hourglass or hinge effect, they are offered a plication procedure. If they have a complex curve greater than 60° or presence of destabilizing hourglass or hinge effect they are offered a grafting procedure. Patients whose rigidity is inadequate for intromission despite oral pharmacotherapy are offered penile prosthesis with manual molding. Informed consent is critical prior to the initiation of any therapy for PD, particularly surgical correction. The risks of reduction of rigidity, diminished penile sensation, delayed ejaculation, shortening of the penis, and persistent or recurrent curvature should all be carefully discussed with the patients and carefully documented in the medical record. It may also be wise to discuss with patients the expected changes in penile shape consistent with the early postoperative period following penile surgery.

Surgery for PD generally falls into two categories: plication procedures for less severe disease and grafting procedures for significant (>60°) curves or the presence of hinge effect. It is beyond the scope of this chapter to detail all the available and practiced surgical techniques. Instead, the Rush University (Chicago) procedures of Tunica Albuginea Plication (TAP) and plaque incision with Tutoplast® (Coloplast, Minneapolis, MN) human pericardial grafting will be detailed below. Other published outcomes are presented in Tables 15.2 and 15.3.

Tunica Albuginea Plication

An artificial erection is created in the operating room using 60 mg of papaverine and infusion of saline using an infusion pump. A circumcising incision is made 1.5–2 cm proximal to the corona and the penis is degloved, exposing Buck's fascia to the base of the penis. Hemostasis is best achieved using bipolar current so as to avoid injury to the sensory nerves.

The segment of Buck's fascia overlying the deep dorsal vein is opened, and the vein opposite the point of maximum curvature is excised. Transverse incisions each 1.0–1.0 cm in length and separated by 0.7–1.5 cm are made directly over the septum. The incision is carried down sharply with the scalpel through the longitudinal tunical fibers, leaving the circular fibers intact. The tunica is plicated using 2-0 braided polyester suture (Tevdek, Teleflex Medical, Fall River MA) in an inverting vertical mattress fashion, thus burying the knot; typically a single central plication suture is placed (Fig. 15.4). The plication is then reinforced with several 3-0 PDS™ sutures (Ethicon, Somerville, NJ) placed in a Lembert fashion. Penile straightness is then rechecked by recreating an artificial erection using saline. Two to three plications are usually sufficient, although anywhere from 1 to 6 plications may be necessary. Once satisfactory straightening has been reached, Buck's fascia and the skin are reapproximated. Xeroform® (Tyco Health Care, Mansfield, MA) dressing is placed over the suture line and covered with sterile gauze. A Coban™ dressing (3M, St. Paul, MN) is lightly wrapped from the glans to the base of the penis.

The dressing is left in place for 3 days, at which time the patient is instructed to remove it at home. Patients are instructed to follow-up for their initial office visit 2 weeks after surgery. From weeks 2–6 patients are instructed in massage and stretch rehabilitation, which is undertaken for 5 min twice daily. Sexual activity is allowed 6 weeks postoperatively. Based upon the recent report by Moncada et al. [61], for those undergoing surgical reconstruction the use of an external penile traction device is recommended beginning 2–3 weeks postoperatively. It should be applied daily for up to 8 h for 3 months to reduce postoperative shortening.

A review of long-term follow-up data for the TAP procedure was recently performed [62].

Table 15.2 Published plication data

References	Patient number	Procedure type	%Straight	%with ED	Diminished sensation (%)	Mean follow-up duration (months)
Daitch et al. [72]	28	Modified corporoplasty (transverse closure of longitudinal corporal incisions)	89	4	Not reported	24.1
Gholami et al. [73]	132	16 Dot plication technique	85	3	Not reported	31
Syed et al. [74]	50	Nesbit plication	90	Not reported	21	84
Savoca et al. [75]	218	Nesbit plication	86.3	13	11	89
Rolle et al. [76]	50	Nesbit plication	100	0	Not reported	Not reported
Bella et al. [77]	23	Minimally invasive intracorporeal plaque incision	91	Not reported	4	25
Greenfield et al. [78]	68	Tunica albuginea plication (modified Nesbit technique)	99	7.3	4	29
Taylor et al. [79]	61	Tunica albuginea plication	93	10	31	72

Table 15.3 Published graft data

References	Patient number	Procedure type	%Straight	%with ED	Diminished sensation (%)	Mean follow-up duration (months)
Gelbard et al. [80]	69	Plaque incision and temporalis fascia grafting	74	14	Not reported	Not reported
El-Sakka et al. [81]	112	Plaque incision with venous grafting	96	12	10	18
Hatzichristou et al. [82]	17	Tunica albuginea free grafting	100	0	Not reported	39
Egydio et al. [83]	33	Tunica albuginea incision and bovine pericardial grafting	87.9	Not reported	Not reported	19
Levine et al. [84]	40	Tunica albuginea incision and human pericardial grafting	98	30	Not reported	22
Kalsi et al. [85]	113	Plaque incision with venous grafting	86	15	Not reported	12
Breyer et al. [86]	19	Porcine small intestine submucosa graft	63	53	Not reported	15
Hsu et al. [87]	48	Plaque incision with venous grafting	90	5	Not reported	Not reported
Taylor et al. [79]	81	Plaque partial excision with human pericardial grafting	91	21	31	58

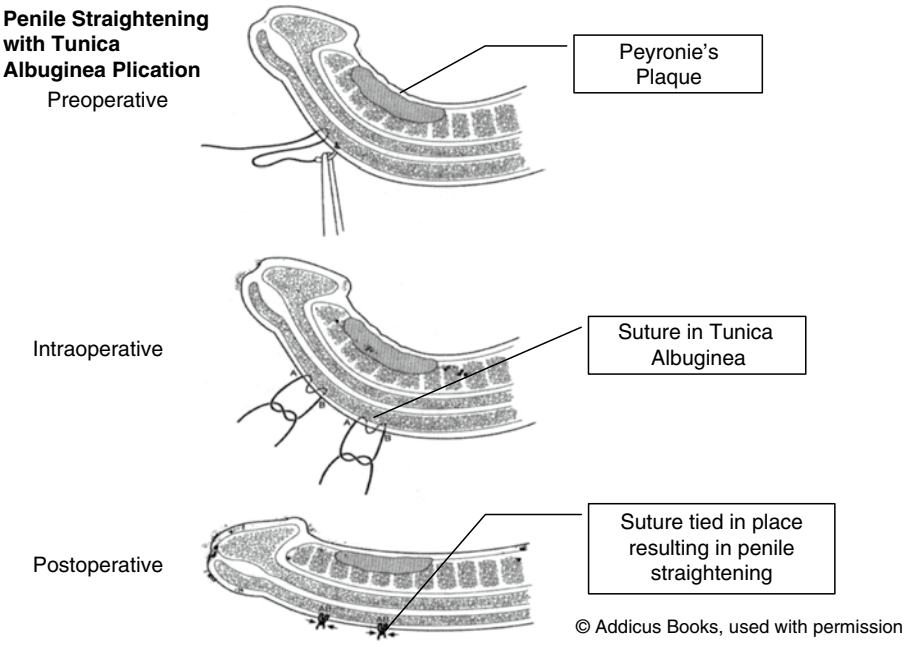

Fig. 15.4 Penile plication surgery

Ninety patients were reviewed, with an average follow-up of 72 months. Ninty-three percent of patients reported resolution of their curvature, with only 2% of patients reporting a recurrence of their curvature postoperatively. Twenty-eight percent of patients did develop noted diminished rigidity, but 88% of patients were still capable of intromission with the use of oral phosphodiesterase-5 inhibitors. Sixty-eight percent of patients felt that their sensation was unchanged, and 98% report continued ability to achieve orgasm. In terms of penile shortening, which is a known complication of plication surgery, 74% of patients subjectively felt that their penis was shorter; however, objective office-based data demonstrated that the majority (82%) of patients did not lose length.

Peyronie's Plaque Incision/Partial Excision and Grafting

Penile reconstruction in the face of severe deformity demands plaque incision or partial excision with the placement of graft tissue over the resulting defect. Many different graft tissues are available, from autologous vein, dermal, or fascial transfer to commercially available "off the shelf" materials. Concerns regarding all grafting procedures include graft contracture, curvature recurrence, neurovascular injury, and impotence; the ideal graft material should be readily available, should possess enough compliance to function with erections, and should have a high rate of efficacy with a low rate of complication [63]. Although the ideal graft material has yet to be confirmed, our preference is the Tutoplast® processed pericardium.

An artificial erection is created in the operating room using 60 mg of papaverine and a saline infusion pump. The penis is degloved via a circumcising incision initiated 1.5–2 cm proximal to the corona. The neurovascular bundle is elevated over the area of maximum curvature and Buck's fascia is incised bilaterally and longitudinal to the urethra. Longitudinal extensions of this incision can be made at a 30° angle to the transverse incision, creating the modified "H" incision and thus resulting in a rectangular defect. In the presence of hinge effect, indentation, or extensive calcification, this tissue should be excised prior to graft placement (Fig. 15.5).

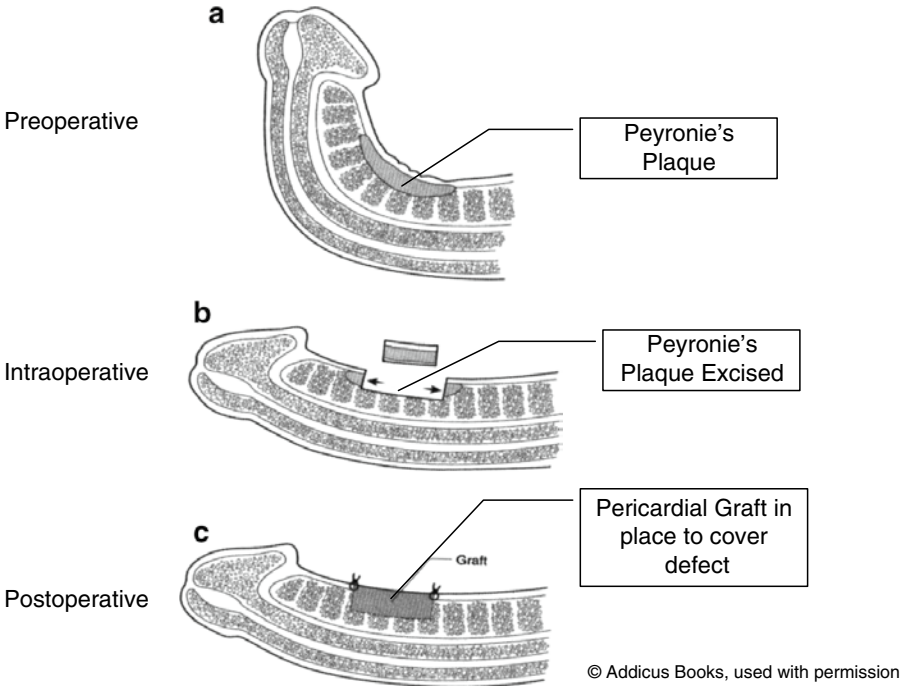

Fig. 15.5 Plaque excision and grafting

Upon partial excision of the plaque the penis is placed on stretch and the pericardial graft is sized appropriately and sutured to the defect. The artificial erection is recreated, and the penis inspected for any residual deformity. If necessary, additional grafting or plication measures may be taken at this time. A recent analysis demonstrated that adding a plication does not compromise postoperative rigidity or cause significant shortening [64]. Buck's fascia and the skin are reapproximated. The same dressing as for the TAP procedure is used, with Xeroform® gauze, a dry sterile dressing, and Coban® dressing.

The Coban dressing is removed on postoperative day 3, and the patient is seen in the office on postoperative day 14. At that time they are instructed on penile massage and stretch therapy as a means to aid in recovery. Small subgraft hematomas are not routinely aspirated unless they are a source for significant postoperative pain, and our experience is that the hematomas resorb with time, causing no residual effect. The use of penile traction devices is encouraged beginning 2–3 weeks postoperatively. This group is also encouraged to use a low dose phosphodiesterase inhibitor nightly on postoperative days 10–50 as pharmacologic erectile rehabilitation [64].

A recent review of our long-term results of Tutoplast grafting for severe PD was recently performed [62]. 111 patients undergoing our grafting procedure were retrospectively reviewed, with an average follow-up of 58 months. Ninety-two percent of patients remained satisfactorily surgically straightened, with 12% in whom their curvatures recurred. Thirty-five percent of patients developed new erectile dysfunction, but 76% were able to achieve intromission with PDE-5 inhibitors. It is notable that 90% of these patients were taking PDE-5 inhibitors prior to their operation. Although 65% of patients felt that they lost length, flaccid stretched penile length measurements in the office demonstrated an average gain of 0.2 cm. Sensation remained intact in the majority of patients, with 89% reporting an ability to achieve orgasm.

Straightening with Penile Prosthesis

Patients presenting with PD and ED can achieve curvature straightening and definitive mechanical erections through the placement of a penile prosthesis. The risks of ED development after surgical correction of PD are well known and described, and all men with baseline ED, vascular comorbidities, or severe curvatures likely requiring significant plaque excision and grafting should be counseled to consider penile prosthesis. Prosthesis choice depends on the patient and surgeon; the medical literature supports the use of semirigid implants [65, 66], two piece implants [67, 68], and three piece implants [69, 70], although patient satisfaction appears to be best with inflatable devices [71]. Our treatment algorithm involves placement of penile prosthesis followed by manual molding and, if necessary, a relaxing tunical incision with or without patch grafting (Fig. 15.2).

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Chapter 16
Disorders of Ejaculation and Male Orgasm

Chris G. McMahon

Keywords Premature ejaculation • SSRI • Transdermal • Acquired • Life-long • Delayed rohasm

Introduction

Ejaculatory dysfunction is one of the most common male sexual disorders. The spectrum of ejaculatory dysfunction extends from premature ejaculation, through delayed ejaculation to a complete inability to ejaculate (known as anejaculation), and includes retrograde ejaculation.

The sexual response cycle can usefully be conceptualized as having four interactive stages: desire, arousal, orgasm, and resolution. Within the sexual response cycle, orgasm/ejaculation in men has both a biological (reproductive) and psychological (reward) endpoint. Arousability and arousal – distinct but interrelated constructs – are precursors to this endpoint. Arousability and/or sexual libido are psychological constructs used to explain variability in the intensity and/or desire for a sexual response. Arousability might best be conceptualized as the organism's readiness to respond. This state of readiness depends on both internal (hormonally "primed" diencephalic brain structures) and external (appropriate partner and situation) stimulus conditions. Sexual arousal or excitement – the organism's actual response to the stimulus conditions – represents both a subjective/cerebral state of sympathetic activation and peripheral physiological responses (e.g. erection) that prepares the man for sexual activity. During sexual activity, increasing levels of sexual arousal reach a threshold that triggers the ejaculatory response, which then typically terminates the sexual episode for the male. The subjective (brain) perception of urethral distension and bladder neck closure of the emission phase of ejaculation is associated with the sensation experienced as "ejaculatory inevitability." The perception of the striated muscle contractions and resulting semen expelled during ejaculation, mediated through sensory neurons in the pelvic region, gives rise to the experience of orgasm, a distinct cortical event, experienced phenomenologically both cognitively and emotionally.

Sexual dysfunction may involve disruption of any of the above phases [1]. This four-stage model is consistent with the overall paradigm shift within urology, where both organic and psychogenic factors are recognized and integrated into our understanding of sexual function and dysfunction. Conceptualizing four stages provides a better heuristic platform for understanding ejaculatory dysfunctions as secondary to disruptions of any stage in the ejaculatory process, leading to appropriate and specific treatments.

Specific to ejaculation and orgasm, the latency to ejaculation, that is, the time (and more importantly, the amount of stimulation) extending from the onset of penile stimulation to the moment of ejaculation, represents a continuum of time that shows variation across men and,

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within men, across situations. Although the great majority of men appear to reach ejaculation and orgasm following several minutes of penile vaginal stimulation and are, along with their partners, quite satisfied with the latency of their ejaculatory response, others report dissatisfaction. For example, some men ejaculate very rapidly after, or sometimes even prior to, penetration and do so with minimal stimulation. Others may ejaculate only with great difficulty or not at all, even following prolonged stimulation. These conditions, as noted above, represent subsets – at opposite ends of the spectrum – that fall into the categories of male ejaculatory disorders.

The Anatomy and Physiology of the Ejaculatory Response

The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways. Neurochemically, this reflex involves a complex interplay between central serotonergic and dopaminergic neurons, with secondary involvement of cholinergic, adrenergic, oxytocinergic, and gamma aminobutyric acid (GABA) agric neurons.

The ejaculatory process integrates actions that occur in the central (CNS) and peripheral nervous systems (PNS). Structures in the CNS that are involved in ejaculation include the medial preoptic area (MPOA), nucleus paragigantocellularis (nPGi), posteromedial bed nucleus of the stria terminalis, posterodorsal medial amygdale, and the medial parvicellular subparafascicular nucleus of the thalamus (Fig. 16.1). While the MPOA is involved in stimulation of ejaculatory response, the nPGi has an inhibitory influence; specifically, descending serotonergic pathways from the nPGi to the lumbosacral motor nuclei inhibit ejaculation. The MPOA can inhibit the nPGi which in turn results in ejaculation [2]. Central control of ejaculation is mediated via spinal ejaculation centres including lumbar spinothalamic (LSt) cells which integrate peripheral signals from the genital areas with excitatory and inhibitory control from supraspinal centres such as the nucleus nPGi.

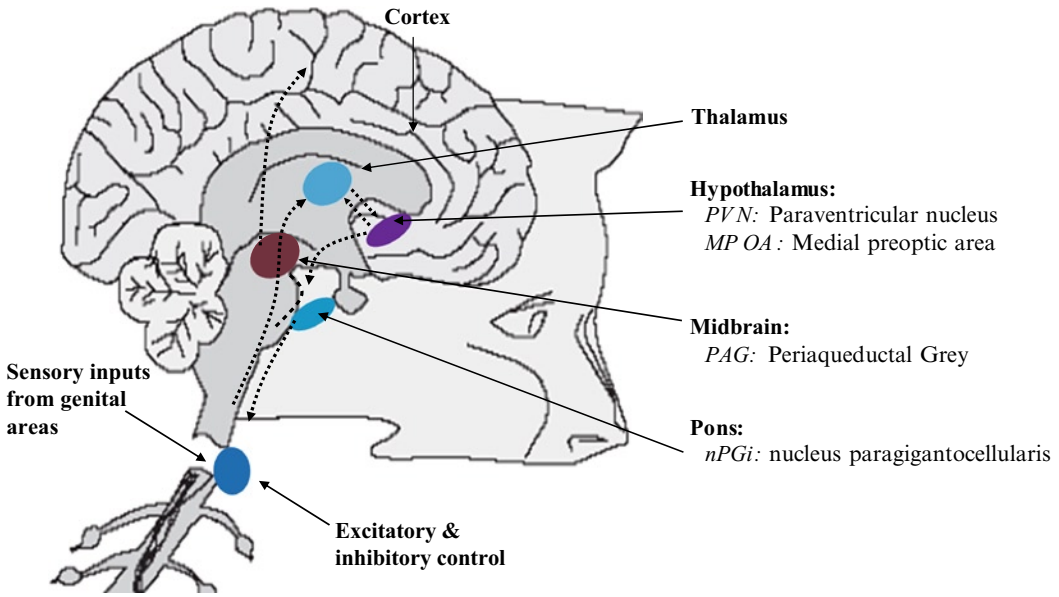

Fig. 16.1 Emission and ejaculation are centrally integrated and highly co-ordinated processes. The brain structures involved in the control of ejaculation include the thalamus, structures in the hypothalamus such as the medial preoptic area (MPOA) and the paraventricular thalamic nucleus (PVN), structures in the midbrain such as the periaqueductal grey nucleus (PAG) and structures in the pons such as the paragigantocellularis (nPGi) nucleus. These structures integrate sensory ejaculation-related inputs from the genital areas with higher excitatory and inhibitory controls

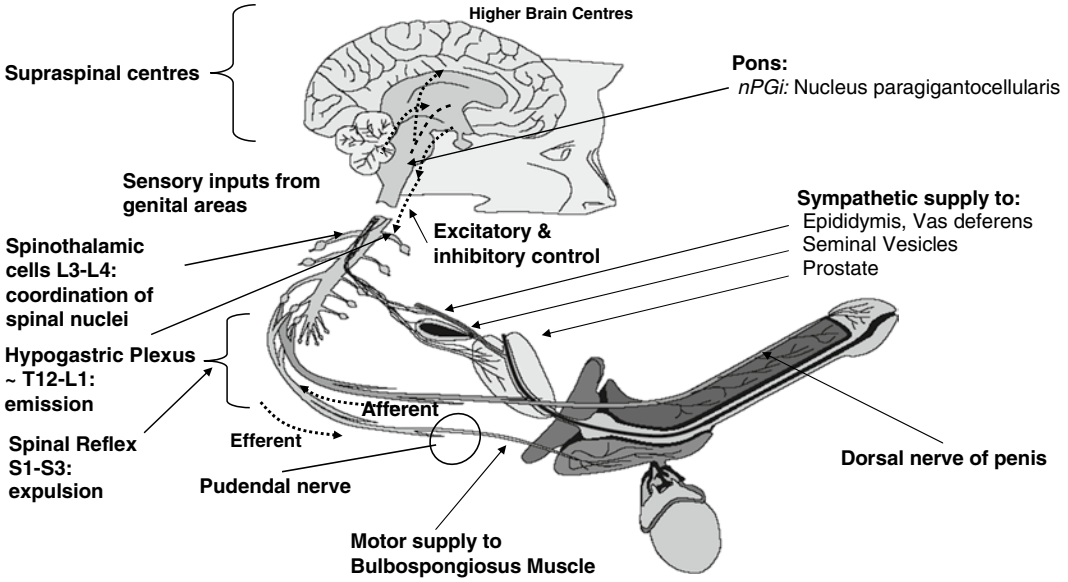

Fig. 16.2 Central control of ejaculation is mediated via spinal ejaculation centres including lumbar spinothalamic (LSt) cells which integrate peripheral signals from the genital areas with excitatory and inhibitory control from supraspinal centres such as the nucleus nPGi. The spinal ejaculation generators send co-ordinated outputs to the anatomic structures that allow ejaculation to occur

The spinal ejaculation generators send co-ordinated outputs to the anatomic structures that allow ejaculation to occur (Figs. 16.2 and 16.3). Several brain areas are activated after ejaculation by ascending fibres from the spinal cord and may have a possible role in satiety and the post-ejaculatory refractory time [3].

Based upon functional, central and peripheral mediation, the ejaculatory process is typically subdivided into three phases: emission, ejection (or penile expulsion), and orgasm (Table 16.1). Emission consists of contractions of seminal vesicles (SV) and the prostate, with expulsion of sperm and seminal fluid into the posterior urethra, and is mediated by sympathetic nerves (T10 to L2). Ejection is mediated by somatic nerves (S2 to S4), and involves pulsatile contractions of the bulbocavernosum and pelvic floor muscles together with relaxation of the external urinary sphincter. Ejection also involves a sympathetic spinal cord reflex upon which there is limited voluntary control. The bladder neck closes to prevent retrograde flow; the bulbocavernous, bulbospongiosus and other pelvic floor muscles contract rhythmically, and the external urinary sphincter relaxes. Intermittent contraction of the

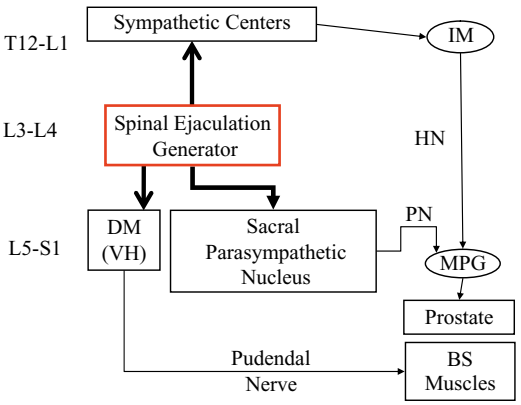

Fig. 16.3 The spinal ejaculation generator controls of the prostate and the bulbospongiosus (BS) muscle. The spinal ejaculation generator projects to the parasympathetic (L5–S1) and sympathetic (T13–L2) preganglionic neurons, and dorsomedial nucleus (DM) motoneurons (L5–L6). The parasympathetic centres project to the prostate via the major pelvic ganglion (MPG) and the pelvic nerve (PN). The sympathetic centres project to the prostate through the intermesenteric ganglion (IMG) and the hypogastric nerve (HN). The motoneurons of the BS muscle project to the muscle through the motor branch of the pudendal nerve. *L* lumbar segment of spinal cord; lumbar spinothalamic; *T* thoracic segment of spinal cord; *VH* ventral horn

Table 16.1 The three stages of normal antegrade ejaculation

Emission	Sympathetic spinal cord reflex (T10–L2)
	Genital and/or cerebral erotic stimuli with considerable voluntary control
	Peristaltic contraction of epididymis and vas deferens
	Contraction of seminal vesicles and prostate
	Expulsion of spermatozoa/seminal/prostatic fluid into posterior urethra
	Ejaculatory inevitability sensation resulting from distension of posterior urethra
Ejection	Parasympathetic spinal cord reflex (S2–S4)
	Limited voluntary control
	Rhythmic contractions of bulbocavernous/pelvic floor muscles
	Bladder neck closure
	Relaxation of external urinary sphincter
Orgasm	Build-up and release of pressure in posterior urethra
	Smooth muscle contraction of accessory sexual organs and urethral bulb
	Sensation due cerebral processing of pudendal nerve sensory stimuli

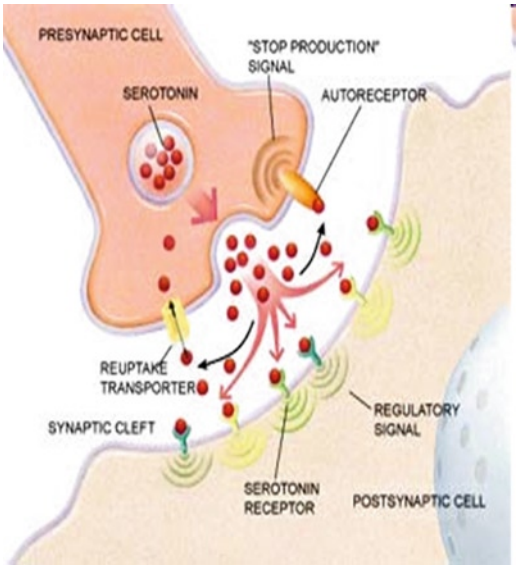

Fig. 16.4 Synaptic cleft 5-HT and 5-HT neurotransmission are regulated by somatodendritic 5-HT1a autoreceptors, presynaptic 5-HT1B 1D autoreceptors, and a 5-HT transporters re-uptake system

urethral sphincter prevents retrograde flow into the proximal urethra [4]. Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the verumontanum and contraction of the urethral bulb and accessory sexual organs.

Many neurotransmitters are involved in the control of ejaculation, including dopamine, norepinephrine, serotonin, acetylcholine, oxytocin, GABA, and nitric oxide (NO) [3]. Of the many studies conducted to investigate the role of the brain in the development and mediation of sexuality, dopamine and serotonin have emerged as essential neurochemical factors. The dopaminergic system, particularly that in the anterior hypothalamus, exerts a sexual facilitatory role [5]. A possible sexual response regulatory role of dopamine is suggested by the observation that dopamine is released in the MPOA of male rats in the presence of an oestrous female, and progressively increases during copulation, eventually triggering ejaculation [6].

Where dopamine promotes seminal emission/ejaculation via D2 receptors, serotonin is inhibitory. Serotonergic neurons are widely distributed in the brain and spinal cord and are predominantly found in the brainstem, raphe nuclei, and the reticular formation. Currently, at least 16 different receptors have been characterized, e.g. 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, etc [7]. Synaptic cleft 5-HT and 5-HT neurotransmission are regulated by somatodendritic 5-HT1A autoreceptors, presynaptic 5-HT1B 1D autoreceptors, and a 5-HT transporters re-uptake system (Fig. 16.4). Stimulation of the 5-HT2C receptor with 5-HT2C agonists results in delay of ejaculation in male rats, whereas stimulation of postsynaptic 5-HT1A receptors results in shortening of ejaculation latency [8], leading to the hypothesis that men with premature ejaculation (PE) may have hyposensitivity of 5-HT2C and/or hypersensitivity of the 5-HT1A receptor [2, 9].

Premature Ejaculation

Introduction

Over the past 20–30 years, the PE treatment paradigm, previously limited to behavioural psychotherapy, has expanded to include drug

treatment [10, 11]. Animal and human sexual psychopharmacological studies have demonstrated that serotonin and 5-HT receptors are involved in ejaculation and confirm a role for selective serotonin re-uptake inhibitors (SSRIs) in the treatment of PE [12–15]. Multiple well-controlled evidence-based studies have demonstrated the efficacy and safety of SSRIs in delaying ejaculation, confirming their role as first-line agents for the treatment of lifelong and acquired PE [16]. More recently, there has been increased attention to the psychosocial consequences of PE, its epidemiology, its aetiology, and its pathophysiology by both clinicians and the pharmaceutical industry [17–22].

Defining Premature Ejaculation

The medical literature contains several univariate and multivariate operational definitions of PE [11, 23–30]. Each of these definitions characterize men with PE using all or most of the accepted dimensions of this condition: ejaculatory latency, perceived ability to control ejaculation, and negative psychological consequences of PE including reduced sexual satisfaction, personal distress, partner distress, and interpersonal or relationship distress.

The first official definition of PE was proposed in 1980 by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) [31]. This definition was progressively revised as the DSM-III-R, DSM-IV, and finally DSM-IV-TR definitions to include the "shortly after penetration" as an ejaculatory latency criterion, "before the person wishes it" as a control criterion and "causes marked distress or interpersonal difficulty" as a criterion for the negative psychological consequences of PE [23, 32, 33]. Although DSM-IV-TR, the most commonly quoted definition, and other definitions of PE differ substantially, they are all authority-based i.e. expert opinion without explicit critical appraisal, rather than evidence-based, and have no support from controlled clinical and/or epidemiological studies [34]. The DSM definitions are primarily conceptual in nature, vague in terms of operational specificity, multi-interpretable, fail to provide any diagnostic intravaginal ejaculatory latency time (IELT) cut-off points and rely on the subjective interpretation of these concepts by the clinician [2, 35, 36]. The absence of a clear IELT cut-off point in the DSM definitions has resulted in the use of a broad range of subjective latencies for the diagnosis of PE in clinical trials ranging from 1 to 7 min [37–45]. The failure of DSM definitions to specify an IELT cut-off point means that a patient in the control group of one study may very well be in the PE group of a second study, making comparison of studies difficult and generalization of their data to the general PE population impossible.

This potential for errors in the diagnosis of PE was demonstrated in two recent observational studies in which PE was diagnosed solely by the application of the DSM-IV-TR definition [20, 22]. Giuliano et al. diagnosed PE using DSM-IV-TR criteria in 201 of 1,115 subjects (18%) and predictably reported that the mean and median IELT was lower in subjects diagnosed with PE compared to non-PE subjects. There was, however, substantial overlap in stopwatch IELT values between the two groups. In subjects diagnosed with PE, the IELT range extended from 0 s (anti-portal ejaculation) to almost 28 min with 48% of subjects having an IELT in excess of 2 min and 25% of subjects exceeding 4 min. This study demonstrates that a subject diagnosed as having PE on the basis of DSM-IV-TR criteria has a 48% risk of not having PE if a PE diagnostic threshold IELT of 2 min, as suggested by community-based normative IELT trial, is used [19].

The first contemporary multivariate evidence-based definition of lifelong PE was developed in 2008 by a panel of international experts, convened by the International Society for Sexual Medicine (ISSM), who agreed that the diagnostic criteria necessary to define PE are: time from penetration to ejaculation, inability to delay ejaculation, and negative personal consequences from PE. This panel defined lifelong PE as a male sexual dysfunction characterized by "… ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the

presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy" [46].

This definition is supported by evidence from several controlled clinical trials. Evidence to support inclusion of the criterion of " …ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration …."

- Operationalization of PE using the length of time between penetration and ejaculation, the IELT, forms the basis of most current clinical studies on PE [47]. IELT can be measured by a stopwatch or estimated. Several authors report that estimated and stopwatch IELT correlate reasonably well or are interchangeable in assigning PE status when estimated IELT are combined with PROs [48–50].
- Several studies suggest that 80–90% of men seeking treatment for lifelong PE ejaculate within 1 min (Fig. 16.5) [51–53]. Reported IELTs <30 s in 77% and <60 s in 90% of 110 men with lifelong PE with only 10% ejaculating between 1 and 2 min. These data are consistent with normative community IELT data, support the notion that IELTs of less than 1 min are statistically abnormal and confirm that an IELT cut-off of 1 min will capture 80–90% of treatment seeking men with lifelong PE [19]. Further qualification of this cut-off to "about one minute" affords the clinician sufficient flexibility to also diagnose PE in the 10–20% of PE treatment seeking men who ejaculate within 1–2 min of penetration without unnecessarily stigmatizing the remaining 80–90% of men who ejaculate within 1–2 min of penetration but have no complaints of PE.

Evidence to support inclusion of the criterion of " …the inability to delay ejaculation on all or nearly all vaginal penetrations…."

- The ability to prolong sexual intercourse by delaying ejaculation and the subjective feelings of ejaculatory control comprise the complex construct of ejaculatory control. Virtually all men report using at least one cognitive or behavioural technique to prolong intercourse and delay ejaculation, with varying degrees of success, and many young men reported using multiple different techniques [54]. Voluntary delay of ejaculation is most likely exerted either prior to or in the early stages of the emission phase of the reflex but progressively decreases until the point of ejaculatory inevitability [55, 56].
- Several authors have suggested that an inability to voluntarily defer ejaculation defines PE [57–60]. Patrick et al. [20] reported ratings of

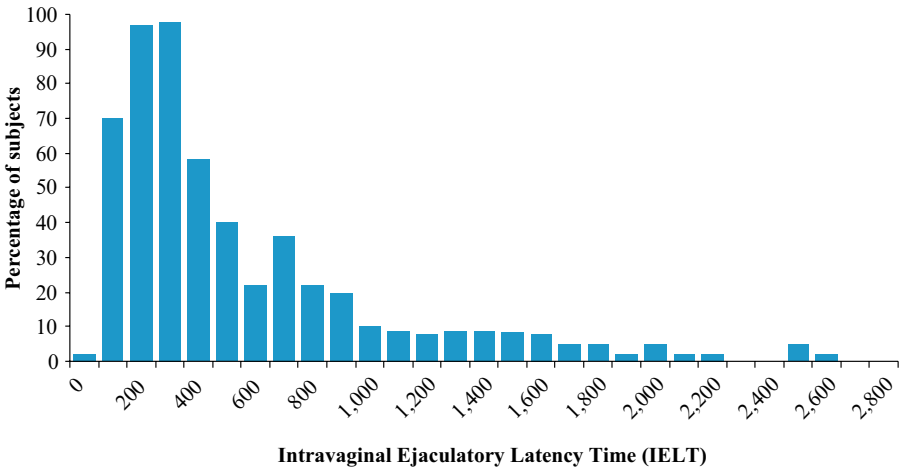

Fig. 16.5 Intravaginal ejaculatory latency time (IELT) measured with stopwatch in 110 men with lifelong premature ejaculation, of whom 90% ejaculated within 1 min after vaginal penetration, including 80% within 30 s

"very poor" or "poor" for control over ejaculation in 72% of men with PE compared to 5% in a group of normal controls. Lower ratings for control over ejaculation were associated with shorter IELT with "poor" or "very poor" control reported by 67.7, 10.2, and 6.7% of subjects with IELT <1 min, >1 min, and >2 min, respectively.

- However, control is a subjective measure which is difficult to translate into quantifiable terms and is the most inconsistent dimension of PE. Control has yet to be adequately operationalized to allow comparison across subjects or across studies. Grenier and Byers [54, 61] failed to demonstrate a strong correlation between ejaculatory latency and subjective ejaculatory control. Several authors report that diminished control is not exclusive to men with PE and that some men with a brief IELT report adequate ejaculatory control and vice versa, suggesting that the dimensions of ejaculatory control and latency are distinct concepts [20, 54, 62]. Furthermore, there is a higher variability of changes in control compared to IELT in men treated with SSRIs [16].
- Contrary to this, several authors have reported a moderate correlation between the IELT and the feeling of ejaculatory control [20, 22, 50, 63]. Rosen et al. [50] report that control over ejaculation, personal distress, and partner distress was more influential in determining PE status than IELT. In addition, the effect of IELT upon satisfaction and distress appears to be mediated via its direct effect upon control [64].
- However, despite conflicting data on the relationship between control and latency, the balance of evidence supports the notion that the inability to delay ejaculation appears to differentiate men with PE from men without PE [20, 22, 65].

Evidence to support exclusion of the criterion of sexual satisfaction

- Men with PE report lower levels of sexual satisfaction compared to men with normal ejaculatory latency. Patrick et al. [20] reported ratings of "very poor" or "poor" for sexual satisfaction in 31% of subjects with PE compared to 1% in a group of normal controls.
- However, caution should be exercised in assigning lower levels of sexual satisfaction solely to the effect of PE and contributions from other difficult to quantify issues such reduced intimacy, dysfunctional relationships, poor sexual attraction, and poor communication should not be ignored. This is supported by the report of Patrick et al. that despite reduced ratings for satisfaction with shorter IELTs, a substantial proportion of men with an IELT <1 min report "good" or "very good" satisfaction ratings (43.7%).
- The current data is limited but suggests that sexual satisfaction is of limited use in differentiating PE subjects from non-PE subjects and was not included in the ISSM definition of PE [20].

Evidence to support inclusion of the criterion of " … the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy."

- Premature ejaculation (PE) has been associated with negative psychological outcomes in men and their women partners [18, 20–22, 65–75]. Patrick et al. reported significant differences in men with and without PE in the PRO measures of personal distress (64% vs. 4%) and interpersonal difficulty (31% vs. 1%), suggesting that this personal distress has discriminative validity in diagnosing men with and without PE.
- The personal and/or interpersonal distress, bother, frustration, and annoyance that results from PE may affect men's quality of life and partner relationships, their self-esteem, and self-confidence, and can act as an obstacle to single men forming new partner relationships [18, 20–22, 65–75]. McCabe [69] reported that sexually dysfunctional men, including men with PE, scored lower on all aspects of intimacy (emotional, social, sexual, recreational and intellectual) and had lower levels of satisfaction compared to sexually functional men (p <0.001 or p <0.01). Rowland et al. [67]

showed that men with PE had significantly lower overall health-related quality of life, total Self-Esteem and Relationship Questionnaire (SEAR) scores, and lower confidence and self-esteem compared to non-PE groups. PE men rated their overall health-related quality of life lower than men without PE ($p \leq 0.001$).

This definition should form the basis for the office diagnosis of lifelong PE. It is limited to heterosexual men engaging in vaginal intercourse as there are few studies available on PE research in homosexual men or during other forms of sexual expression. The panel concluded that there is insufficient published evidence to propose an evidenced-based definition of acquired PE [46]. However, recent unpublished data suggests that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress, suggesting the possibility of a single unifying definition of PE.

The evidence suggests that the multivariate evidence-based ISSM definition of lifelong PE provides the clinician a more discriminating diagnostic tool. The IELT cut-off of about 1 min captures the 90% of men with PE who actively seek treatment and ejaculate within 1 min but also affords the clinician sufficient flexibility to also diagnose PE in the 10% of PE treatment seeking men who ejaculate within 1–2 min of penetration. If the ISSM definition is used, men who ejaculate in <1 min but report adequate control and no personal negative consequences related to their rapid ejaculation do not merit the diagnosis of PE. Similarly, men who have IELTs of 10 min but report poor control, dissatisfaction, and personal negative consequences also fail to meet the criteria for PE.

Epidemiology of Premature Ejaculation

Premature ejaculation (PE) has been estimated to occur in 4–39% of men in the general community [21, 54, 76–80] and is often reported as the most common male sexual disorder, despite a substantial disparity between the self-reported incidence of PE in epidemiological studies [80] and that suggested by community based normative stopwatch IELT studies [19]. However, most epidemiological studies are limited by their reliance on either patient self-report of PE or inconsistent and poorly validated definitions of PE [20, 22, 80]. A multinational, community based, age-ranging stopwatch IELT study demonstrated that the distribution of the IELT was positively skewed, with a median IELT of 5.4 min (range, 0.55–44.1 min), decreased with age and varied between countries [19]. (Fig. 16.6) Using an epidemiological approach to assess PE risk, the authors regarded the 0.5 and 2.5 percentiles as acceptable standards of disease definition in this type of skewed distribution, and proposed that men with an IELT of less than 1 min (belonging to the 0.5 percentile) have "definite" PE, while men with IELTs between 1 and 1.5 min (between 0.5 and 2.5 percentile) have "probable" PE [29]. These normative data supports the notion that IELTs of less than 1 min are statistically abnormal compared to men in the general western population.

Classification of Premature Ejaculation

The population of men with PE is not homogenous. In 1943, Schapiro classified PE as either primary (lifelong) or secondary (acquired) [81]. Recently, Waldinger [82] expanded this classification to include lifelong PE, acquired PE, natural variable PE, and premature-like ejaculatory dysfunction (Table 16.2).

Lifelong PE is a syndrome characterized by a cluster of core symptoms including early ejaculation at nearly every intercourse within 30–60 s in the majority of cases (80%) or between 1 and 2 min (20%), with every or nearly every sexual partner and from the first sexual encounters onwards. Acquired PE differs in that sufferers develop early ejaculation at some point in their life having previously had normal ejaculation experiences. Acquired PE may be due to sexual performance anxiety [72], psychological or relationship problems [72], erectile dysfunction (ED) [83], prostatitis [84], hyperthyroidism [85],

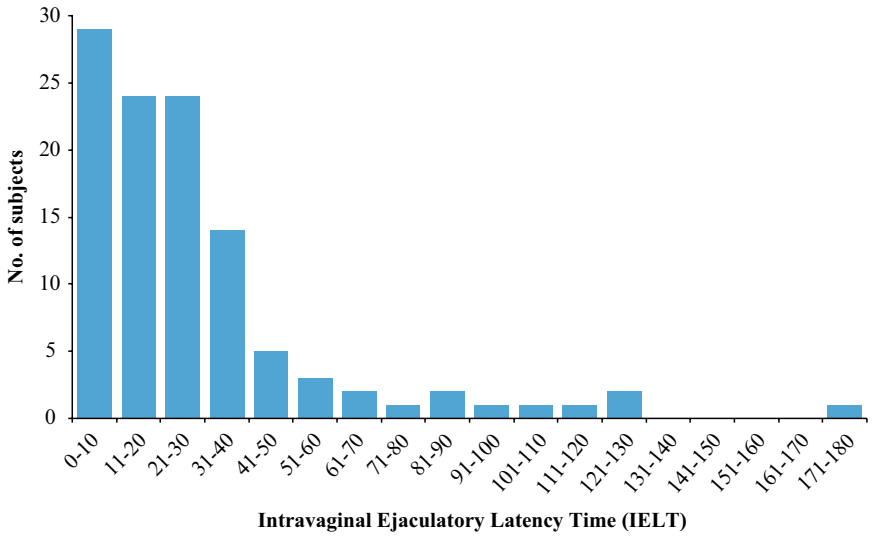

Fig. 16.6 Distribution of IELT values in a random cohort of 491 men with a median IELT of 5.4 min [19]

Table 16.2 The four premature ejaculation (PE) syndromes [82]

Variable	Lifelong premature ejaculation	Acquired premature ejaculation	Natural variable premature ejaculation	Premature-like ejaculatory dysfunction
IELT	Very short IELT (<1–1.5 min)	(Very) short IELT (<1.5–2 min)	Normal IELT (3–8 min)	Normal or long IELT (3–30 min)
Frequency	Consistent	(In)consistent	Inconsistent	(In)consistent
Aetiology	Neurobiological and genetic	Medical and/or psychological	Normal variation of ejaculatory performance	Psychological
Treatment	Medication with or without counselling	Medication and/or psychotherapy	Psycho-education, reassurance	Psychotherapy
Prevalence	Low	Low	High	High

or during withdrawal/detoxification from prescribed [86] or recreational drugs [87]. In a study of 1,326 consecutive men with PE, lifelong PE was present in 736 men (74.4%), and acquired PE was present in 253 men (25.6%) [52]. In natural variable PE, the ejaculation time is never consistently rapid but merely coincidental and situational. This type of PE should be regarded as a normal variation in sexual performance and is characterized by inconsistent and irregular early ejaculation, often with reduced ejaculatory control [88]. Men with Premature-like Ejaculatory Dysfunction complain of PE but have a normal ejaculatory latency of 3–6 min. It is characterized by a pre-occupation with a subjective but false perception of PE with an IELT within the normal range but often with reduced ejaculatory control.

In 261 potent men with self reported PE, Serefoglu et al. [89] reported that the majority of the men were diagnosed with lifelong PE (62.5%); the remaining men were diagnosed as having acquired (16.1%), natural variable PE (14.5%), or premature-like ejaculatory disorder (6.9%). Men with lifelong PE had significantly lower mean self-reported IELT (20.47 ± 28.90 s), whereas men with premature-like ejaculatory dysfunction had the highest mean IELT (286.67 ± 69.96 s, $p = 0.001$).

The Aetiology of Premature Ejaculation

Historically, attempts to explain the aetiology of PE has included a diverse range of biological and psychological theories (Table 16.3). Most of these proposed aetiologies are not evidence-based

Table 16.3 Proposed aetiologies of premature ejaculation

Psychogenic	Anxiety
	Psychosocial problems
	Early sexual experience
	Frequency of sexual intercourse
	Ejaculatory control techniques
	Evolutionary
	Psychodynamic theories
Biological	Genetic predisposition
	Penile hypersensitivity
	Hyper-excitable ejaculatory reflex
	Arousability
	Erectile dysfunction
	Hyperthyroidism
	Prostatitis
	Chronic pelvic pain syndrome (CPPS)

and are speculative at best. Psychological theories include the effect of early experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity, and psychodynamic explanations. Biological explanations include evolutionary theories, penile hypersensitivity, central neurotransmitter levels and receptor sensitivity, degree of arousability, the speed of the ejaculatory reflex, and the level of sex hormones.

There is little empirical evidence to suggest a causal link between PE and any of the factors thought to cause PE. There is, however, limited correlational evidence to suggest that lifelong PE is genetically determined and related to the inherited altered sensitivity of central 5-HT receptors and acquired PE is due to high levels of sexual anxiety, ED, or lower urinary tract infection.

Ejaculatory latency time is probably a biological variable, which is genetically determined and may differ between populations and cultures, ranging from extremely rapid through average to slow ejaculation. This is supported by animal studies showing a subgroup of persistent rapidly ejaculating Wistar rats [15], an increased familial occurrence of lifelong PE [14], and a moderate genetic influence on PE in the Finnish twin study [90]. Hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptors have been suggested as a possible explanation of lifelong PE [2, 91]. Men with low 5-HT neurotransmission and probable 5-HT2C receptor hyposensitivity may have their ejaculatory threshold genetically "set" at a lower point and ejaculate quickly and with minimal stimulation, whereas men with a higher set-point can sustain more prolonged and higher levels of sexual stimulation and can exert more control over ejaculation. This is supported by the recent report that genetic polymorphism of the 5-HTT gene determine the regulation of the IELT and that men with LL genotypes have statistically shorter IELTs than men with SS and SL genotypes [92].

Premature Ejaculation and Performance Anxiety

Anxiety has been reported as a cause of PE by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of PE despite scant empirical research evidence to support any causal role [57, 81, 93]. Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation [57, 93]. The possibility that high levels of anxiety and excessive and controlling concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognizing the prodromal sensations that precede ejaculatory inevitability has been suggested as a possible cause of PE by several authors [1, 59, 60, 94–96].

As most men with PE are aware of their anxiety and the sources of that anxiety tend to be relatively superficial, treatment success with these behavioural approaches is anecdotally reported as relatively good in the short term but convincing short-and long-term treatment outcome data from RCTs are lacking [58, 97–99]. Cognitive behavioural therapy when combined with pharmacotherapy, is an effective intervention for acquired PE related to sexual performance anxiety and a substantial proportion of men report

sustained improvements on ejaculatory latency and control following cessation of pharmacotherapy [28, 52, 56].

Premature Ejaculation and Co-Morbid ED

Recent data demonstrates that as many as half of subjects with ED also experience PE [21, 83, 100–104]. The Global Study of Sexual Attitudes and Behaviors (GSSAB) reported odds ratio for ED in men with PE ranging from 3.7 to 11.9 according to region [83]. ED appears more prevalent in men with acquired PE compared to lifelong PE with odds ratios of 9.6 versus 2.5, respectively [105]. Furthermore, PE is more common with increasing severity of ED after adjustment for age [101, 106, 107]. el-Sakka [107] reported co-morbid PE in 52.4% of subjects with severe ED compared with 29.5% with mild ED (Fig. 16.7).

There is a complex bidirectional relationship between ED and PE. Subjects with ED may either require higher levels of manual stimulation to achieve an erection or intentionally "rush" intercourse to prevent early detumescence of a partial erection, resulting in ejaculation with a brief latency. This may be compounded by the presence of high levels of performance anxiety related to their ED which serves to only worsen their prematurity. Subjects with PE may also instinctively attempt to control ejaculation by reducing the level of excitation, leading to ED. Jannini [30] reported PE in 24% of subjects prior to the development of ED. Thus, although reduced time to ejaculation is only rarely an early manifestation of erectile dysfunction, it may occur when the man has an unstable erection due to fluctuation in penile blood flow. In this case, the man may reach ejaculation quickly to compensate for the weak erection.

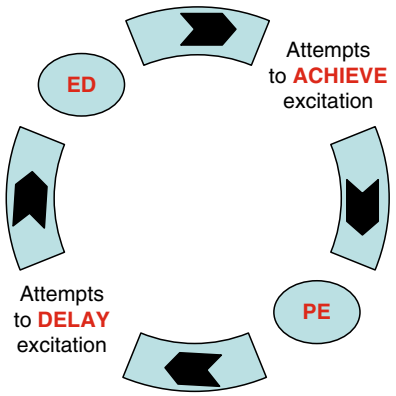

Fig. 16.7 Bidirectional relationship between erectile dysfunction and premature ejaculation [30]

Premature Ejaculation and Other Sexual Dysfunctions

Hypoactive sexual desire may lead to PE, due to an unconscious desire to abbreviate unwanted penetration. Similarly, diminished sexual desire can be a consequence of chronic and frustrating PE. Interesting, low sexual desire may be due to a lack of sexual arousal, such as in erectile dysfunction. Premature ejaculation and low desire, singly or in combination, are, in fact, significantly associated with severe rather than mild erectile dysfunction at presentation [107]. There is limited but increasing evidence to support a potential role for PDE5Is used alone or combined with daily or on-demand SSRIs in the treatment of A-PE in men with co-morbid erectile dysfunction [108].

Premature Ejaculation and Partner Sexual Dysfunction

Finally, female sexual dysfunctions (such as anorgasmia, hypoactive sexual desire, sexual aversion, sexual arousal disorders, and sexual pain disorders, as vaginismus [109]) may also be related to acquired PE. The female dysfunction may be secondary to the male PE with or without erectile dysfunction, and can be considered as a frequent complication of this condition. In other cases, PE may be the result of hidden female

arousal difficulties [110]. Such partner influences emphasize the need to diagnose and treat the couple, not simply the patient [111].

Premature Ejaculation and Hyperthyroidism

Data from animal studies suggest anatomic and physiological interactions between brain dopamine and serotonin systems and the hypothalamic-pituitary thyroid axis. There is evidence to indicate a link between depression and thyroid hormones [112, 113]. Chronic treatment with thyroxine (T4) is an effective therapy of depression [114–117]. The 5-HT2A receptor is up-regulated in the cortex of suicide victims [118], down-regulated by antidepressant drugs [119], and seems to be under TH regulation. Levels of 5-HT2A receptor mRNA in the rat frontal cortex are decreased during thyroxine deficiency and increased during chronic thyroxine treatment indicating thyroid hormone involvement in 5-HT2A receptor regulation in adult brain [120, 121].

The majority of patients with thyroid hormone disorders experience sexual dysfunction [85, 101]. Corona et al. [101] reported a significant correlation between PE and suppressed TSH values in a selected population of andrological and sexological patients. Carani et al. [85] subsequently reported a PE prevalence of 50% in men with hyperthyroidism which fell to 15% after treatment with thyroid hormone normalization. [51, 122] failed to demonstrate an increased incidence of thyroid dysfunction in lifelong PE, consistent with the notion that hyperthyroidism appears to be a cause of only acquired PE. Treatment of acquired PE secondary to hyperthyroidism requires thyroid hormone normalization with anti-thyroid drugs, radioactive iodine, or thyroidectomy. Although occult thyroid disease has been reported in the elderly hospitalized population [123], it is uncommon in the population who present for treatment of PE and routine TSH screening is not indicated unless clinically indicated.

Premature Ejaculation and Chronic Prostatitis

Acute and chronic lower urogenital infection, prostatodynia, or chronic pelvic pain syndrome (CPPS) is associated with ED, PE, and painful ejaculation. The relationship between chronic prostatitis, CPPS, and premature ejaculation is supported by several recently published studies which focus more on epidemiology and largely ignore treatment. Most of these have are limited by poor study design including inconsistent or absent methodologies of microbiological diagnosis of prostatitis and the lack of a validated questionnaire for combined evaluation of chronic prostatitis and sexual dysfunction.

Painful ejaculation is a common symptom of chronic prostatitis or CPSS and is included in all prostatitis symptom scores. In 3,700 men withw benign prostatic hypertrophy (BPH), painful ejaculation was reported by 18.6% and was associated with more severe lower urinary tract symptoms (LUTS), and a 72 and 75% incidence of ED and PE, respectively [124]. Several studies report PE as the main sexual disorder symptom in men with chronic prostatitis or CPPS with a prevalence of 26–77% [125–129].

Prostatic inflammation and chronic bacterial prostatitis have been reported as common findings in men with both lifelong and acquired PE [84, 130, 131]. Shamloul and el-Nashaar [131] reported prostatic inflammation and chronic bacterial prostatitis in 64 and 52% of men with PE. The 41.4% incidence of prostatic inflammation in men with lifelong PE parallels was reported by Screponi [84], but it is inconsistent with the proposed genetic basis of lifelong PE, and assumes the presence of prostatic inflammation from the first sexual experience. Although physical and microbiological examination of the prostate in men with painful ejaculation or LUTS is mandatory, there is insufficient evidence to support routine screening of men with PE for chronic prostatitis. The exact pathophysiology of the link between chronic prostatitis, ED, and PE is unknown. It has been hypothesized that prostatic inflammation may result in altered sensation and

modulation of the ejaculatory reflex but evidence is lacking [131].

Although treatment of chronic prostatitis improves LUTS, there is little published data to suggest a parallel improvement in PE and other sexual dysfunction symptoms [132–134]. El-Nashaar and Shamloul [134] reported that antibiotic treatment of microbiologically confirmed bacterial prostatitis in men with acquired PE resulted in a 2.6-fold increase in IELT and improved ejaculatory control in 83.9% of subjects.

Delayed Ejaculation, Anejaculation, and Anorgasmia

Any psychological or medical disease or surgical procedure which interferes with either central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor, or the somatic afferent nerve supply to the penis can result in delayed ejaculation, anejaculation, and anorgasmia. As such, the causes of delayed ejaculation, anejaculation, and anorgasmia are manifold (Table 16.4).

Table 16.4 Causes of delayed ejaculation, anejaculation, and anorgasmia

Psychogenic	Inhibited ejaculation
Congenital	Mullerian duct cyst
	Wolffian duct abnormality
	Prune belly syndrome
Anatomic causes	Transurethral resection of prostate
	Bladder neck incision
Neurogenic causes	Diabetic autonomic neuropathy
	Spinal cord injury (SCI)
	Radical prostatectomy
	Proctocolectomy
	Bilateral sympathectomy
	Abdominal aortic aneurysmectomy
	Para-aortic lymphadenectomy
Infective	Urethritis
	Genito-urinary tuberculosis
	Schistosomiasis
Endocrine	Hypogonadism
	Hypothyroidism
Medication	α-Methyl dopa
	Thiazide diuretics
	Tricyclic and serotonin re-uptake inhibitors (SSRI) antidepressants
	Phenothiazine
	Alcohol abuse

Definition, Terminology, and Characteristics of Men with Delayed Ejaculation

Delayed (DE), Retarded Ejaculation (RE), or Inhibited Ejaculation (IE) are probably the least common, least studied, and least understood of the male sexual dysfunctions. Yet its impact is significant in that it typically results in a lack of sexual fulfilment for both the man and his partner, an effect further compounded when procreation is among the couple's goals of sexual intercourse.

Problems with "difficulty" in ejaculating may range from varying delays in the latency to ejaculation to complete inability to ejaculate (anejaculation). Reductions in the volume, force, and sensation of ejaculation may occur as well. At the extremes are anejaculation (time) and retrograde ejaculation (direction), but more commonly encountered is inhibited, retarded, or delayed ejaculation (DE). A final disorder, anorgasmia, refers to a perceived absence of the orgasm experience, independent of whether or not any or all of the physiologic concomitants of ejaculation have taken place.

Terminology and Definition

Retarded ejaculation, delayed ejaculation, inadequate ejaculation, inhibited ejaculation, idiopathic anejaculation, primary impotentia ejaculations, and psychogenic anejaculation have all been used synonymously to describe a delay or absence of male orgasmic response. If a distinction is to be made, usually inhibited

ejaculation is characterized by the complete absence of ejaculation, although no clear consensus exits. Herein, the preferred terminology Delayed Ejaculation (DE) is meant to describe any and all of the ejaculatory disorders resulting in a delay or absence of ejaculation.

DSM-IV-TR defines DE as the persistent or recurrent delay in, or absence of, orgasm after a normal sexual excitement phase during sexual activity that the clinician, taking into account the person's age, judges to be adequate in focus, intensity, and duration. The disturbance causes marked distress or interpersonal difficulty; it should not be better accounted for by another Axis I (clinical) disorder or caused exclusively by the direct physiologic effects of a substance or a general medical condition [33]. Similarly, the Second International Consultation on Sexual Dysfunction defines DE as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm after sufficient sexual stimulation, which causes personal distress [3].

There are no clear criteria as to when a man actually meets the conditions for DE, as operationalized criteria do not exist. Given that most sexually functional men ejaculate within about 4–10 min following intromission [20], a clinician might assume that men with latencies beyond 25 or 30 min (21–23 min represents about two standard deviations above the mean) who report distress or men who simply cease sexual activity due to exhaustion or irritation qualify for this diagnosis. Such symptoms, together with the fact that a man and/or his partner decide to seek help for the problem, are usually sufficient for a DE diagnosis.

The Prevalence of Delayed Ejaculation and Characteristics of Men with DE

The prevalence of ejaculatory disorders is unclear, partly because of the dearth of normative data for defining the duration of "normal" ejaculatory latency, particularly regarding the right "tail" of the distribution (i.e. beyond the mean latency to orgasm). Furthermore, larger epidemiologic studies have not subdivided various types of ejaculatory disorders (e.g. delayed vs. absent), further limiting our knowledge. In general, DE is reported at low rates in the literature, rarely exceeding 3% [80, 135, 136]. The prevalence of DE appears to be moderately and positively related to age, which is not surprising in view of the fact that ejaculatory function as a whole tends to diminish as men age.

Failure of ejaculation can be a lifelong problem or an acquired problem. It may be global and happen in every sexual encounter or intermittent or situational. Normative descriptive data from large samples of DE men have not been available, but a recent analysis identified 25% of a clinical sample suffering from lifelong DE, with the remainder reporting a secondary problem [135]. While coital anejaculation is frequently the treatment driver (especially for extremely religious individuals referred for fertility problems), men also seek treatment when distressed by their inability to achieve orgasm in response to manual, oral, or vaginal stimulation by their partner. Many men with acquired DE can masturbate to orgasm, whereas others, for multiple reasons, will or cannot. Loss of masturbatory capacity secondary to emotional or physical trauma is also seen. Approximately 75% of one clinical sample [135] could reach orgasm through masturbation, while the remainder either would not or could not.

Similar to men with other types of sexual dysfunction, men with DE indicate high levels of relationship distress, sexual dissatisfaction, anxiety about their sexual performance, and general health issues – significantly higher than sexually functional men. In addition, along with other sexually dysfunctional counterparts, men with DE typically report lower frequencies of coital activity [137]. A distinguishing characteristic of men with DE – and one that has implications for treatment – is that they usually have little or no difficulty attaining or keeping their erections – in fact they are often able to maintain erections for prolonged periods of time. But despite their good erections, they report low levels of subjective sexual arousal, at least compared with sexually functional men [138].

Pathophysiologies Commonly Leading to Ejaculatory Disorders, Including DE

A number of pathophysiologies have been associated with ejaculatory problems (Table 16.4). These include congenital disorders as well as ones caused by trauma, infection, disease, and treatment for other disorders. When a medical history or symptomatology so indicates, investigation of such possible aetiologies may be necessary.

Congenital Disorders

Typical congenital problems include Mullerian duct obstruction, caused by failure of complete absorption of Mullerian duct remnants in the male; Wolffian duct abnormalities which may compromise vas deferens, ejaculatory duct, and seminal vesicle functioning; and prune belly syndrome.

Traumatic Damage

Traumatic damage may result from prostate surgery and colorectal surgery including surgery for correction of an imperforate anus.

Antegrade (normal) ejaculation requires a closed bladder neck (and proximal urethra). Surgical procedures that compromise the bladder neck closure mechanism may result in retrograde ejaculation. Transurethral incision of the prostate (TUIP) results in retrograde ejaculation in 5% [139] to 45% [140] of patients and is probably related to whether one or two incisions are made and whether or not the incision includes primarily the bladder neck or extends to the level of the verumontanum. The importance of contraction of the urethral smooth muscle at the level of the verumontanum has been hypothesized to be important in preventing retrograde ejaculation [141]. Transurethral resection of the prostate (TURP) carries a higher incidence of retrograde ejaculation than does TUIP. The reported incidence of retrograde ejaculation following TURP ranges from 42% [142] to 100% [143]. Although these men may have some antegrade ejaculation and usually experience orgasmic sensation, both events may be reduced as part of the changes that occur in the male sexual response as a man ages. Retrograde ejaculation and failure of emission can be distinguished by examination of a post masturbatory specimen of urine for the presence of spermatozoa and fructose. After radical prostatectomy, ejaculation is bound to be lost since the seminal vesicles are removed with the prostate gland. Erectile impotence was common until detailed anatomical studies showed where the parasympathetic nerves ran on the surface of the prostate gland, and a nerve sparing operative technique was developed [144]. A sensation of orgasm is often preserved despite loss of ejaculation.

Infective Disorders

Sexually transmissible infections such as gonorrhoea or non-specific urethritis can produce cicatrisation and obstruction anywhere in the male reproductive tract, especially if treatment is delayed. Urinary infection, especially if complicated by epididymitis, can also produce obstruction that may be situated at ejaculatory duct level. Schistosomiasis is endemic in large parts of Africa and is seen with increasing frequency in tourists returning from Africa who have contracted the disease while enjoying water sports. The disease may present with haemospermia [145], and fibrosis and calcification may lead to genital obstruction. Genito-urinary tuberculosis can cause great damage to the male reproductive tracts, and since healing occurs with calcification, the lesions may be irreparable.

Neurological Disorders

Various cancers in the pelvic region, as well as their treatment (surgical or radiotherapy), may interfere with normal ejaculatory function. Finally, spinal injury and other neurological disorders are prime candidates for ejaculatory dysfunction.

Male Pelvic Cancers

Quality of Life (QoL) in general and sexual functioning in particular has become very important in the well being of cancer patients. Due to modern surgical techniques, improved quality of drugs for chemotherapy, and modern radiation techniques, more patients can be successfully treated without largely compromising sexual functioning.

Prostate Cancer

Prostate cancer (CaP) has become the most common non-skin malignancy in men in Western countries. External-beam radiotherapy (EBRT) and brachytherapy (BT) are, together with the radical prostatectomy (RP), the most common and effective treatments for localized PC. Regardless of the introduction of very modern radiotherapy (RT) techniques, sexual functioning after CaP treatment remains problematic for many patients.

Ejaculatory disturbances following RT of PC were reported in as early as the 1980s [146]. More recent studies have evaluated the impact of RT on sexual desire, ejaculation, and orgasm. After EBRT, a decline in sexual desire was reported by 43% of 64 patients and a decreased frequency of orgasm by 57%; all men reported a decrease in ejaculate volume [147]. Using a validated questionnaire, Borghede and Sullivan [148] reported a decrease in the ability to ejaculate in 56% of the patients. Good prognostic factors for sexual functioning preservation following RT were low age and higher frequency of intercourse.

Early BT studies also assessed sexual functioning. Herr [149] reported already in 1979 on 51 patients treated with retropubic Iodium-125 seeds, with loss of ejaculate experienced by 6% of the patients. In a later study, dry ejaculation was reported by 16% of the patients after BT [150]. In both studies, all patients had previously undergone a TURP. For the first time a discomfort with ejaculation was mentioned in two studies (up to 25% of the patients) [151, 152]. This result is quite common in clinical practice after BT, due to oedema of the prostate possibly reducing the elasticity of the urethra and inducing discomfort with ejaculation. In some patients, discomfort with ejaculation did not disappear even 18–24 months after BT [153]. Also, decreased interest in sex, sexual desire, and libido was mentioned in up to 50% of the patients evaluated [148, 152–154].

Several studies on the aetiology of post-RT decreased libido and ejaculatory disorders have been reported. Daniell et al. [155] studied retrospectively levels of testosterone (TST) and other hormones after RT of PC. TST was found to be low 3–8 years after EBRT with lower levels found in older patients. Although testes are very sensitive to radiation, spermatogenesis is more easily affected than androgen productions. The radiation dose calculated in the testes of men irradiated for PC is only 3–8% of the dose that could possibly affect androgen production and explain a decrease in TST. A TURP carries a high incidence of retrograde ejaculation because it is thought to disrupt the closure mechanism of the vesical neck; this could explain ejaculatory disturbances in most patients following RT with previous TURP.

Rectal Carcinoma

Not much is known about sexual functioning following RT of rectal carcinoma. Pre-operative RT for rectal cancer has been associated with a reduction in the rate of local relapse and possibly an advantage in survival. Pre-operative RT with the total mesorectal excision (TME) in low stage rectal cancer has become a common procedure in Europe. A sharp dissection of the mesorectum associated with visualization and preservation of the pelvic autonomic nerve leads to excellent results regarding erectile and ejaculatory functioning. Only one study has specifically studied the effects of pre-operative RT for rectal carcinoma on male sexual functioning and concluded that it may impair male sexual functioning [156]. However, numbers were too small to draw final conclusion.

Testicular Cancer

Germ cell tumours of the testis are relatively rare, accounting for about 1% of all male cancers. The long-term survival for early disease approaches 100%. Because testicular cancer affects mainly young men in their sexual and fertile life, sexual functioning and ejaculatory disorders are particularly important. The side effects of retroperitoneal lymph node dissection (RPLND) for residual mass after chemotherapy for non-seminomatous cancer are better documented than sexual sequelae of elective abdominal RT for seminoma. Dry ejaculation occurs in the majority of the patients in non-nerve sparing techniques. As a result of careful anatomical studies, the technique of RPLND has been modified with nerve sparing so that antegrade ejaculation is now maintained in 80–100% of patients [157]. Libido and orgasm seem to be normal in these patients.

Following RT, deterioration in sexual functioning has been reported between 1 and 25% of the patients [158–162]. Tinkler et al. [160] reported on 237 patients after orchiectomy and abdominal RT and compared these data to 402 age-matched controls. In almost all parameters studied including erection, ejaculation, and libido, patients scored less than controls (reduction in orgasm, in libido, and interest in sex). Specifically, there was no difference in the ability to ejaculate during sexual activity, but the RT patients reported a noticeable reduction in the amount of semen compared to before treatment [160]. Caffo et al. [161] evaluated toxicity and QoL of 143 patients treated for early-stage testicular cancer. Twenty-three percent reported a decreased libido, 27% problems with getting an orgasm, and 38% ejaculation disturbances, including premature ejaculation. A decrease in sexual desire, in orgasm, and volume or semen was negatively correlated with age [158]. Jonker-Pool et al. [159] reported on three groups of patients, after RT, wait and see, and chemotherapy. RT patients reported decreased libido in 22% compared to 12% in the wait and see group and 30% in the chemotherapy group. Decrease of absence of ejaculate was reported in 15, 7, and 21% in the three groups, respectively; decreased orgasm in 15, 12 and 30%, respectively. Although the differences were not statistically significant, in the RT group ejaculation and orgasm disturbances were higher than in the wait and see group. Similar results were reported by Arai et al. [163]. PE was reported in up to half of the patients [162, 163], but it was the same as recalled before treatment [162].

The superior hypogastric plexus is responsible for ejaculation and it is mediated by the sympathetic system; it is a fenestrated network of fibres anterior of the lower abdominal aorta. The hypogastric nerves exit bilaterally at the inferior pole of the superior hypogastric plexus, and have connections with the S1–S2 roots. Normal emission requires integrity of this system. During RPLND these nerves are difficult to recognize and might be damaged, resulting in decreased semen volume or dry ejaculation. Pathways for ejaculation are included in the RT fields for rectal and prostate carcinomas. Damage of the sympathetic nerves could be caused by radiation, but the dose does not seem enough to completely explain the dysfunction. Orgasm is even more complex than ejaculation since it is also affected by cortical input.

Spinal Cord Injury

The ability to ejaculate is severely impaired by spinal cord injury (SCI). Bors and Comarr highlighted the impact of the level and completeness of SCI on the post injury erectile and ejaculatory capacity (Table 16.5) [164, 165]. Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury. Less than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Ejaculation rates are higher (15%) in patients with both lower motor neuron lesions and an intact thoracolumbar sympathetic outflow. Approximately 22% of patients with an incomplete upper motor neuron lesion and almost all men with incomplete lower motor neuron lesions retain the ability to ejaculate. In those patients capable of successful ejaculation, the sensation of orgasm may be absent and retrograde ejaculation often occurs.

Table 16.5 Correlation of erection, ejaculation, and intercourse with level and severity of SCI [165]

Cord lesion		Reflexogenic erections (%)	Psychogenic erections (%)	Successful coitus (%)	Ejaculation (%)
Upper motor neuron lesion	Complete	92	9	66	1
	Incomplete	93	48	86	22
Lower motor neuron lesion	Complete	0	24	33	15
	Incomplete	0	1	100	100

Psychological Aetiologies of Delayed Ejaculation

Like most other sexual dysfunctions, unless a clear pathophysiology has been identified, DE may be best understood as an interaction of organic and psychogenic factors. That is, a biological set-point for ejaculatory latency is affected by multiple organic and psychogenic factors in varying combinations over the course of a man's life cycle. Appropriate assessment requires an appreciation of how these factors combine to inhibit ejaculatory response for any particular individual. Among those factors that are psychogenic and/or behavioural, a number of possibilities have been proposed. Although none has been identified or accepted as the primary determinant of DE, some explanations have received more support than others, and some appear more plausible than others.

Psychodynamic interpretations emphasize psychosexual development issues and have attributed lifelong DE to a wide range of conditions, including fear, anxiety, hostility, and relationship difficulties [166–168]. Although some of these factors may contribute to DE in individual men, no well-controlled studies provide broad support, at this point, for any of the various hypotheses for mentioned above [169].

Masters and Johnson [11] were the first to suggest that DE in some men might be associated with orthodoxy of religious belief. Such beliefs may limit the sexual experience necessary for learning to ejaculate or may result in an inhibition of normal function. Many devoutly religious men have masturbated only minimally or not at all, and for some, guilt and anxiety about "spilling seed" may have led to idiosyncratic masturbatory patterns, which in turn resulted in DE. Such men often had little contact with women prior to marriage and, although they may have dated, were less likely than their secular counterparts to experience orgasm with a partner, especially through intercourse.

Apfelbaum [170] coined "autosexual" orientation to describe men with DE who prefer masturbation to partnered sex. Many men with DE engage in self-stimulation that is idiosyncratic in the speed, pressure, duration, and intensity necessary to produce an orgasm, yet dissimilar to what they experienced with a partner. Thus, they precondition themselves to possible difficulty attaining orgasm with a partner and, as a result, experience acquired DE. These men appear able to achieve erections sufficient for intercourse despite a relative absence of subjective arousal [170], and their erections are taken as erroneous evidence by both the man and his partner that he was ready for sex and capable of achieving orgasm. Finally, disparity between the reality of sex with the partner and the use of sexual fantasy (whether unconventional or not) during masturbation is another potential cause of DE. This disparity may take any number of forms: body type, orientation, and sex activity performed [171].

In summary, delayed or absent ejaculation can be a lifelong or an acquired problem. Many psychodynamic explanations have been offered for DE and these may account for the problem in specific individual cases. More likely, men with DE derive greater arousal and enjoyment from masturbation than from intercourse, an "autosexual" orientation that may involve an idiosyncratic and vigorous masturbation style that interferes with the ability to attain orgasm [172–177]. In fact, masturbatory frequency and style may be predisposing factors for DE, since a substantial portion of men who present with coital DE report high levels of idiosyncratic masturbatory activity [173–177]. Disparity between the

reality of sex with the partner and the sexual fantasy used during masturbation may inhibit sexual arousal and thus represent another contributor to DE [171, 178]. And finally, the evaluative/performance aspect of sex with a partner often creates "sexual performance anxiety," a factor that may contribute to DE. Specifically, anxiety surrounding the inability to ejaculate may draw the man's attention away from erotic cues that normally serve to enhance arousal [172].

Conclusion

Recent epidemiological and observational research has provided new insights into the ejaculatory dysfunction especially PE and its associated negative psychosocial effects. Recent normative data suggests a median IELT of 5.4 min that men with an IELT of less than 1 min have "definite" PE, while men with IELTs between 1 and 1.5 min have "probable" PE. The first contemporary multivariate evidence-based definition of lifelong PE was developed in 2008 by a panel of international experts, and characterizes lifelong PE as "…ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy" [46]. This definition is limited to heterosexual men engaging in vaginal intercourse. There is insufficient published evidence to propose an evidenced-based definition of acquired PE.

Although there is insufficient empirical evidence to unequivocally identify the aetiology of PE, there is limited correlational evidence to suggest that some men may have a genetic predisposition to lifelong PE related to altered sensitivity of central 5-HT receptors and that acquired PE is most common in men erectile dysfunction and/or high levels of sexual performance anxiety. The off-label use of some SSRIs and clomipramine, along with the development of new on-demand drugs for the treatment of PE, such as dapoxetine, has drawn new attention to this common and often ignored sexual problem.

Delayed or absent ejaculation can be a lifelong or an acquired problem. Any psychological or medical disease or surgical procedure which interferes with either central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor, or the somatic afferent nerve supply to the penis can result in delayed ejaculation, anejaculation, and anorgasmia.

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Chapter 17
Priapism

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Keywords Ischemic priapism • Non-ischemic priapism • Malignant priapism • Erectile dysfunction • Distal surgical shunt • Proximal surgical shunt

Background

Priapism represents one of the greatest challenges in therapeutic management among erectile disorders [1]. Priapism is defined as a prolonged and persistent penile erection lasting greater than 4 h, unassociated with sexual interest or stimulation [2, 3]. It constitutes a true disorder of erection physiology, associated with risks of structural damage to the penis and permanent erectile dysfunction. It results from a disturbance in the mechanisms governing the regulatory control of penile detumescence and initiation/maintenance of penile flaccidity. However, the disorder is a poorly recognized condition by many medical professionals [3].

In this chapter, we will give an introduction to priapism and its clinical significance, discuss the etiologic and pathophysiologic properties of the disorder and its currently recommended treatment guidelines, and discuss its relevance in regards to the patient with cancer.

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Historically, the term priapism comes from the Greek god *Priapus*, who was worshipped as a god of lust, fertility, and protector of horticulture [4]. Priapus has been memorialized in numerous sculptures for his giant phallus. While the penis is recognized as the organ most often affected, priapism of the clitoris has also been reported [5]. The penis is composed of spongy erectile tissue; two large columns on the dorsum or top of the penis, known as the corpora cavernosa and one column located on the ventral or underside of the penis called the corpus spongiosum. In priapism, it is typically the corpora cavernosa that become engorged leading to a persistent erection, although involvement of the corpus spongiosum has been observed resulting in tricorporal priapism [4, 6].

In order to understand the potential mechanisms involved in creating priapism, and thus the modalities used for treatment, it is essential to understand the neural and vascular pathways that function during normal penile erection. The process of penile erection is dependent on an intact central and peripheral nervous system, stable hormonal status, and three vascular processes working together simultaneously and synergistically. These processes involve a neurologically mediated increase in penile arterial inflow, relaxation and dilatation of cavernosal smooth muscle, and restriction of venous outflow from the penis [7]. In concordance, the return of sympathetic tone, along with constriction of cavernosal smooth muscle and increased venous outflow is required for detumescence and return of a flaccid penis. Priapism likely results when there is an

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imbalance along one of the pathways in this regulatory mechanism.

A classification system has been developed to assist with the practical understanding of priapism and facilitate its clinical management. Priapism has been divided into three main categories: ischemic, nonischemic, and stuttering priapism [2].

Ischemic priapism, also termed veno-occlusive or low-flow priapism, is a persistent erection marked by rigidity of the corpora cavernosa and little or no cavernous arterial inflow [2]. It consists of an imbalance in the vasoconstrictive and vasoregulatory mechanisms, predisposing the penis to an ischemic environment [8]. Deoxygenated blood in the penis becomes trapped, creating venous congestion. The tissue ischemia and increased pressure generated within the corporal bodies lead to the pain and penile rigidity, clinically seen with ischemic priapism [8]. Studies have shown that ischemic priapism lasting longer than 24 h results in erectile dysfunction (ED) rates as high as 90% [9]. Therefore, ischemic priapism constitutes a true medical emergency and must be treated in a time-sensitive manner [1, 2].

Conversely, nonischemic priapism, also termed arterial or high-flow priapism, is a persistent erection caused by unregulated cavernous arterial inflow [2]. Nonischemic priapism results from a disruption in the cavernous arterial inflow (generally traumatic) resulting in an arteriolar-sinusoidal fistula. The cavernous environment does not become ischemic due to continuous influx of arterial blood [2]. In concordance, the corpora are tumescent but not rigid, and patients usually do not complain of pain with erection [4]. For this reason, nonischemic priapism is not a medical emergency and does not require emergent intervention. However, it should be addressed in a timely manner.

The last type, stuttering priapism, also termed intermittent or recurrent priapism, is characterized by recurring episodes of ischemic priapism. The recurrent episodes may increase in frequency and or duration, potentially developing into major episodes of ischemic priapism [2]. Conversely, any person who has suffered from ischemic priapism may be at risk for developing stuttering episodes. These episodes generally last under 4 h prior to remission [4, 10]. However, episodes are painful and commonly arise during nocturnal sleep, after morning erections, or preceding or following sexual stimulation [4]. Despite having varied etiologies which will be discussed in the following section, both stuttering and ischemic priapism result in the same consequences, namely, ischemic damage to the corporal tissue potentially leading to permanent ED. Therefore, all episodes of recurrent priapism that progress to prolonged erections longer than 4 h should be treated promptly, according to the guidelines set for ischemic priapism [3]. The ultimate goal of the treating urologist is to prevent recurrent stuttering priapism by using local or systemic pharmacotherapies which address the underlying pathophysiology of this disease state. This will be discussed in detail later in this chapter.

Epidemiology of Priapism and Patient Populations at Risk

Priapism is associated with a number of different disease states, and numerous clinical contexts have risk associations for developing the disorder [1, 2, 11]. Epidemiologic studies remain largely elusive, and an estimated population risk of priapism, either in terms of incidence or prevalence is largely unknown [3]. Several epidemiologic reports have suggested that incidence rates of priapism range between 0.5 and 1 case per 100,000 person-years (the number of patients with the first episode of priapism divided by the accumulated amount of person-time in the study population) [3, 12–14]. However, these studies may in fact underestimate the true prevalence of priapism because previous studies only included prolonged erections that required medical intervention. While priapism is a rare disorder in general, specific patient populations (neurological conditions, hematologic dyscrasias, malignancies) are affected with greater frequencies and comprise a major risk cohort for the development of priapism [3]. For example, populations with

sickle cell disease (SCD) demonstrate lifetime probabilities of developing priapism between 29 and 42% [3, 10, 15–17]. In the United States alone, over 70,000 individuals live with SCD, and worldwide, estimates are as high as 20–25 million [18]. In 2008, in a study by Bennett and Mulhall, 39 cases of SCD priapism were followed over 8 years and evaluated for ED. Of the men followed, 73% admitted prior episodes of stuttering priapism while only 5% had ever been counseled or were aware that priapism was a complication of SCD [19]. This demonstrates the need for greater awareness and education surrounding priapism among the medical community and the public [1]. New efforts are leaning towards prevention rather than focusing solely on treatment of priapism. Therefore, greater understanding of the populations at risk and the causes of priapism is essential.

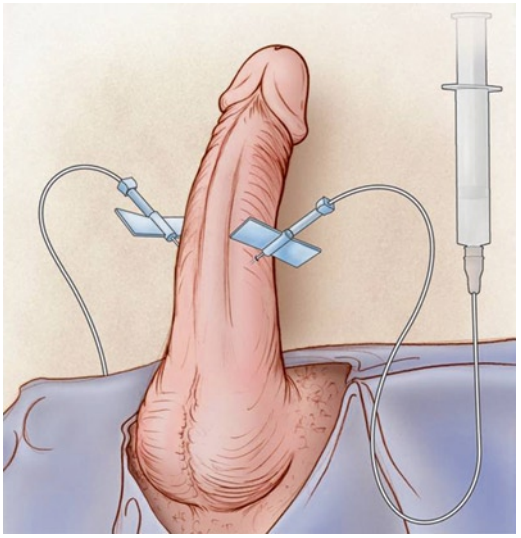

Fig. 17.1 Initial assessment of priapism requires assessment of corporal blood flow by: inspection of aspirate (color, consistency), corporal blood gas (pH, PO_2, PCO_2) or color Duplex Ultrasound. No Doppler flow is evident in ischemicpriapism [67]

Diagnosis of Priapism

When any patient presents with a prolonged erection, a detailed medical history and physical examination should be performed [1, 2]. It is important to distinguish the type of priapism as treatment options vary between them. The clinical history should elicit information about the duration of priapism, existence of preceding factors, any relieving maneuvers or clinical treatments used, previous priapism episodes, presence of pain, existence of etiologic conditions or comorbidities, and erectile function status before the priapism episode. The penis should be inspected and palpated which may denote the extent of tumescence or rigidity, the degree of corporal body involvement (i.e., tricorporal priapism), and the presence and severity of tenderness. Performing abdominal, perineal, and rectal examinations may help to reveal signs of trauma or malignant disease [11]. Several laboratory tests are recommended in the evaluation of priapism [1, 2]. These include a complete blood count, white blood cell differential, and platelet count, which may reveal hematologic abnormalities or the presence of an acute infection. A urine toxicology screening for psychoactive drugs and to identify legal and or illegal drugs may also be performed [1, 2, 11]. After careful history taking, a Doppler ultrasound and or a cavernous arterial blood gas test will be useful in differentiating between ischemic and nonischemic priapism [2, 3, 8].

In cavernous arterial blood gas testing, the direct visualization of the aspirated blood is a critical determinant [11] (Fig. 17.1). In patients with ischemic priapism, the aspirated blood is hypoxic and dark, whereas in nonischemic priapism, the blood is oxygenated and therefore, bright red. Upon analysis, cavernous blood gas values for ischemic priapism will typically show a PO_2 of less than 30 mm Hg, PCO_2 of greater than 60 mm Hg, and a pH below 7.25; whereas cavernous blood gas values for nonischemic priapism will show a PO_2 of greater than 90 mm Hg, PCO_2 of less than 40 mm Hg, and pH of 7.40 consistent with normal arterial blood at room air [3, 11]. Color duplex ultrasonography is another reliable diagnostic method for distinguishing ischemic from nonischemic priapism (Fig. 17.2). Patients with ischemic priapism will show minimal or absent blood flow in the cavernosal

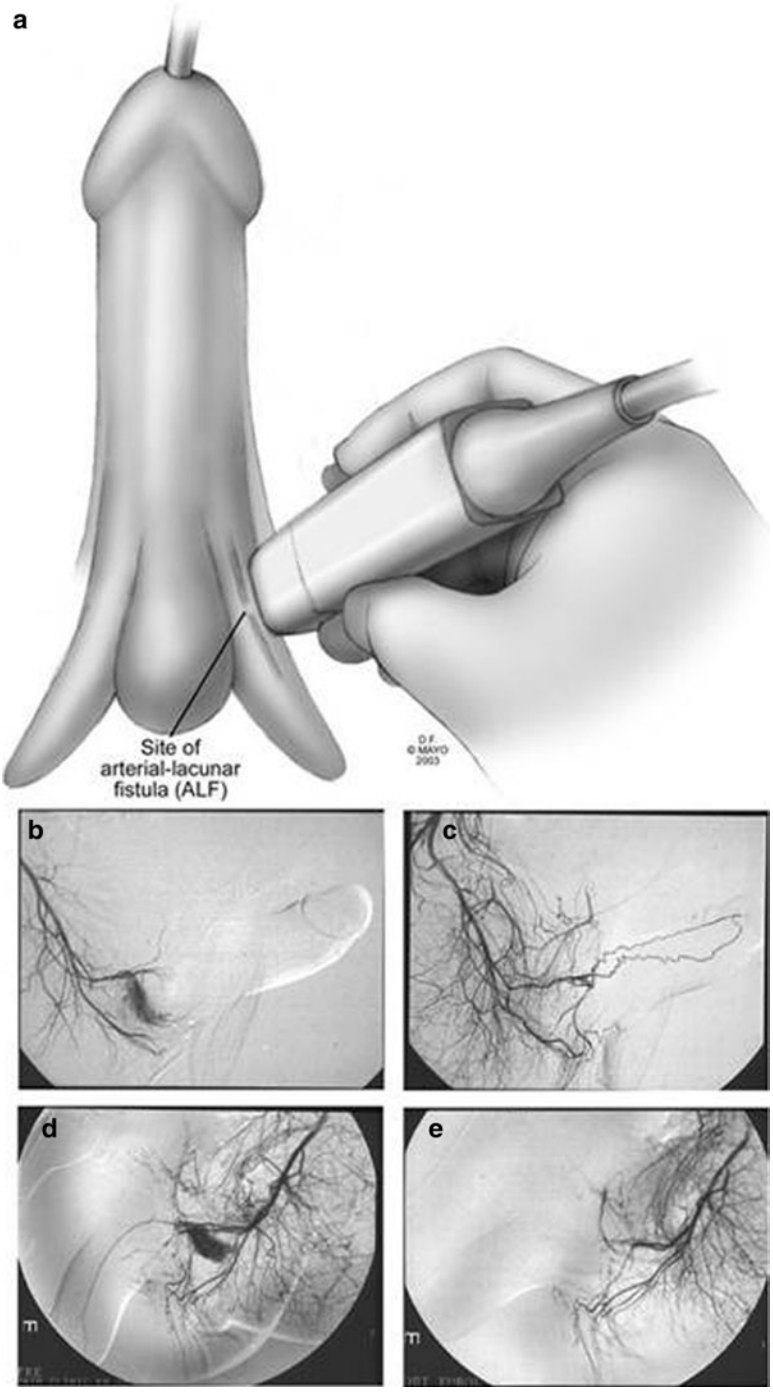

Fig. 17.2 Color Doppler ultrasonography of the penis and perineum is recommended in the evaluation of priapism, when the history or examination suggests penile trauma. Doppler ultrasonography for localization of fistula correlates well with selective pudendal angiography; characteristic fistula blush is shown [67]

arteries as well as within the corpora cavernosa; while patients with nonischemic priapism will demonstrate normal to high blood flow velocities in the cavernosal arteries with evidence of blood flow in the corpora cavernosa [2, 3, 11]. Ultrasonography has an added benefit over arterial blood gas analysis in that it may also reveal anatomic abnormalities, such as a cavernous arterial fistula or pseudoaneurysm, which helps confirm nonischemic priapism diagnoses [11]. However, the color duplex ultrasonography should be done in the lithotomy or frogleg position, scanning the perineum first and then the entire penile shaft and should not be used as an alternative to arterial blood gas testing if it impedes prompt treatment of ischemic priapism [2, 3, 11].

Pathophysiology of Priapism

Ischemic Priapism

Ischemic priapism is the most common cause of priapism, accounting for more than 95% of all priapic episodes [4]. The etiology of veno-occlusive priapism is predominated by SCD. However, a wide variety of clinical correlates exist in the literature, including trauma, neurological conditions (multiple sclerosis, spinal cord tumor with compression, neurotoxins), hematologic dyscrasias (sickle cell anemia, thrombocytosis, and thalassemia), malignancies, intracavernous injection therapy, pharmacological and drug exposures (psychotropic and antidepressant medications, and illicit drugs), as well as idiopathic circumstances [8, 20–22]. While recent advances in the field of ED have led to a greater understanding of the pathogenesis underlying some presentations of priapism, more research is necessary to fully understand the molecular biology of priapism and develop new avenues for treatment. Conventional understanding is that adverse conditions such as hematogenous factors or traumatic situations of the penis or perineum alter the normal vascular anatomy and physiology of the penis [23, 24]. Recent investigations suggests an imbalance between vasoconstrictive and vasorelaxatory mechanisms may also apply, predisposing the penis to hypoxia and ischemia [22]. These changes cause apoptosis, failure of corporal smooth muscle contraction when activated via appropriate stimulus, and upregulation of hypoxia-induced growth factors in the penis [22]. This results in damage to the corporal smooth muscle and vascular endothelium [3, 4, 22]. This idea of venous congestion and enhanced blood viscosity has served as a pathophysiologic basis for priapism associated with various clinical presentations, including SCD [23], assorted hematologic dyscrasias [24–27], parenteral hyperalimentation [28, 29], hemodialysis [30], and heparin-induced platelet aggregation [31]. In ischemic priapism, time dependent changes in the corporal metabolic environment occur, resulting in progressive hypoxia, hypercarbia, and acidosis [2, 4, 8]. For these reasons, ischemic priapism is a medical emergency that demands prompt medical treatment.

Nonischemic Priapism

Nonischemic priapism is much rarer than ischemic priapism and is predominately associated with traumatic injuries [2]. Trauma-induced priapism involves a different pathophysiologic basis than ischemic priapism. The mechanism involves excessive arterial inflow to the penis, resulting from disruption of the structural anatomy of the penile arterial circulation [32–37]. Cavernous blood gases do not show hypoxia, hypercarbia, or acidosis but rather are routinely completely normal [2, 3, 8].

The most common injuries reported are to the corporal bodies or perineum [8]. The trauma may be a blunt injury or a penetrating force that results in laceration of the cavernous artery or one of its tributaries within the corpora [8]. Mechanisms include: straddle injury, coital trauma, kicks to the penis or perineum, pelvic fractures, birth canal trauma to the newborn male, and vascular erosions complicating

metastatic cancer infiltration of the corpora cavernosa [36, 38–41]. While blunt trauma is still the most commonly reported etiology, high-flow priapism has also been described following surgical interventions such as cold-knife urethrotomy, Nesbit corporoplasty, and deep dorsal vein arterializations [42, 43]. Simplistically, "any mechanism which lacerates a cavernous artery or arteriole can produce unregulated pooling of blood in sinusoidal space with consequent erection" [4].

Stuttering Priapism

Stuttering priapism can result from episodes of ischemic priapism and vice-versa; therefore, it shares many of the same etiologic factors as previously discussed for ischemic priapism [2]. While the cause of stuttering priapism remains idiopathic in some cases, recent studies have shown recurrent priapism to be related to a defective phosphodiesterase type 5 (PDE5) regulatory function in the penis, resulting from altered nitric oxide and cyclic guanosine monophosphate (cGMP) signaling mechanisms which control erectile function [8, 22, 44]. Nitric oxide (NO) is a chemical released from the endothelium lining the trabeculae of the corpora cavernosa that together with its neuronal sources results in vasodilation during erection. A leading proposal in this regard, is that NO becomes dysfunctional in association with underlying disease states [22]. From this understanding, novel modalities of treatment have evolved, and it is this cohort of priapism that will benefit most from medical management that focuses on the prevention of priapism.

Medical Management

The most common complication of priapism is complete ED, which has been reported to be as high as 59% [2, 3, 22]. Therefore, the most critical factor in maintaining erectile function is immediate treatment of men presenting with priapism and prevention of future episodes [22]. Patients treated within 12–24 h will have a more favorable response than those with delayed treatment. Patients with prolonged priapism (>36 h) and recurrent episodes are more likely to suffer ED due to impaired corporal smooth muscle function and fibrosis. Corporal ischemia lasting more than 24 h results in varying degrees of irreversible penile fibrosis with endothelial and smooth muscle cell destruction [45]. If left untreated, ischemic priapism results in global penile fibrosis with significant impairments in erectile function. This group of patients may ultimately need to pursue penile implant surgery because pharmacologic therapy will almost certainly fail [3]. Prompt recognition and treatment of ischemic and recurrent priapism are essential for optimal outcomes.

The primary goal of medical therapy for ischemic priapism is to relieve the pain and decompress the corporal bodies, thus reducing ischemia and the risk of tissue necrosis/injury [2, 8]. For ischemic priapism, any duration greater than 4 h warrants immediate decompression of the corpora cavernosa [1, 2, 8]. If treatment is delayed beyond 4 h, the penis has begun to undergo a number of cellular and molecular changes that result in tissue injury and place the patient at risk for development of ED [8]. One may proceed earlier if a patient is in severe pain, but action *must* be taken if 4 h has elapsed. For patient comfort, a dorsal nerve block or local penile shaft block with lidocaine can be administered prior to treatment [8]. A scalp vein needle (19- or 21- gauge) should be inserted directly into the penile shaft for corporal body decompression and therapeutic aspiration of old blood and the injection of an alpha adrenergic agonist (such as phenylephrine) [1–3]. Sympathomimetic agents are applied because of their contractile effects which may facilitate detumescence [1, 2]. The patient should be monitored for potential side effects resulting from alpha agonist entry into systemic circulation. If the patient experiences hypertension, headache, reflex bradycardia, tachycardia, or any cardiac arrhythmia with the administration of an alpha agonist, the patient may have to undergo surgical treatment to alleviate

the priapism [8]. Phenylephrine, a selective alpha-1 agonist, is the preferred medication since it minimizes the risk of cardiovascular side effects, as it is devoid of beta adrenergic agonist activity, as opposed to epinephrine [1, 2]. However, if phenylephrine is unavailable, other alpha adrenergic agonists may be used, such as etilefrine, ephedrine, epinephrine, norepinephrine, or metaraminol (Table 17.1). Phenylephrine administration, suggested in doses of 100–1,000 mcg, should be injected directly into the corpora cavernosa. After 5 min has elapsed, if the penis is still rigid, consideration should be given to repeat dosing or moving to aspiration of blood and direct injection of phenylephrine or dilute saline/phenylephrine irrigation of the corporal bodies until detumescence occurs [1–3]. If after a reasonable duration (some suggest 1 h) and dose escalation of phenylephrine (some suggest 1,000 mcg of diluted phenylephrine over 1 h) the penis is still tumesced, then a Doppler ultrasound should be considered to evaluate the status of the cavernosal arterial flow in the penis [1–3]. The penis may simply be edematous with restored corporal arterial flow and not in a persistent ischemic state [8].

Ischemic priapism of extended durations, i.e., greater than 48 h, is unlikely to resolve with intracavernous injection/irrigation therapy, and therefore, surgical shunting should be performed as first line treatment for these cases [1–3].

For priapism specifically related to SCD, medical therapies such as intravenous hydration, oxygenation, alkalinization, and exchange transfusion may be performed; however, these interventions should not precede the first line treatment for all episodes of ischemic priapism: aspiration/irrigation in combination with intracavernous alpha agonist injection therapy [1–3, 8, 46] (Fig. 17.3). However, some patients with SCD-associated priapism will fail conservative measures and need surgical shunting to definitively treat an acute episode of ischemic priapism resistant to aspiration and irrigation of the penis [19].

Nonischemic priapism is not a medical emergency and therefore, the initial management of nonischemic priapism may be observation [1, 2]. Aspiration/irrigation and administration of intracavernous injection therapy is not recommended [2]. In early presentations of nonischemic priapism, ice or pressure packing may cause vasospasm and thrombosis of the ruptured artery leading to closure of the fistula and alleviation of the erection [2, 8]. More than 50% of patients with nonischemic priapism will have spontaneous resolution if left untreated [2]. Therefore, if the erection persists, prior to any discussion of invasive interventions or surgical management, the patient should be advised of his chances for spontaneous resolution and preservation of erectile ability despite the continued presence of an erection [2, 8] (Fig. 17.3). Surgical procedures for patients with nonischemic priapism are available and will be discussed in the surgical management section.

For patients with stuttering priapism, while first line therapy remains the same as for ischemic priapism, new preventive treatment options are being studied and tested in a number of retrospective case controlled studies. The use of antiandrogens, 5-alpha reductase inhibitors, gonadotropin-releasing hormone agonists, for prevention and sympathomimetic intracavernous injection therapies for immediate patient self-administration have shown to be successful medical management options for some patients suffering with stuttering priapism [1–4] (Table 17.1).

Systemic hormonal therapy acts to suppress the androgenic effects on penile erection. These treatment options work by exploiting the known regulators of male sexual function by targeting the hormonal axis [4]. This is accomplished through gonadotropin releasing hormone agonists (GnRH agonists); suppressing pituitary function through feedback inhibition with diethylstilbestrol (DES); blocking androgen receptors with antiandrogens; and reducing testicular and adrenal synthesis with drugs such as ketaconazole [2, 4]. To date, there has only been one randomized placebo-controlled trial in which DES, a synthetic estrogen, was used to treat patients with stuttering priapism. The study showed that DES caused termination of the stuttering episode in all patients; however, in more than 50% of the

Table 17.1 Pharmacologic therapies for priapism

Drug	Class/Mechanism	Dosage	Administration	Adverse effects	Special considerations
Sympathomimetics (α-adrenergic agents)					
Phenylephrine	α_1 agonist	100–200 μg every 5–10 min until detumescence (maximum 1000 μg)	Intracavernous injection	Hypertension, tachycardia, palpitations, headache, arrhythmia, sweating	Preferred agent based on selectivity
Epinephrine	α, $\beta_{½}$ agonist	10–20 μg every 5–10 min until detumescence	Intracavernous injection	Hypertension, tachycardia, palpitations, headache, arrhythmia, sweating	Potential for cardiac stimulation based on β-adrenergic receptor activity
Etilefrine	α_1, $\beta_{½}$ agonist	5–10 mg	Intracavernous injection	Transitory palpitations, Hypertension, tachycardia, headache, arrhythmia, sweating	Potential for cardiac stimulation based on β-adrenergic receptor activity
		25–100 mg maximum in 24 h usually at bedtime	Oral		
Antiandrogens					
Leuprolide	Gonadotropin-releasing hormone agonist	7.5 mg once a month	Intramuscular injection	Hot flashes, gynecomastia, loss of sexually induced erections, asthenia	Not applicable for children
Bicalutamide	Androgen receptor antagonist	50 mg once a day	Oral tablets	Hot flashes, gynecomastia, diarrhea, asthenia, loss of libido	Precaution if moderate to severe hepatic impairment
Flutamide	Androgen receptor antagonist	250 mg every 8 h	Oral capsules	Hot flashes, gynecomastia, diarrhea, loss of libido, edema, rash	Monitor for liver dysfunction
Finasteride	5-alpha reductase inhibitor	1–5 mg/day	Oral	Impotence, decreased libido, postural hypotension, dizziness, ejaculation disturbances	Use with caution in hepatic impairment
Miscellaneous					
Baclofen	γ-Aminobutyric acid agonist	20–40 mg once a day (bedtime)	Oral tablets	Drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension, nausea	Possible role for "neurogenic" priapism
Sildenafil Tadalafil	PDE5 Inhibitors	Sildenafil 25–50 mg daily. Tadalafil 5–10 mg, 3×/week	Oral tablets	Headache, dyspepsia, flushing, diarrhea, myalgia, abnormal vision, epistaxis	Contraindicated with use of nitrates or other PDE5 inhibitors. Only administer under conditions of complete penile flaccidity Results in LFTs increased

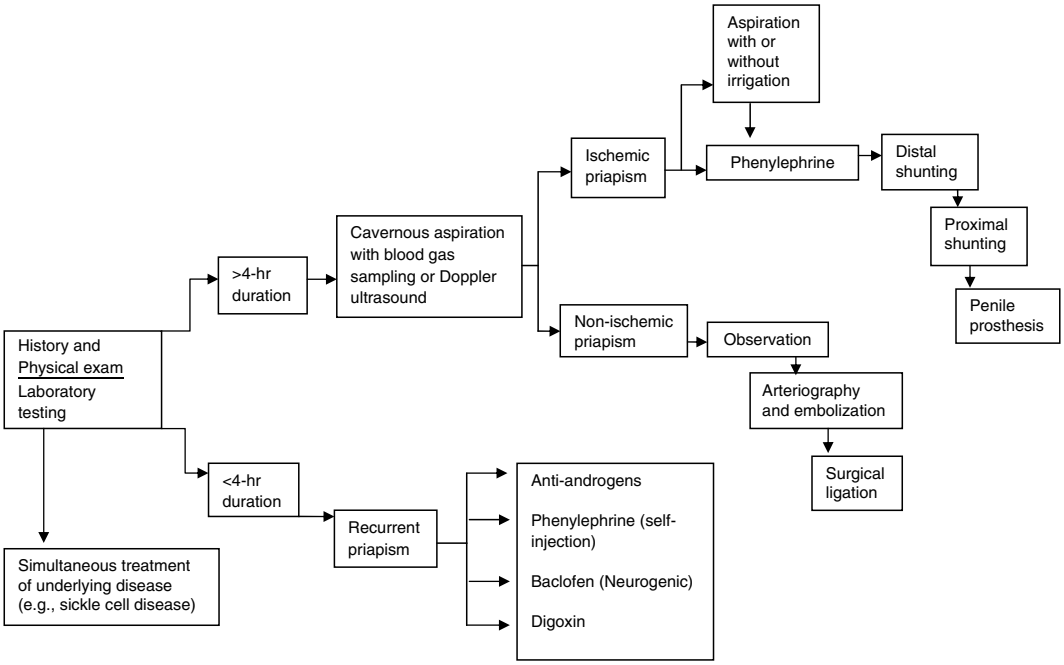

Fig. 17.3 Algorithm for management of priapism (Campbell-Walsh urology)

patients (5 out of 9) recurred termination of treatment [47]. Others describe similar results in case reports, although long-term estrogen therapy is not recommended due to potential cardiovascular side effects and development of ED and gynecomastia [4, 48, 49].

GnRH agonists, such as goserelin acetate and leuprolide acetate have been used in the management of stuttering priapism in several case reports (Table 17.1) [49, 50]. GnRH agonists work by suppressing luteinizing hormone (LH) through the process of receptor downregulation after an initial stimulation effect. Initially, GnRH agonists stimulate LH production, which in turn stimulates the testes to produce more testosterone (known as the "flare" phenomenon). Because of the desensitization of the LHRH receptor, production of both LH and testosterone decreases after a few weeks and will go to castrate levels. Chronic dosing of GnRH with as-needed patient self-administered penile injections of alpha adrenergics have been reported to effectively manage ischemic stuttering priapism [49, 51].

Antiandrogens such as flutamide, bicalutamide, and chlormadinone work by causing direct suppression of penile androgen receptors [4]. These agents have also been shown to be effective in a number of case reports relieving stuttering priapism without the resultant loss of libido side effect, commonly found with GnRH agonists and estrogen therapy (Table 17.1) [52–54].

Finasteride, a 5-alpha reductase inhibitor which inhibits the conversion of testosterone to dihydrotestosterone is another medical therapy that has shown promise in treating idiopathic as well as stuttering priapism. In a small study by Rachid-Filho et al., finasteride, was administered for 120 days with tapering doses to men with recurrent priapism secondary to SCD. In this study, prior to the initiation of finasteride, the mean episodes of priapism per patient were 22.7 and after 4 months of finasteride treatment, the mean priapic events was reduced to 2.1 [55]. Therefore, the authors concluded that finasteride may decrease the number of recurrent episodes of priapism with fewer side effects. However, further large scale studies are needed to further corroborate these findings (Table 17.1).

Baclofen, a gamma-aminobutyric acid (GABA) derivative, is a muscle relaxant and antimuscle

spasm agent shown to be beneficial in a single study in patients suffering from recurrent reflexogenic erections [4]. Both rat and human studies have demonstrated that baclofen inhibits penile erection and ejaculation through its GABA activity [56–58]. These recurrent erections are associated with muscle spasticity in men with spinal cord lesions and neurologic disease. While the characteristics and pathophysiology of this form of priapism are still being studied, several reports have described a beneficial response with the use of intrathecal baclofen [59–61]. These studies suggest that oral baclofen therapy fails to elicit the same response in patients as intrathecal baclofen dosing [59, 61] (Table 17.1). The current literature neglects to categorize this type of priapism as ischemic or nonischemic, so additional studies are needed to assess the congruence or lack thereof between recurrent reflexogenic erections and ischemic stuttering episodes [4].

Some men who are initiated on systemic therapy for stuttering ischemic priapism may not see a therapeutic effect immediately. Therefore, patients may require intracavernous self-injections at home with sympathomimetic agents such as phenylephrine on an interim basis until ischemic priapism has been alleviated.

Lastly, although oral PDE5 inhibitors, such as sildenafil or tadalafil, are commonly used as medical treatment for ED, exerting erectogenic effects new scientific evidence has shown they have a paradoxical effect in alleviating recurrent/stuttering priapism [44, 62–65]. PDE5 inhibitors work under the theory that PDE5 becomes downregulated in the penis, as a result of altered signaling of the NO pathway. This mechanism allows cGMP to build up in the corpora cavernosa, and therefore cGMP cannot be degraded due to lack of PDE5 function; thus, prolonged corporal smooth muscle relaxation and associated priapism occur [1–4, 22, 64, 65].

In a small case series, Burnett and colleagues have shown that daily PDE5 inhibitor therapy reduces ischemic priapism episodes in men with stuttering priapism [63]. Long-term therapy with PDE5 inhibitors alleviated priapism in men with idiopathic priapism as well as SCD-associated priapism without affecting their normal erectile capacity [44, 66]. In these studies, the initial dose of sildenafil citrate was 25 mg oral daily with escalation up to 50 mg daily, and doses of tadalafil at 5–10 mg three times a week with fair success results. PDE5 inhibitors should be started in patients under conditions of complete penile flaccidity and not during a recurrent/stuttering episode. Efficacy is usually seen within 2–4 weeks of dosing [4] (Table 17.1). The current use of PDE5 inhibitors for stuttering ischemic priapism is contraindicated by the packaging labels and therefore considered investigational [2]. Most treatment options available today fail to prevent episodes of priapism and their pathological consequences. It is here that PDE5 inhibitors offer promising new treatment possibilities for the prevention of stuttering priapism in this patient population [22]. Consequently, multicenter, randomized, placebo-controlled trials are under way to further evaluate the potential use and benefit of PDE5 inhibitors for the treatment of stuttering priapism [4].

Surgical Management

Ischemic or recurrent priapism, refractory to medical therapy, may require surgical intervention [2]. Prior to proceeding with surgery, the placement of needles both distally and proximally into the corpora cavernosa with the patient in lithotomy position may offer an additional approach for maximally irrigating the corporal bodies although this does require general anesthesia [8]. However, after medical management options have been exhausted or the patient is unable to tolerate therapy, surgical management becomes necessary.

The goal of surgery is to create a channel or fistula that allows the deoxygenated blood to drain from the corpora cavernosa returning the penis to a flaccid state and thus reduce pressure facilitating inflow of arterial blood [2, 8]. This is most often accomplished through the creation of a *shunt*. Following resolution of the priapic event, most fistulas spontaneously resolve [2, 8].

Table 17.2 Types of surgical shunt procedures for ischemic priapism

Distal shunts	
Percutaneous distal shunts	
Winter (corporoglanular) shunt	Large biopsy needle is inserted through glans into corpora cavernosum several times creating multiple fistulae
Ebbehoj (corporoglanular) shunt	#11 blade scalpel is percutaneously passed multiple times through glans into corpus cavernosum creating openings in the tunica albuginea resulting in larger fistulae
T-shunt (corporoglanular) shunt	Modified Ebbehoj using #10 blade scalpel and turning scalpel 90 degrees when pulling out creating "T-shaped" openings in tunica albuginea
Open distal shunts	
Al-Ghorab	A 1 cm incision is made distal to coronal sulcus with excision of 5x5 cone segment of distal tunica albuginea from each corporal body
Burnett "snake" maneuver	Modification of Al-Ghorab shunt. A Hegar dilator is used to evacuate ischemic blood through a distal tunical window
Proximal shunts	
Open proximal shunt	
Quackels or sacher (corporo-spongiosal) shunt	In lithotomy position, bulbocavernosus muscle is dissected from corpus spongiosum and 1 cm staggered ellipses of tissue are incised/excised from spongiosal/corporal bodies
Corporo-saphenous vein or superficial/deep dorsal vein shunts	
Grayhack shunt	The saphenous vein is ligated and anastomosed with corpora cavernosa
Barry shunt	The superficial or deep dorsal vein is ligated and anastomosed to the corpora cavernosa

There are two main types of shunt procedures, distal and proximal (Table 17.2). Distal corporoglanular shunts are the first line surgical therapy as they have fewer complications and are relatively easy to perform [2, 11, 67, 68]. The first shunt is called the Winter shunt, as described by Winter. This distal corporoglanular shunt is often used initially, since it can be performed at bedside [3]. The penis should be adequately anesthetized locally with a penile-glans block done under a general or local anesthesia. The tips of the penile corpora cavernosum should be palpated and localized. An 11 scalpel is sewn to puncture the glans skin, then a large tru-cut biopsy needle is inserted bilaterally through the glans into the corpora cavernosa creating several core biopsy windows or fistulae. Multiple fistulae are needed so that enough communication channels are created to allow the penis to detumesce [3, 8, 67, 68]. The puncture site may be closed with a figure eight 3-0 chromic suture [8] (Fig. 17.4). For the next 12 h, the patient should squeeze the penis every few minutes to decrease the blood from pooling in the penis. This procedure may be repeated, or an additional shunt procedure may be performed if a partial erection (>50%) persists [3, 8, 67]. The success rate of these procedures ranges between 50 and 65% [24]. Swelling of the glans and detumescence represent an adequate response to treatment [8].

An alternative to a Winter shunt is another distal corporoglanular shunt, the Ebbehoj Shunt (Fig. 17.4). The penis is locally anesthetized, while a #11 blade scalpel is passed percutaneously several times bilaterally through the glans into the corpora cavernosa. The blade is inserted in such a way as to avoid the urethral meatus and pulled back to create an opening in the tunica albuginea between the glans and corporal bodies [8, 11, 67, 68].

A recent modification of this shunt, called the T-Shunt, involves using a #10 blade scalpel (Fig. 17.4). The scalpel is placed vertically into the glans and through the corpus cavernosum. Then, turning 90 degrees away from the urethra, the scalpel is pulled out creating a "T-shaped" opening in the tunica albuginea. Both shunts may be performed unilaterally or bilaterally, [8, 11, 67, 68] and puncture sites may be closed using 3-0 chromic sutures in the glans [8].

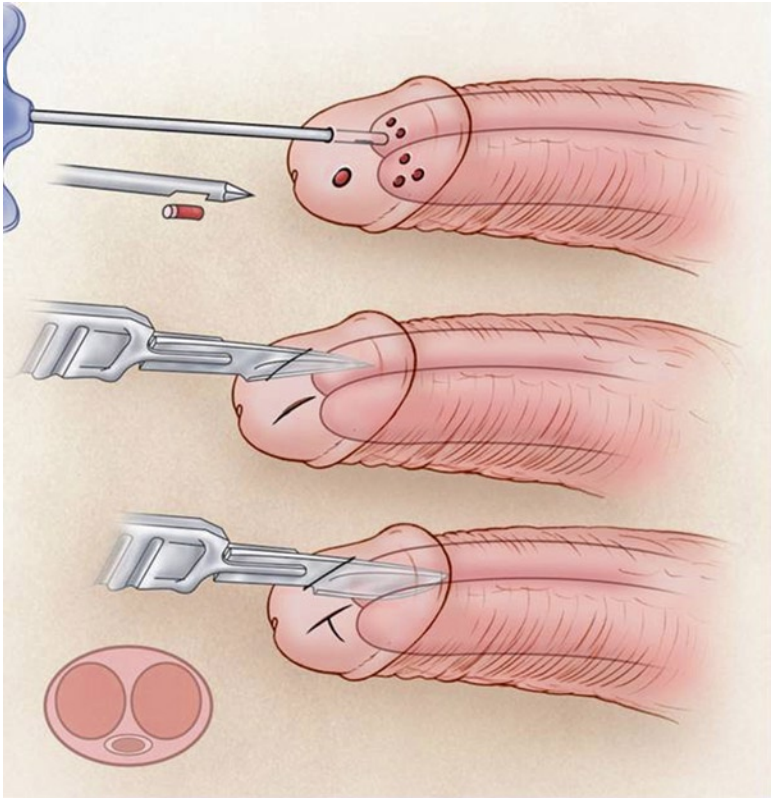

Fig. 17.4 Percutaneous distal corporoglanular shunts may be performed in outpatient setting after penile block. The objective is to create a corpus cavernosum – glans communication for drainage and permit resumption of cavernous arterial inflows. Three surgical options are: Winter, Ebbehoj or T-shunt described by Lue [67]

If the previously described percutaneous distal shunts are tried and are unsuccessful, an Al-Ghorab shunt is performed [8, 11, 67, 68]. A 1–2 cm curvilinear incision is made on the dorsum of the glans 1 cm distal to the coronal sulcus. The spongy corpus spongiosal tissue is pushed aside to delineate the tunica albuginea of the corpora cavernosa and segments of approximately 5×5 mm of the distal tunica albuginea is sharply excised from each corporal body. Dark blood will drain from the corporal bodies, and once detumescence occurs then reapproximation of the skin with absorbable sutures is performed [8, 11, 67, 68] (Fig. 17.5). Care is taken not to obliterate the spongy vascular space of the glans penis.

Recently, a modification of the distal corporoglanular Al-Ghorab shunt has been described by Burnett and Pierorazio [69] (Fig. 17.6). The procedure involves the passage of a 9–11 mm Hegar dilator proximally into each corporal body through the tunical window in an effort to more efficiently drain ischemic blood from the congested corpora cavernosa. It has been postulated that complete blood evacuation from the priapic penis may reduce penile fibrosis and thus preserve erectile capacity. Early results suggest that patients refractory to more conservative surgical corporoglanular shunts benefit from this "snake" maneuver, although larger studies need to be conducted to confirm this [69].

In general, distal shunts fail when the windows or fistulae between the corpora cavernosum and spongiosum are not large enough to create adequate drainage of blood to result in detumescence [8]. When distal shunts fail, a proximal shunt is the next line of treatment [2, 8].

The Corporo-spongiosal shunt, also known as the Quackels or Sacher Shunt is a proximal shunt that can be performed with the patient

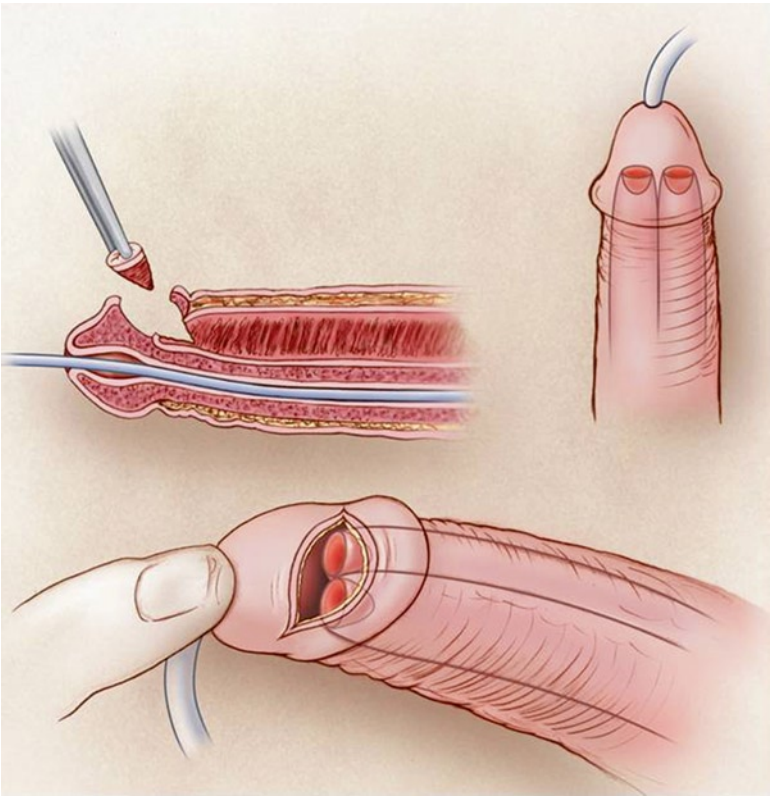

Fig. 17.5 Open corporoglanular shunt is indicated if percutaneous shunting fails to reestablish cavernous blood inflow (best assessed by color Doppler ultrasound). The Al-Ghorab shunt requires the excision of circular cone segments of distal tunica albuginea (5×5 mm) [67]

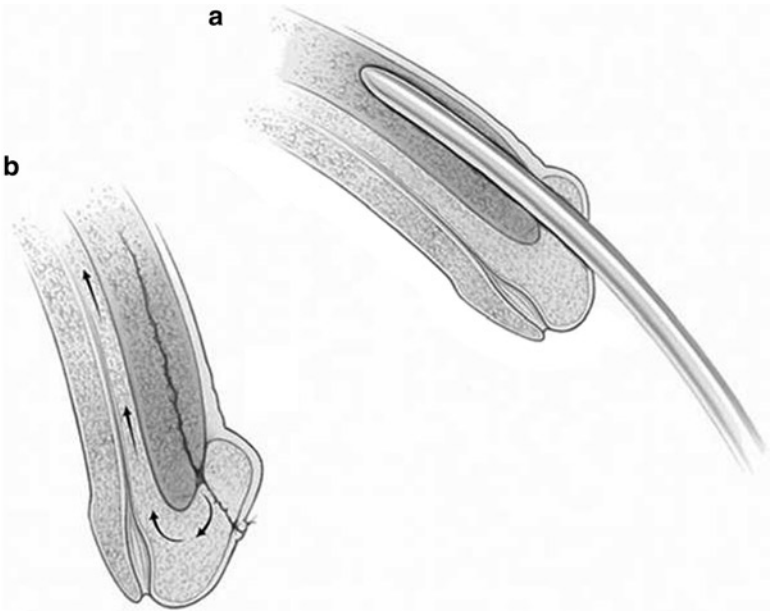

Fig. 17.6 Burnett has described a modification of the Al-Ghoab distal penile corporoglanular shunt for refractory ischemic priapism. The open distal shunt technique is modified to include insertion of a Hegar dilator in the distal copora; no tunica albuginea is removed. The corporoglanular channel permits milking out of thrombus in the operating room and reestablishes CC to glans drainage once the glans skin is sutured [69]

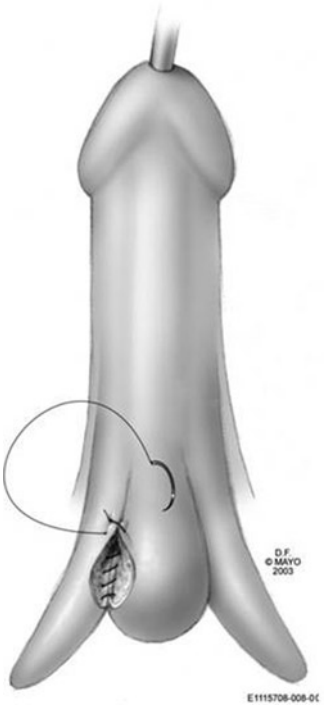

Fig. 17.7 The proximal open shunt technique to establish communication between the corpus spongiosum and corpus cavernosum was first described by Quackles, in 1964. It has the inherent complication of creating an unwanted urethra – cavernous fistula or urethral stricture [69]

placed in the lithotomoy position. In this position, the bulbuspongiosus muscle is dissected from the corpus spongiosum, though a perineal incision (Fig. 17.7). Alternatively, a transverse scrotal incision may be used. While carefully avoiding the urethra, 1 cm long ellipses of tissue are incised or excised from the spongiosal and corporal bodies. If this is being done bilaterally, consideration should be given to staggering them, especially if a transverse scrotal approach is utilized, to minimize urethral stricture or fistula formation. The incisions/excisions should be in close proximity to each other to facilitate the closure of the puncture sites [8, 11, 69]. A running 5-0 PDS suture can be used to approximate the walls of the two openings in the spongiosum and corpora. If detumescence does not occur, this technique may be performed bilaterally to maximize drainage [8].

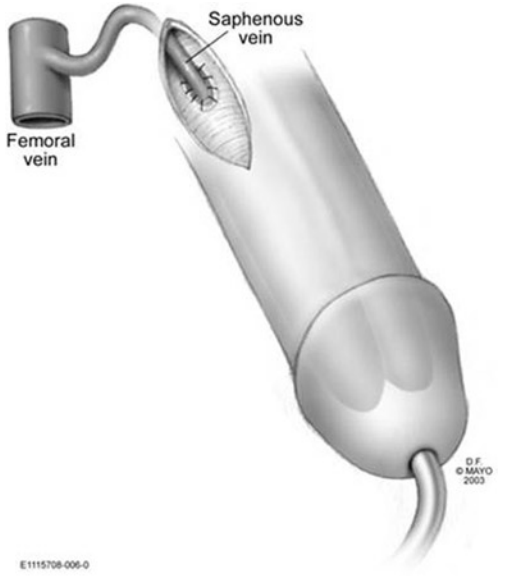

Fig. 17.8 Venous bypass to control priapism was first described by Grayhack, in 1964. The Grayhack shunt mobilizes the saphenous vein below the junction of the femoral vein and anastamoses the vein end to side in CC. Vein shunts may be complicated by local thrombus formation and pulmonary embolism [69]

Another proximal shunt procedure called the corporo-saphenous vein or Grayhack shunt may be performed (Fig. 17.8). Due to the technical difficulties of this procedure and complication rates, it is rarely used [8, 11, 69]. This procedure involves making an incision at the base of the penis exposing the tunica albuginea of the corpus cavernosum. Another incision is made approximately 3–4 cm below the inguinal ligament, in the sapheno-femoral junction, so that the saphenous vein can be identified and mobilized. The vein is ligated distally and the proximal end is burrowed beneath the skin and drawn into the penile wound and anastomosed with the tunica albuginea [8, 11, 69]. A protocol of intermittent penile squeezing is recommended [8]. Another proposed proximal shunt is the Barry Shunt. The superficial or deep dorsal vein is identified taking care not to injure the dorsal artery or sensory nerves. It is ligated distally and divided. The proximal limb is spatulated on its ventral surface and anastomosed to the corpora cavernosa end to side in a tension-free manner. The efficacy of this shunt is limited.

The Grayhack and Barry shunts are historical procedures proposed to alleviate severe priapic events and in practice have not been as successful as expected. Therefore, corporoglanular and corporo-spongiosal shunt procedures are preferred [8]. However, the success rates for the newly described distal corporoglanular shunts (T-shunt and Snake maneuver) may obviate the need for corporo-spongiosal shunts in the majority of refractory episodes of ischemic priapism.

For all shunt procedures, the patient should receive peri-operative and postoperative antibiotics [8]. Following the procedure, intermittent manual squeezing and milking of the penis will help keep the shunt open and prevent the recurrence of priapism. Circular pressure dressings should be avoided as they can compromise the shunt and decrease venous drainage. Sometimes the penis may appear partially erect after a shunt procedure due to postischemic hyperemia. In these cases, intracavernosal pressure monitoring or color duplex Doppler imaging may be performed to assess penile vascular arterial blood flow status or to evaluate the effectiveness of the shunt procedure [8].

Proximal shunts are performed when distal shunts are unsuccessful in reestablishing blood drainage and producing penile detumescence. However, these procedures have more complications [8]. ED rates are higher for the proximal shunts, Quackels and Grayhack, (about 50%) when compared to the distal shunts (25% or less) although patient selection and time to treatment may explain these differences [2] (Table 17.3).

Other complications associated with shunt procedures involve urethral damage and fistulae, purulent cavernositis, skin necrosis, perineal abscess, as well as pulmonary embolus after the Grayhack procedure [2, 3, 8]. Oftentimes, penile vascular dysfunction may actually be a consequence of significant fibrosis resulting from repeated and prolonged episodes of priapism, rather than the result of the shunt procedure itself [3, 8]. In these patients, who have undergone extended durations of ischemic priapism, some authorities suggest that immediate placement of a penile implant may be more beneficial than proceeding with a surgical shunt [70]. Significant fibrosis, which is commonly found in these patients, makes surgery more difficult with higher complication rates [3, 70].

In patients with nonischemic priapism, where conservative measures and observation have failed to deliver a desirable outcome, invasive interventions such as embolization or surgery offer an

Table 17.3 Case series of shunt surgery for venocclusive priapism

Author	Year	Patient number	Etiology of priapism	Duration of priapism	Shunt type	Functional erections
Nixon [11]	2003	28	NM	NM	NM	25%
El-Bahnasawy [8]*	2002	35	Idiopathic, ICI	48 h (6–240)	Various	43%
Lawani [12]	1999	17	NM	NM	NM	45%
Pryor [13][a]	1998	–	NM	NM	NM	<24 h 56%, >24 h 11%
Kulmala [9]	1996	124	Various	NM	Various	Overall, 69% 92% <24 h, 22% >7 days; 88% <30 years, 40% >50 years
Chakrabarty [10]	1996	5	SSD	NM	NM	Dependent on patient age and duration of priapism
Kaisary [14]	1986	14	NM	NM	Various	86% <12 h
Proca [15]	1979	6	NM	NM	NM	32%
Richard [16]	1979	8	NM	NM	Sapheno-cavernous	70%
Winter [2]	1978	105	NM	NM	NM	
Ebbehoj [3]	1977	18	NM	NM	NM	55%

ICI intracavernosal injection therapy; *SSD* sickle cell disease; *NM* not mentioned

[a] Data cited in a book chapter

* Two patients regained erectile function after surgical closure of shunt [8]

Table 17.4 Most common primary sites of metastasis to the penis

Primary tumor	No. cases
Genitourinary	229
Bladder	106
Prostate	91
Kidney	20
Testis	11
Ureter	1
Gastrointestinal	56
Rectosigmoid	48
Colon	4
Pancreas	1
Liver	1
Stomach	1
Anus	1
Other (lung, tonsil, nasopharynx, sarcoma, leukemia, lymphoma, melanoma, bone)	20
Total	305

effective approach to management. If the patient requests immediate resolution and elects embolization, penile arteriography should be performed in concert with interventional radiology. Nonpermanent embolization materials such as autologous clots or absorbable gels and permanent materials consisting of coils, ethanol, polyvinyl alcohol particles, and acrylic glue are available options [3]. While both will achieve close to a 75% resolution rate, the use of nonpermanent materials is preferred to the use of permanent material due to the latter's association with ED postprocedure (5% with absorbable vs. 39% with permanent substances) [2, 3]. If angiographic embolization fails then penile exploration and direct surgical ligation of sinusoidal fistulas or pseudoaneurysms may be performed with the assistance of intraoperative color duplex ultrasonography [2].

For those patients refractory to all treatment strategies or who have irreversible ED, a penile prosthesis represents the only management option available [2, 3].

Priapism and Cancer

Local primary or metastatic neoplastic processes are known to carry priapism risks. Hematologic malignancies including leukemia and multiple myeloma have also been identified for their risk associations with priapism occurring in up to 50% of patients with chronic granulocytic leukemia [71, 72]. As a result of this, it is important that patients with cancer be aware of these risks and symptoms. While primary penile carcinomas are one of the rarest male genital tract tumors, in some countries they represent a significant health problem affecting 10–20% of the population [73–75]. To date, metastases to the penis have been reported in over 300 cases in the literature and represent the next most common penile tumor after primary squamous cell carcinoma [76–78]. The corpora cavernosa are most often affected, followed by the glans and corpus spongiosum [79]. The most common primary sites of metastasis to the penis are of genitourinary tract origin (70%) and gastrointestinal tract origin (23%). Congruently, the most common primary organs to metastasize to the penis include the bladder, prostate, rectosigmoid colon, and kidney [80, 81]. Other less common sites have been documented (Table 17.4) [81].

When a malignant neoplasm invades the corpora cavernosa, 40% of those cases will develop "malignant priapism" [81, 82]. Malignant priapism is believed to be a result of spread of malignant cells into the cavernous sinuses and draining veins of the corpora cavernosa [39, 79]. Tumor infiltration leads to stasis or thrombosis of the venous sinuses and irritates the neural pathways [80]. The venous drainage of the penis becomes blocked while the patent cavernous sinuses fill with blood, becoming distended and eventually resulting in a painful erection [39]. Increased venous congestion and enhanced blood viscosity has served as the pathophysiologic basis for priapism associated with local primary or metastatic neoplasias [84–87]. A duplex Doppler ultrasound of the penis and perineum will determine if the etiology of malignant priapism is ischemic versus nonischemic. If nonischemic priapism is diagnosed, the preferred treatment is embolization.

While the route of tumor spread remains controversial, the leading theories suggest that

urogenital carcinomas can cause priapism either by local direct invasion and growth into the adjacent tissue, arterial embolism, hematogenous, retrograde venous, or lymphatic routes, or instrumental spread [88]. While it is possible that more than one route of dissemination may occur in a single case, the most accepted route, is direct extension, explaining the common finding of proximal invasion of the tumor into the corpora cavernosa [74]. The most common histological finding of metastasis to the penis is the replacement of tumor into one or both corpora cavernosa [87]. Occasionally, penile metastases are diagnosed prior to identification of the primary cancer site [73].

Priapism associated with malignancy may be ischemic, secondary to veno-occlusion or nonischemic, secondary to high arterial blood flow. Malignant priapism can be refractory to standard first line therapies such as aspiration/irrigation and injection of alpha-agonists, leaving the differentiation of ischemic versus nonischemic priapism difficult to ascertain by blood gas analysis [39]. However, malignant priapism is most often ischemic, because metastasis causes mechanical impedance to venous flow, resulting in reduced oxygenated blood flow to the penis predisposing to ischemia [8]. Therefore, malignant priapism demands the same urgent treatment as ischemic priapism to prevent tissue damage and ED.

The most common signs and symptoms observed in penile metastasis, in order of frequency, are malignant priapism (40%), urinary retention, penile nodules, ulceration, perineal pain, edema, generalized swelling, broad infiltrative enlargement, dysuria, and hematuria [88, 89]. In a study of ten cases of penile metastases, malignant priapism and broad infiltrative enlargement were the most common clinical findings with an incidence of almost 83% and 73%, respectively [74]. These findings were followed by difficult urination in 64% and multiple painless nodular involvement in 18% of the patients [74].

Various diseases or infections can mimic one another; therefore, it is important to differentiate penile metastasis from idiopathic priapism, Peyronie's disease, venereal/infectious ulcerations, and primary penile carcinomas. Treatment modalities are different depending on the etiology of the malignant priapism, and a delay in therapy may result in permanent ED for that patient [90].

A penectomy is the most accepted and widely used therapy to alleviate intractable pain, which is a common sequela of tumor infiltration into the penis. In cases where the patient has solitary nodules or localized distal penile involvement, no single therapy has been shown to be superior except for local excision or total penectomy [74]. Of note, when the penis has become completely infiltrated with a malignancy, the management is a penectomy. When the penis appears to be rigid secondary to erection, an ultrasound may be used to differentiate between complete infiltration of tumor mimicking priapism versus ischemic priapism secondary to tumor implant. In which case, one may be able to perform local excision and spare complete penectomy.

Currently, there are no definitive recommendations regarding treatment with radiotherapy, hyperthermia in combination with radiotherapy, or chemotherapy for penile metastases. Further studies are needed to evaluate their use in the management of malignant priapism. Total penectomy and local excision of solitary nodules or distal penile involvement are still the treatments of choice. However, in patients with metastasis to the penis from leukemia, bilateral cavernotomy may be performed [74]. Due to the correlation of metastatic penile lesions with advanced disease, prognosis is unfortunately poor in these patients with survival after presentation being limited and the majority of patients dying within 1 year [89–93]. Penile metastases can be diagnosed prior to the primary cancer site. In 80–90% of patients, metastasis to the penis usually represents widespread disease, with rare instances of isolated metastases having been documented [74].

Although metastatic penile cancers are relatively rare, they still present a challenging problem with guidelines for treatment lacking or resulting in permanent ED. Additional research is warranted in order to better understand the mechanisms behind penile metastases so we can effectively treat these patients earlier, and with the hope of a better prognosis.

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Part III
Patient Assessment

Chapter 18
The Sexual Health Interview: Male

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Keywords Questionnaires • Communication • Confidentiality

Introduction

The diagnosis of cancer in men, whether localised and limiting with good chance of remission or for those men with late presentation with metastasis and poor prognosis can be a devastating life event. For many men, once the diagnosis has been acknowledged, the priority for that man and his close confidants is to maximise the chance of remission and recovery. Some men will wish to remain sexually active throughout any treatment process. The associated anxieties and fears will need careful attention to minimise disruption to an individuals' sex life and that of his partner when present. A good sexual life may be a beneficial factor in overall maintenance of good quality of life in both the short and medium term. Broaching the subject with men as part of the assessment and management plan is crucial. Management of secondary matters of health care such as the effect on sexual function, the effect on fertility and the potential complications of any interventions whether these be medical – including chemotherapy and radiotherapy or surgical need careful attention. Setting the scene and attending to these matters with sensitivity is good practice for all physicians managing cancer care. These matters will be discussed further as well as strategies for taking a sexual history in this chapter.

Background Review

This literature review will review the published evidence around taking a good sexual history and the impact and influence this may have on an individual's well being with regards to both sexuality and fertility.

The Cochrane Database of Systematic Reviews (2007) suggests that "Sexual Dysfunction is one of the more prevalent long-term complications following many types of cancer treatment" [1] and estimates that sexual dysfunction occurs in 60–90% of men following radical prostatectomy and in 67–85% following radiotherapy. Multifactoral causes are identified including "surgery, radiation, chemotherapy, hormone therapy, changes in serum testosterone levels, lowered functionality and an increase in symptoms of depression or anxiety". Yet despite this, taking a sexual history from men known to be experiencing cancer is not standard practice.

Various studies published between 2005 and 2007 have discussed sexual function in relation to treatment for prostate cancer. Trinchieri et al. [2] assessed sexual function according to a multidisciplinary comprehensive approach in patients with localised prostate cancer who were treated with radical prostatectomy. Depression

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associated with the fear for intervention is related with erectile dysfunction measured by IIEF (International Index of Erectile Function) scores before surgery, but depression index scores improve after surgery showing that the role of counselling and oral treatment facilitates recovery after surgery in patients with optimal erectile function before treatment. As such this should be assessed carefully prior to surgical intervention. Assessment for concerns about penis size and willingness to engage in early interventions post surgery may be helpful. There are several papers in the literature (dealt with elsewhere in this book) on penile length concerns after radical pelvic surgery. This could be an issue for a man about to undertake this type of surgery and by taking a sexual history, the physician would have an opportunity to address such fears. Kohler et al. [3] undertook a pilot study to evaluate the effect of the early use of the vacuum erection device (VED) on erectile dysfunction (ED) and penile shortening after radical retropubic prostatectomy (RP), as these were identified as important concerns for men choosing among treatment alternatives for localised prostate cancer. Twenty eight men undergoing RP were randomised to early interventions (1 month after RP, group 1) or a control group (6 months after PR, group 2) using a "traditional VED protocol". This study found that initiating the use of a VED protocol at 1 month after RP improves early sexual function and helps to preserve penile length.

Kurtz et al. [4] carried out a study to evaluate the impact of cancer treatments on sexuality and relationships. A questionnaire was sent out to 50 oncology patients concerning relationship changes, sexual dysfunctions, changes in self-esteem and body image. The patients had been in a stable relationship at least for 1 year. Before the onset of cancer, 84% describe their relationship as (very) good, but during the treatment period almost half (44%) of them noticed deterioration in their relationship. Eighty percent of respondents showed a decrease in their sexual relationship, while 16% expressed no significant change at all, 4% had described an improvement in their sexual relationship. About three quarters of patients had answered that their self-esteem had diminished along with a poorer sense of body image. Eighty-four percent did not receive any counselling regarding possible changes in sexuality and relationship during the course of the cancer treatment. Thirty-six had felt a strong need for such counselling in order to have a better understanding of how the various treatments affect their sex life.

Peltier et al. [5] found that counselling and re-education with a multidisciplinary approach offers an effective post treatment recovery of erectile function. An epublished article by Eberhard et al. [6] assesses the prevalence of sexual dysfunction in testicular germ cell cancer (TGCC) patients 3–5 years after treatment, and relates the findings to biochemical hypogonadism, treatment intensity and the expected prevalence in the Swedish male population. They found that a higher proportion of TGCC patients than comparators were likely to report low sexual desire as well as ED 3–5 years after completion of therapy, and that these sexual dysfunctions were not significantly associated with treatment intensity or hypogonadism.

As this current literature demonstrates, early assessment of sexual function following diagnosis of cancer is important to allow early intervention and treatment that can preserve and optimise sexual function post treatment. However, there is little published evidence specifically in terms of the influence and effect that taking a good sexual history can have on a man's well being during the diagnosis and treatment of cancer.

The effects of cancer and its treatments on fertility in men are also well documented. However, less well documented is the evidence to support sexual history taking in men with cancer in order to preserve and protect their chances of fathering children. Knoester et al. [7] assessed fertility issues for men with newly diagnosed prostate cancer. They demonstrated that with the increased use of prostate-specific antigen screening, younger men are being diagnosed with prostate cancer. A subset of these men is still interested in potentially having children after cancer treatment. To their knowledge, the topic of future fertility in patients with newly diagnosed prostate cancer had not previously been reported.

Chapple et al. [8] looked at the perceptions and experiences of young men recently diagnosed and treated for cancer. They set out to explore fertility issues for young men who had been diagnosed and treated for cancer and to examine communication problems surrounding these fertility issues. Narrative interviews were conducted with 21 young men previously treated for cancer in the United Kingdom. Eighteen talked about fertility issues at some length. A qualitative interpretive approach was taken; combining thematic analysis with constant comparison. They found that communication about sperm storage was sometimes difficult and embarrassing. Young men wanted the opportunity to bank their sperm but decisions were often rushed. Some would have appreciated counselling and were unprepared for the process of sperm banking and criticised facilities. Uncertainty about fertility status caused worries for the future. This study concluded that more still needs to be done to help young men with cancer to address issues of fertility and that all adolescents and young men treated for cancer should be offered sperm banking if their fertility may be affected. They should be offered counselling at every stage by professionals who feel comfortable talking about the subject. Interactive, educational CD-ROMs or websites may be useful. Physical facilities for sperm banking should be improved.

Tschudin and Bitzer [9] identified that with advances in treatment, the number of young cancer survivors who may benefit from fertility preservation are growing. The aim of their study was to review the literature investigating psychological aspects of fertility issues and fertility preservation in patients undergoing fertility-compromising therapy for cancer or other life-threatening diseases, previous to or during their reproductive lifespan. Articles were identified in PubMed, Embase and PsycLIT as well as manually retrieved from literature citations for the time period from 1999 to 2008. Inclusion criteria were: (i) qualitative or quantitative design, (ii) focus on patients previous to or during their reproductive lifespan and (iii) dealing with aspects such as (1) impact of fertility issues in cancer patients or (2) health professionals' and/or patients' attitudes towards fertility preservation or (3) counselling. Twenty-four studies were identified. According to the studies on aspect (1), fertility is an important issue for cancer patients. Health professionals as well as patients and parents consider fertility preservation as an important option for young cancer patients; all parties involved, however, were noted to have knowledge and information deficits. Patients recalling counselling about the impact of cancer treatment on fertility ranged from 34 to 72%. This literature review suggested that counselling is far from being offered globally to all patients at risk, and that providing information seems to be selective. The existing literature demonstrates the need for and the limits of current counselling. Future research should target the means to facilitate the decision-making process for patients and health professionals.

Given the impact of cancer and it's treatment on sexual function and fertility, as demonstrated above, and that the studies that were identified demonstrated that young men with cancer were generally keen to maximise their chances of having children, it would be pertinent to conclude that maintaining sexual function would be one of the ways to optimise the mechanical maintenance of fertility, even if there could be concomitant chemical, physiological or pharmacological complications. Clearly, good clinical practice in addressing these issues is to offer a sexual history assessment to all men suspected of, diagnosed with or treated for cancer in order for the physician to be able to facilitate the appropriate intervention and support.

Helping Communication About Sex Between Patients and Physicians

> Physicians must remember that they do not have to be expert sexologists, have perfect sexual relationships with their own partner, or share the values or attitudes of their patients to make them more comfortable discussing sexual matters: they need to be good interviewers which requires a different skill set entirely [10].

While it may not take very long to ask the simple question "any sexual concerns" [11], the physician may appear indifferent or impolite by devoting a very short amount of time to a topic where there is evidence that the diagnosis will have a marked impact on sexual function. Our advice is to ensure that first the patient is ready to talk about their sexual life and then taking the time to both put the patient at ease and allow him to start talking about his problems or concerns. Physicians will often wonder what to ask and we will demonstrate that there are common themes which are replicable across a number of clinical scenarios.

It is often assumed that there is reluctance by the patient to talk about topics of a sexual nature. In one study, men with the most severe sexual dysfunction and older men were the most reluctant to disclose sexual symptoms to a physicians [12]. In a general study of 62 medical practices in Australia, 50 consecutive patients were asked by questionnaire about sexuality and ED. One thousand two hundred and forty questionnaires were evaluated where the average age of the patient was 56 years. ED was reported in 37.1% of the men but only 11.6% of the participants with ED had been treated for it [13]. To identity the possible barriers to addressing sexual health problems, Marwick [14] identified that 71% of patients were worried that their doctor would dismiss their sexual concerns if raised (Table 18.1). Nearly as many (68%) felt that their doctor would be uncomfortable or embarrassed at discussing sexual matters. Even in clinical scenarios where sexual dysfunction is well recognised, very few patients will spontaneously report their sexual dysfunction. In a study by Montejo et al. [15], 14% of patients on a selective serotonin reuptake inhibitor (SSRI) spontaneously reported sexual dysfunction but the number rose to 55% reporting a dysfunction when asked directly by their physician. A recent study from Gotenburg [16] found that for self reported sexual activity and satisfaction in Swedish 70 year olds, as the decades have progressed, more men (and women) are reporting quality and quantity of sexual experiences to have improved. A number of reasons are highlighted but importantly physicians need to be aware that good sexual function remains important throughout an individual's life and well into their elderly years.

There is evidence that patients may raise sexual issues from a number of recent studies. Seventy-six percent of patients were interviewed in the large European Erectile Dysfunction Study (EDOS) of which there were 7,824 participants on the treatment of ED and standard practice conditions who reported that they (and not their physicians) were the ones who had initiated the discussion about ED [17].

In the Global Study of Sexual Attitudes and Behaviours (GSSAB), Hartman et al. [18] investigated the behaviours and attitudes of men and women aged 40–80. This study was across 30 countries and involved 2,700 men and women. In most countries sexuality is considered an important aspect of life and that the importance of sexuality does not decrease significantly with age. Physician–patient communication shows an overall dissatisfied situation with a need for change. Only 9% of the worldwide sample reported that a physician had asked them about sexual problems in the last 3 years, with the number rising slightly to 11% in Germany.

Table 18.1 The barriers for addressing sexual health problems

Clinician discomfort
Patient discomfort
Insufficient training
Underestimation of the prevalence of the sexual concerns
Time pressure
Perceived treatment options [14]

Enhancing the Opportunity

There is some investigation of the effectiveness of using questionnaires to improve both the report rate of sexual dysfunction and physician–patient communication in sex specific problems such as ED and general medical practice. Read et al. [19] found that sending a questionnaire

increased the frequency of diagnosing a sexual dysfunction from 2% overall to 35% for men and 42% for women. Many of the respondent patients raised the matter or problem with their doctor. A second study by Kitai et al. [20] found that the number of consultations about sexual problems in the year after sending patients, in Israel, a questionnaire about their sex life was higher than the number from the 2 previous years combined. A third study by Hartmann and Burkart [21] identified that there was a concern by physicians that patients would reject an offer to talk about sexuality but the study refuted this concern. Work by Radley et al. [22] in Sheffield has developed and evaluated a web based electronic pelvic floor symptoms assessment questionnaire for women. This has demonstrated that information about symptoms not usually screened for, but relevant, in certain clinical practice can easily be elicited by an on line questionnaire. This might be transferable as one way to offer sexual history assessment to men attending oncology units. Interviews about sexual dysfunction can be carried out in a systematic focused and time efficient way which can be satisfactory and constructive for both physicians and patients. A patient questionnaire about sex was met with a high level of acceptance with 54% of discussion of sexual health being prompted by it. Two-thirds of the men were over the age of 50 years (55.7 years). The opening of physician–patient discussion about sexual problems was: 38.9% a direct question from the patient, 57.6% as a result of the patient's questionnaire and 15.9% as a result of the physician prompting about the matter. This would suggest that the initiation to talk about ED (and we assume also other sexual problems in men) is more likely to come from the patient than the physicians.

The initial phrasing used to open a discussion about sexual health is highly important for the sustained success of communication and development of an effective working alliance. Hartmann and Burkart [21] found that asking about a sexual problem was the most likely phrase used by physicians to open the discussion on ED (25.8%). Referring to the patients' questionnaire (17.1%); asking about general conditions or life situation (9%) and directly asking about sex life in general (8.7%) were also important. Referring to a patients' illness or complaints, asking about the duration of sexual problems, explicitly expressing a readiness to talk about the problem, or asking about the relationship with their spouse were all less than 7% each. It is also important to remember that relationships conflicts may occur for patients with sexual dysfunction with this being as high as 34.5% in the study by Hartmann and Burkart [21]. It was identified that in 44.3% of cases the patient's partner also reported as having a sexual problem.

Concurrent factors such as emotions associated with depressive mood and not with anxiety appear to be strongly associated with sexual dysfunction [23]. Any treatment approaches orientated to reduce anxieties such as relaxation and systemic desensitisation might be less efficient than interventions aimed at elevating mood during sexual activity if this is the case. As mood disorder is common following diagnosis of life-threatening diseases this is important to assess carefully.

Recent evidence also shows that patients have a preference to receive sexual health information from their healthcare provider who initiates the conversation (45.1%) or from their provider once the patient initiates the conversation (31.5%), although nearly a fifth would prefer to receive sexual health information from their provider after filling out a questionnaire addressing sexual concerns [24]. In only a small proportion did patients describe feeling much less comfortable when their provider was of the opposite gender.

Other studies have identified factors that may hinder the discussion of sexual concerns including the fact that the physician appeared to be rushed for time, seemed disinterested or embarrassed, was too young or old or of the opposite sex [25].

Getting Started

The challenge of the sexual conversion is very different from many discussions that physicians will have with their patients about

other medical problems. There may be unclear definitions with unclear questions for evaluation. There is often discomfort for the physicians and patient with no learned role model of conversion to get going. However by normalising responses and experiences, patients can be helped to understand that their sexual problems are common and that there can be a number of interventions to assist the man.

To initiate the sexual conversation, the focus does not need to be on finding a solution in the first instance but by mentioning to patients that many other men who have been diagnosed with cancer may have mentioned to the physician that they have noticed changes in their sexual well being. Follow this by asking has this been a bother to you? It may be that this is something that your partner has remarked upon? Other helpful opening questions included would you like to tell me about your current sexual relationship(s) if you are having any? Are you satisfied with your current sexual life? Direct questions such as have you or your partner any sexual problems at this time or any sexual concerns that you would like to discuss may facilitate or open a discussion. Identifying whether the problem is bothering the man or causing distress will help the physician to identify the importance of continuing to ask about these problems. Secondary factors such as difficulties with pain may also need to be attended to.

Preparing the Patient

Although the situation may be raised by the patient by mentioning the problem, or a brief question being asked to the patient by the physician such as "any sexual concerns", it may be helpful to prepare the patient by sending them a introductory letter or information sheet about the effect that the diagnosis of cancer may have upon their general sexual well being. When taking a sexual history from patients although it may be assumed that the problems is happening now because of the diagnosis of the cancer, or the associated treatment, a good sexual history will ensure that other precipitating, perpetuating and predisposing factors are identified which may require considerable attention before being able to restore good sexual function. As with most areas in clinical medicine, think beyond the symptom. By this we mean that if a patient describes a problem of sexual function, enquire about all of the sexual cycle and not just the present problem. Also consider cormorbid conditions which may also be aggravating the problem such as Peyronie's disease or androgen deficiency in men who have ED. Always be aware of possible avoidance strategies that either the physician or the patient may employ to either define or limit the amount of information that is disclosed. Starting with general principals, using indirect questions, employing active listening and ensuring that a common language is found should facilitate the discussion of sexual matters and may be a useful adjunct before proceeding with direct questions. Throughout, attempt to support and encourage the man about discussing his sexual problems without appearing condescending. Appreciate the considerable effect and courage that may be necessary for a patient to raise the matter by giving him appropriate and sensitive feedback.

Taking a Sexual History from the Man

We always start by getting some general epidemiological information about the man and his partner including details about age, marital status, duration of the current relationship and his occupation. The general time devoted to work by both the man and his partner is important in evaluating the work home balance and the potential for this to act as a major stressor in the domestic environment. We encourage the man to bring his partner to the assessment wherever possible and note this on our case record.

Using the techniques above, we go on to identify and encourage the man to give a general description of his problems. We want to identify

the date of onset as accurately as possible and the age at the time of the onset of the problem. It is important to identify if the problem came on gradually or rapidly and to get an accurate descriptor of the problem. The original participant should be enquired about and this is not always directly the diagnosis of the cancer or secondary to it. We like to identify perpetuating factors and to know when the last successful experience occurred for the man. We enquire about the frequency of the problem and whether this is every time, on the majority of occasions or less than half of those occasions. Factors that improve or worsen the condition are asked about. Attempts of treatment so far should be enquired about and for sexual problems this specifically should address issues of medication, both prescribed and nonprescribed (including for example sildenafil and other oral agents for ED), access to sexual therapy or relationship therapy, and other more invasive investigations as well as involvement with any clinical trials. At this stage we also identify the motivation for the individual seeking help, their expectations of treatment and what has caused them to attend now.

Erectile Function

We ask the patient to rate and assess their rigidity and frequency of erections. We ask specifically about erections upon awakening, during the night (when the man may awaken), during foreplay and intercourse, during masturbation, during oral sex, looking at erotica and spontaneously. Sensitivity about enquiring about some of these latter situations and prefacing the question with "if this is relevant to you" is necessary. The patient may rate rigidity, full, partial (in which cases they should be asked to rate it between 1 and 100%), absence or not applicable. Frequency is rated as every day, 2–3 times a week, once a week, less than once a week, less than once a month or never. If erections are full we want to know if the erection is lost before entering the partner, on entry on the partner or after entering the partner. It is also important to know if the erection is lost before or after ejaculation. Other factors which are important to identify include whether the morning erections are partial and how long it is since the last full erection. Overall, is the main problem attaining or maintaining an erection or both. Is there pain on erection and if so this should be described? Is there any deformity such as bending at the time of erection? We enquire whether the penis has decreased in size since the problem began, or whether it has increased in size. Erections during masturbation are enquired about and whether these are full partial or absent and whether these are better than those present during sexual intercourse or not.

We go on to ask questions about ejaculation and whether there are areas of concern. If so we encourage them to describe whether it is premature (rapid), inhibited or without expulsion despite the experience of orgasm (retrograde). The duration of the ejaculatory problem is noted and whether the man is able to ejaculate with a flaccid penis. We also ask about the amount of ejaculate and whether this is less than it used to be.

Questions around sexual interest and the frequency of spontaneous interest are identified. Any change and the onset of change are also asked about.

We make enquiry about background issues of sexuality including evidence of good sex education, any evidence of lack of a sexual relationship, and the last experience of sexual activity if a man is not currently in a relationship or having occasional sex with other persons. We also identify in the sexually active man, who initiates sexual events and how often this is happening? Information about previous sexual trauma or abuse should be asked about and if so, has he ever had any therapy for this.

Associated factors in the sexual history should include evidence of concurrent physical illness which may affect sexual function, concurrent to any related cancer diagnosis. This may include diabetes mellitus, certain endocrine problems, cardiovascular issues, common urological factors and similar.

A surgical history is taken including any other abdominal or pelvic surgery or whether a vasectomy has been undertaken. Psychiatric history current and past is important to enquire about as well as any evidence of depressive features with low mood, disturbed appetite, disturbed sleep pattern, lack of energy and enthusiasm etc. We always ask patients whether they believe psychological factors are playing a part in the current problem. Enquiry about alcohol intake, the use of non-prescribed recreational drugs and whether the man smokes cigarettes.

We ask about whether the patient is prescribed any drugs for any of the medical or psychiatric issues identified or for the cancer related condition. Particularly, pertinent to the patient with cancer is a thorough history detailing exposure to chemotherapy and radiation, regimens used and duration of exposure.

Other issues should be enquired about particularity about other possible anxieties or stresses in the mans' life asking about issues of work, finance and family issues (including children and parents).

A relationship history should be enquired about starting with the current wellness of the partner. Go on to ask if there have been difficulties within the relationship either in the past or current. The general well being, psychiatric state and presence or otherwise of sexual problems in the partnership be identified. Issues of contraception are enquired about and information about any children in the household. If there is a previous history of cancer, it is useful to identify if sexual function was affected at that time and how this was managed.

It is important to think carefully about not asking the following set of questions but it may be that the setting and timing may need to be adjusted from the preliminary assessment. These are particularly around issues of homosexuality and gay experiences and extra marital and extra relationship affaires. Enquiry about history of sexual transmitted infection should also be asked about at this time.

Specific issues in the history affecting sexuality and fertility and cancer may relate to both the patient and his partner. Therefore, where possible, if the man is in a relationship the sexual history could be taken during a consultation involving both partners. This would also be a good opportunity for education and dispelling myths that might be held by the patient or his partner relating to both cancer and sexuality. It would be relevant to note how the partners are both responding to the diagnosis or treatment of cancer – are they adjusting to the change in circumstances and is the rate of change for each of the couple impacting on their relationship in terms of communication and intimacy? There may be issues of "loss" for either or both of the partners; of the sexual or healthy self, or relating to the loss of fertility or a perceived loss of masculinity or sexual identity, which may accompany both the illness and its treatment. Partners of men with cancer may have concerns about whether they have caused the cancer or might make the cancer worse by sexual contact. Both the man and his partner may also be concerned about whether the cancer might be passed from the man to his partner during sexual or intimate contact. The couple may benefit from counselling to accommodate changes they may feel they need to make in response to the cancer or its treatment for example considering having a child at a time when they had not planned to do so and may benefit from referral for genetic counselling if there is a hereditary factor to the cancer. A sensitive sexual history taken at a time when the man and his partner may feel less inclined to be sexual than usual, may help them to reframe their approach to their sexual relationship and see that as well as sex for procreation it may also provide comfort, relaxation, intimacy, pleasure and pain relief during a time of personal and relationship stress. It should also be noted that men being treated for cancer who are imunosuppressed are likely to experience oral and genital fungal infections and ulcers. As well as feeling sore and uncomfortable generally and during sexual and intimate contact, this may also add to feelings of being unattractive. Where possible treatment should be offered to minimise such side effects, the impact of these on sexuality and intimacy should not be underestimated.

General Comments

The physician should maintain optimism during the assessment period identifying any fears and uncertainties that the man may have. Assess throughout for suitability for any subsequent psychosexual interventions and therapy and uncertainty about the role of engaging such interventions which are useful when coming to formulate the current situation for the man. Our ethos has always been working in multidisciplinary teams and sharing information during assessment that is valuable. Working with colleagues across disciplines, as will happen with cancer treatment with, for example, physicians, psychotherapists and pain specialists are all important when making a formulation of the best intervention that may be useful for the man with sexual dysfunction. Throughout the assessment process short term interventions may be useful and these may be augmented by working with the couple. Any assessment of sexual function and the raising of such issues should be ongoing throughout the illness and treatment process to allow for changes along the way where possible partners should be included in this process and their issues addressed, as they may impact directly on the patient. Normalisation of changes and fluctuations in sexual response may be reassuring for both the man and his partner. Supporting adjustment to change and encouraging creativity in the sexual relationship, with a sense of humour, will allow most men and their partners to feel relaxed to express any concerns or limitations allowing the physician to refer for appropriate and timely support and interventions.

Conclusions

As this chapter has demonstrated, cancer and treatment interventions can impact physically, emotionally and relationally on the sexual function and fertility of men and their partners. Despite a growing body of empirical evidence documenting this, sexual history assessment is still not standard practice among physicians working with men with cancer. This appears to be in part due to real and perceived barriers to asking about sexual function among physicians relating to their own practice, knowledge, education and training and also assumed of their patients' embarrassment or offence with such questions (Table 18.2). However, studies above show that these barriers can be overcome or are unfounded. If this is considered in terms of clinical governance, the evidence to suggest that early assessment for potential or pre-existing sexual function or fertility difficulties is likely to allow timely and effective interventions or treatments clearly that negates failing to address these physician issues. It is our opinion that any physician working with men with cancer can and should learn how to take a sexual history.

Table 18.2 Potential barriers for discussing sexual health with patients

Patient barriers
Emotional factors (shame, guilt, anxiety, embarrassment)
Age
Perception that sexual function is not a medical problem
Lack of awareness about possible treatment options
Physician characteristics (gender, age, appearance, speciality)
Lack of privacy to discuss (e.g. clinic rooms)
Poor reimbursement under insurance schemes
Clinician barriers
Embarrassment of raising the subject
Feeling overwhelmed by other healthcare issues
Lack of specific training in sexual medicine issues
Feeling therapeutically uncomfortable using psychosexual counselling interventions
Lack of awareness of association with other conditions

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Further Resources

- The Porterbrook Clinic (www.shsc.nhs.uk/porterbrook) has used a standardised data collection sheet to assist the taking of a sexual history over the last decade. This has been shared at various training events and modified by colleagues in different countries. A copy of the sexual history data collection form is available from the authors.

Chapter 19
The Sexual Health Interview: Female

Sharon J. Parish and Sheryl A. Kingsberg

Keywords Questionnaires • Communication • Confidentiality

Introduction

Sexuality is the quintessential biopsychosocial phenomenon. It is an integration of emotional, somatic, intellectual, and social aspects of an individual [1]. Sexual practices encompass a wide range of activities. Sexual intimacy may be central to the maintenance of long-term relationships, particularly for females. Sexuality involves the relationship between the individual and society, and it is influenced by social and religious views. Sexual functioning may be integral to a woman's identity, self-esteem, and sense of personal efficacy. Sexual behavior requires the acquisition of skills that involve the complex integration of physical and emotional behaviors [1]. Given the complexity of these interfacing domains, it is not surprising that when sexual problems develop they can have a significant impact on social functioning and emotional well-being.

Obtaining a comprehensive sexual history that encompasses the wide scope described above can be a clinical challenge. It requires a spectrum of advanced clinical skills that include sexual medicine, knowledge about sexual anatomy, physiology and pathology; sexual problem history taking; empathy skills; and behavioral counseling. In this chapter, we will discuss the rationale and approach to screening and assessing women's sexuality and sexual complaints in the clinical setting. Where relevant, we will suggest specific strategies applicable to the cancer patient. We will describe how the sexual response cycle and other models for understanding sexual response provide a framework for sexual history taking. We will emphasize how the sexual health interview fits into in the general evaluation of female patients. Although female sexual disorders have been studied far less extensively than male sexual disorders, we will present recommendations based on the best available knowledge.

Epidemiology and Rationale

Sexual concerns and problems are common. A 1999 survey of adults' sexual behavior (ages 18–59 years) revealed that 43% of women have sexual problems that are associated with poor quality of life [2]. In the more recent Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking (PRESIDE) Study, around one in eight women experienced distress associated with any sexual problem [3]. Women with any sexual disorder experience low feelings of happiness and diminished physical and emotional satisfaction. Sexual activity and overall health are related, as are sexual activity and happiness. Women undergoing present or past treatment for gynecological, breast, and other cancers may suffer particular personal and

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relationship distress, depending on the nature of their therapy and its impact on sexuality. However, only one third or less of women who have sexual disorders seek medical consultation [3].

Clinicians rarely ask about sexual problems, thus detection rates are consequently low. In one study in which clinic physicians were trained to take a screening sexual history, 53% of patients reported a sexual problem [4]. When polled, 91% of the patients said they considered questions about sexuality an appropriate part of the interview. These data demonstrate the high prevalence of sexual problems, improved detection with focused training in history-taking skills, and patient acceptance of such discussions.

Although 50% may report problems, generally less than half of these women experience personal distress regarding their sexual dysfunction, such that it would meet established criteria for a sexual disorder [5]. One challenge in the clinical setting is therefore to identify which patients would benefit from addressing sexual problems.

Despite the prevalence of the classic sexual dysfunctions, what patients more commonly want to discuss are "sexual concerns." Women may have questions about their sexual behavior with regard to frequency, techniques to reach orgasm, masturbation, and fantasy. Women may have concerns about communication, disparate attitudes or value systems, sexual orientation, and about the role of sexuality in their overall relationship. They may have inadequate knowledge about sexual function regarding: developmental issues in adolescence; sexual changes with aging, medical illness, disability, or pharmacological treatment; and changes with pregnancy, breastfeeding; or infertility. These "sexual concerns" may evolve into sexual disorders if they result in intrapsychic distress or conflict between partners.

Sexual Problems in Women with Cancer

Sexual complaints are common in women who have previously or are currently undergoing treatment for breast and other cancers. Many cancer treatments directly affect sexual functioning as well as indirectly impact other related physical aspects of functioning (e.g., premature menopause, fatigue) and potentially cause disfigurement (e.g., ostomy, weight changes, scarring). Sexual problems are a common consequence of breast cancer treatments, both short and long term. Following surgery or radiation for early stage ovarian or uterine cancer, 50% develop a new sexual dysfunction in the subsequent year [6]. Estimates of incidence of sexual dysfunction in women treated for breast and gynecologic cancers range from 30 to 100%, depending on the direct effects of the cancer treatment on genital function and the indirect effects of cancer treatment on overall sexual function.

Need for Improved Sexual Health Dialogs

Despite increased professional awareness of sexual problems in the last decade and increasing demand from patients, female sexual disorders remain underdiagnosed and undertreated. Only 25% of general physicians actually take sexual histories, citing lack of training as the most common reason for not doing so [7]. A recent study of older adults revealed that only 22% reported having discussed sexuality with their physician since the age of 50 [8]. An international study of 27,500 men and women revealed that half of all sexually active participants had at least one sexual problem; but only 19% had sought medical care for the problem, and only 9% reported being asked about sexual health in the previous 3 years [9]. In mature U.S. adults aged 40–80 in this population-based survey, only 15% of women had been asked by a doctor about possible sexual difficulties during a routine visit in the past 3 years, but more than one-half (54%) believed that a physician should routinely ask patients about their sexual function [10].

Patient Barriers to Sexual Health Dialogs

Patients and physicians acknowledge the lack of discussion of sexuality in clinical settings and thus underdiagnosis of sexual problems. Both parties may have attitudes, beliefs, expectations, and behaviors that interfere with effective communication and thwart detection and diagnosis of sexual concerns and disorders.

Patients want to discuss sexual issues, but perceive significant barriers. For example, in one study of 500 adults, male and female, 71% of surveyed patients felt their physician does not have time, 68% did not want to embarrass the physician, and 76% believed no treatment was available [11]. They fear their doctor will dismiss their sexual concerns. Gott and Hincliff studied the barriers to older female patients seeking treatment in an English general practice setting [12]. The women ages 50–92 years reported that the most significant barriers were the general practitioner's attitudes toward later life sexuality, the attribution of sexual problems to "normal aging," the perception of sexual problems as "not serious," shame/embarrassment and fear, and lack of knowledge about available resources. A web-based survey about seeking help for sexual problems involving 3,807 women revealed that half (54%) would like to but did not because they would be embarrassed (22%), did not think they could get help (17%), or it did not occur to them to seek help from a doctor (12%). Half of participants who consulted physicians felt that the doctor listened (52%) without reluctance (49%) or avoidance (48%); but only 39% felt that the physician appreciated the significance of their problem to them, and fewer (24%) felt that the doctor helped them with their nervousness in talking about sex [13].

Patients report nonempathic judgmental responses, physician discomfort, concerns regarding privacy, and a lack of cultural sensitivity. They may experience shame about the nature of their sexual problem or may be reluctant to discuss a particular sexual relationship. Many patients do not have confidence in their physician's skills in managing sexual problems and do not believe that they would receive effective treatment.

Physician Barriers to Sexual Health Discussions

Why do physicians fail to routinely address sexual problems? The most common reasons include not knowing what to ask or what to offer after opening "Pandora's box." Physicians report numerous specific barriers to addressing sexual problems including embarrassment; underestimation of the prevalence; insufficient knowledge about the diagnosis of sexual function and dysfunction; inadequate training in communication skills; lack of information about treatment options; apprehension that their inquiries may offend the patient; low recognition that healthy sexual activity is important; time constraints; inadequate reimbursement; lack of privacy; cultural and language barriers; personal discomfort about sex including language and ageism; and the assumption that all people are married, heterosexuals, and monogamous [14]. Other reasons include fear of sexual misconduct charges, unfamiliarity with certain sexual practices, and personal history of sexual trauma [15]. Physicians may have difficulty remaining objective and separating their personal views from those of their patients [16]. They may have limited sexual experience, unresolved issues regarding their own sexuality, or concern about developing sexual feelings toward patients.

Physicians also reported gender as a significant barrier to sexual history taking. In one survey of a multidisciplinary practice, male and female physicians reported significant discomfort interviewing patients of opposite sexes [17].

Detection of Hypoactive Desire and Related Female Sexual Problems

In the recently published study PRESIDE, low desire was reported in 39% (age-adjusted estimate) of subjects and was the most common sexual problem observed [3]. Sexually related personal distress was present in 23% of subjects, and distressing low desire was present in 10% of

women. Despite this substantial prevalence, the majority of physicians rate their knowledge of female sexual dysfunction as only fair to poor; and their level of comfort parallels their self-assessed knowledge. In a systematic survey of an academic primary care practice, 90% of clinicians reported little confidence in making the diagnosis of Hypoactive Sexual Desire Disorder (HSDD), 90% of physicians had never screened a patient for HSDD [18].

Barriers to Sexual Health Dialogs in Female Cancer Patients

Women with cancer and their partners have numerous sexual concerns such as, "Will sex cause my cancer to spread?" and "Will sex cause radiation, chemotherapy or the cancer itself to be spread to my partner?" However, these concerns and emerging sexual problems are infrequently addressed directly. Oncologists may believe that the sexuality is much less important than elimination of the cancer, and their patients may initially share a one-dimensional, "survival at all cost" view. In one study, fewer than half of cancer specialists took sexual histories in their new gynecologic cancer patients, and the majority (80%) felt that they had insufficient time to explore sexual issues [19]. Although only 21% of oncologists in another study discussed sexual issues, 100% of physicians and patient believed that the topic should have been raised before and during their treatment [20].

Oncologists cite other similar barriers to those described by generalist physicians. Unclear about the relative importance of sexual concerns as compared to cancer and its treatment, they may avoid the topic. They may be uncertain about the effects of treatment on disease progression, such as with the use of topical estrogen therapy for dyspareunia in breast cancer survivors, and reject exploring alternatives to addressing bothersome sexual symptoms. Cancer specialists note other barriers including the lack of resources to provide support, no role model to follow, and that it is a "medical tradition not to ask" [20].

Nearly all women with cancer wish to discuss sexuality but are reluctant to do so because of fear of rejection by their physician [21]. The reluctance of patients to raise the topic may lead clinicians to believe that a patient has adjusted to or accepted changes in sexual function or that they have no concerns. In one study, although 74% of patients believed their oncologist should raise sexual issues, these discussions did not occur two thirds of the time [22]. Women undergoing cancer treatment note a general lack of knowledge about what to expect and feel ill prepared when sexual problems occur. They cite potential benefits of discussing sexual issues, which include normalizing the emergence of problems, knowledge about cause and duration of problems, and providing an opportunity and permission to ask about sexual activity. Overall, female cancer patients consider sexual health to be one of the most important aspects of quality health care and prefer their physician to validate its importance by initiating and conducting conversations about sexuality.

Physicians' Desire for Sexual Health Education

Physicians' previous training in general communication skills has been reported as the strongest predictor for sexual history taking [23], whereas those who perceive that they have a lack of experience in treating sexual problems are least likely to do so. While physicians typically do not receive adequate training in sexual medicine and sexual history taking, they believe that they should address sexual problems and that they need more training. Practicing physicians can gain increased comfort and experience in managing sexual problems by incorporating routine sexual health questions into their practice, by addressing the barriers discussed above, by sharing cases with colleagues, and by exploring their own attitudes toward sexuality [16]. Participation

in education, targeted at improving skills, increasing knowledge, and encouraging awareness of personal biases, is the key to minimizing obstacles that interfere with practitioners optimally addressing sexual health. Despite multiple barriers physicians can learn to initiate discussions about sexual problems, which are acceptable and desirable, to conduct sexual evaluations, and to manage common sexual disorders.

Models for the Female Sexual Response

The traditional Sexual Response Cycle of Masters and Johnson [24], modified by Kaplan [25], begins with desire and progresses in a linear manner through the phases of the sexual response cycle: arousal (excitement, plateau), orgasm, and resolution. More recently, Rosemary Basson developed a nonlinear model of female sexual response that integrates emotional intimacy, sexual stimuli, and relationship satisfaction (Fig. 19.1) [26].

This model recognizes that female sexual functioning: (1) is more complex and is not as linear as male sexual functioning and; (2) many women initially begin a sexual encounter even when feeling little sexual interest (i.e., sexual neutrality). The decision to be sexual is based on the goal of increasing intimacy rather than a particular hunger for sexual activity. Women have many reasons for engaging in sexual activity other than simply sexual drive; and sexual neutrality or being receptive to, rather than initiating sexual activity, is considered a normal variation of female sexual functioning. Basson also suggests that the order of response may vary such that arousal and desire are so intertwined they are not distinct phases; and even if they are distinct, arousal may often precede desire. Clinicians are well served to consider that there are several models of sexual response that may be considered when interviewing women about sexual function. The clinician may explain the models in simple terms and then phrase questions to determine which best resonate with a woman and/or apply to her relationship. This approach allows the clinician to explore the range of

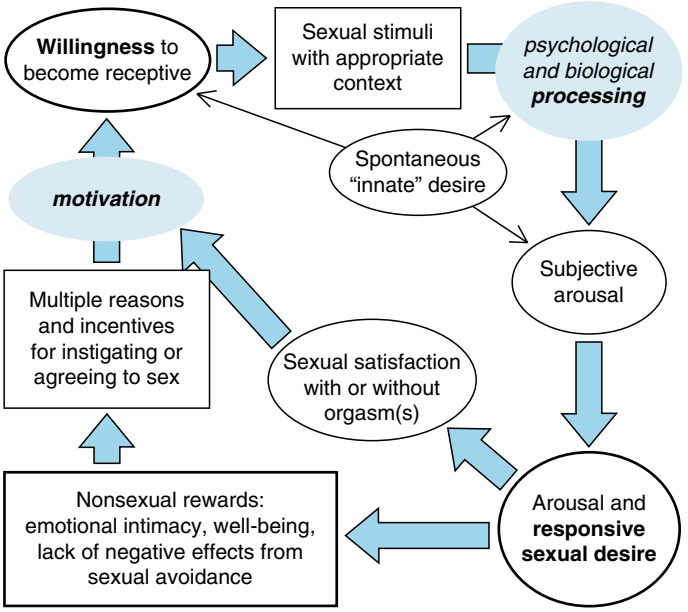

Fig. 19.1 Alternative model for female response cycle

possible normal sexual responses and put a particular woman's experience into context.

The Female Sexual Disorders: An Overview of Classification

In order for the clinician to conduct an appropriate and focused sexual health interview, the clinician should learn and understand the distinctions between the classical sexual disorders. According to the DSM IV TR [27], there are six sexual disorders that encompass dysfunctions across the sexual response cycle (Table 19.1).

Understanding Sexual Desire and its Components

Decreased sexual desire is the most common sexual complaint in community samples [3]. HSDD is defined in the DSM IV TR as persistent or recurrent deficient or absent sexual fantasies/thoughts and/or desire for or receptivity to sexual activity. It is the clinician who determines if desire is "deficient," only after taking into account factors that affect sexual functioning such as age, physical conditions, and life context such as relationship duration.

Women and healthcare professionals are often at risk for underestimating the complexity of such a simple sounding concept as "desire," and this may interfere with effectively assessing the underlying causes for desire problems. Psychiatrist Stephen B. Levine suggests a biopsychosocial model such that desire is comprised of three discrete but interrelated components [28]. *Drive* is what he labels the first component. This is the biological component which is comprised of neuroendocrine mechanisms (hormones, neurotransmitters, and their interactions) and evidenced by spontaneous sexual interest. Unprompted sexual thoughts, erotic daydreams, sexual dreams or sensations such as genital tingling are signs of drive. The second component is a more *Cognitive* component, which reflects a person's expectations, beliefs, and values about sex. *Motivation* is what Levine labels the third component of desire, and it reflects the emotional or interpersonal factors that contribute to a woman's willingness to engage in sexual activity. Motivation is impacted by the quality of a relationship; psychological functioning; and concerns about health, children, and other psychosocial factors. In evaluating the specific complaint of low sexual desire, it is important for the clinician to ask about and differentiate between these three components of desire.

Table 19.1 DSM IV TR classifications of female sexual dysfunctions

Sexual desire disorders
Hypoactive sexual desire disorder – absence or deficiency of sexual fantasies and/or desire
Sexual aversion disorder – aversion to and avoidance of genital sexual contact with a partner
Sexual arousal disorders
Female sexual arousal disorder – inability to attain or maintain adequate lubrication-swelling response of sexual excitement
Orgasmic disorders
Female orgasmic disorder – delay in or absence of orgasm after a normal sexual excitement phase
Pain disorders
Dyspareunia – genital pain associated with sexual intercourse
Vaginismus – involuntary contraction of the perineal muscles preventing vaginal penetration

Organizing a Biopsychosocial Approach to Sexual Dysfunction

To conceptualize and organize the assessment of sexual dysfunctions, clinicians can employ an approach that combines the affected phase(s) of the sexual response cycle; the biological, psychological, and social causes; and the roles of predisposing, precipitating, and maintaining factors [29]. Although these dimensions are not absolutely discrete, the integration of these concepts can serve as a guide to formulating an

explanatory model for a patient's problem. Some general considerations may be helpful:

- Psychological problems can produce sexual dysfunction in the absence of physical pathology.
- Almost all organic problems evoke psychological reactions, such as performance anxiety, and "spectatoring" (obsessive self-observation during sex), which inevitably exacerbate the disorder.
- Sexual function and dysfunction can be a learned phenomenon, subject to behavioral conditioning and learned inhibition.

In some patients, the sexual problem may be clearly initiated by an organic or psychogenic cause, especially in younger, healthier individuals. Psychogenic problems usually begin abruptly are situational or episodic, and are temporally related to specific events or stressors. Organic problems are gradual, persistent, and progressive; progress from partial to absolute; and correlate with the progression of medical disease. While specific characteristics may help differentiate organic from psychogenic etiologies, most sexual problems are multifactorial, especially in older patients with complex medical illness. The best approach is (1) to create an explanatory model for the interaction of causal factors and their relative influence on the sexual response cycle and (2) identify and focus on those causes and factors that are amenable to intervention.

The Three Windows Approach to Understanding Biopsychosocial Factors

Graham and Bancroft describe another model called the "three windows approach" that can help contextualize factors related to a sexual problem [30]. The "windows" include a women's *current situation* (e.g., relationship difficulties), the *vulnerability of the individual* (e.g., negative attitudes, sexual abuse), and *health-related factors that alter sexual function* (e.g., mental and physical health). The three windows approach can assist in considering the biological, social, and psychological factors related to sexual complaints and organizing the clinician's diagnostic approach.

Optimal Sexual History Taking

Most patients (over 90%) believe that it is a physician's role to address sexual health concerns and are grateful when their doctor initiates the discussion [4]. In fact, patients prefer their practitioner to open the conversation about sexual health. Practitioners can enhance communication about sex by maintaining a nonjudgmental, respectful attitude; by using empathy and normalizing statements; and not by appearing rushed or uncomfortable. Women report feeling more at ease talking to their doctor about sexual concerns when the physician is kind and understanding, shows concern, is professional, and appears comfortable with the topic. Having seen the physician before and feeling the doctor knows them are also important to women when discussing sexual issues [14].

Screening and Detection of Sexual Problems

As discussed above, clinicians infrequently screen for sexual problems. If practitioners do take sexual histories, they most commonly focus on sexually transmitted disease risk assessment and prevention and/or contraception rather than sexual problems. Improving screening procedures does improve recognition [4].

The Screening Sexual History

The sexual history should take place in a private setting in which confidentiality is assured. The patient should be clothed to eliminate the

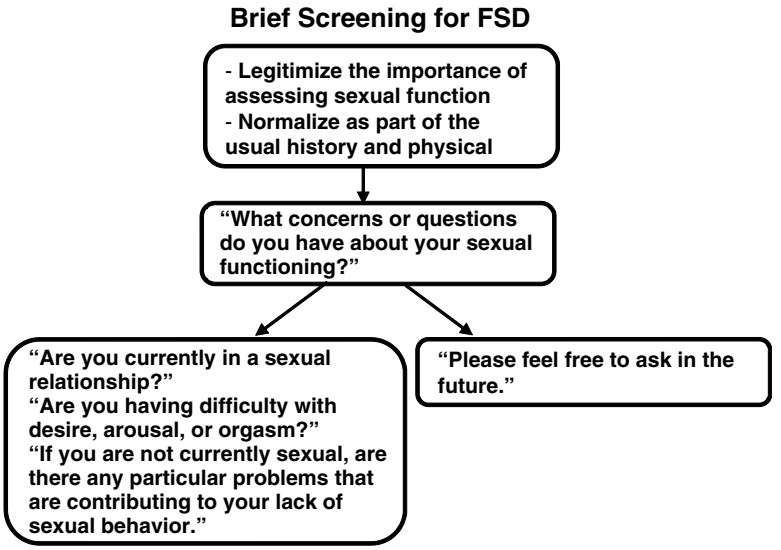

Fig. 19.2 Screening for FSD. Adapted from Kingsberg and Janata [31]

anxiety and sense of vulnerability that are commonly experienced when sitting in an examination gown.

Taking a sexual history in a regular new patient or follow up visit is appropriate and communicates the routine nature of the inquiry and the importance of the topic to overall health. The clinician may find it easier to start the sexual history by discussing less sensitive issues such as menstruation followed by the more sensitive topic of sexual function [20]. The screening sexual history can be inserted into the medical interview where the clinician finds it appropriate and when the questions arise naturally. Opportunities include the urogenital or gynecologic review of systems, or when asking about social habits such as smoking and alcohol intake, or when discussing relationship issues. The clinician can initiate the discussion by asking permission and universalizing and normalizing the process: "May I ask you some questions that I ask all my patients?" The interviewer can determine whether a patient is in a sexual relationship and ask about the nature of that relationship: "Are you having a meaningful relationship at this time?" "How is it?"; "Are you sexually involved in this relationship?" Then direct sexual problem screening questions might include: "Are you satisfied with your sexual function?" or "How has your illness affected your sexual function?"

The questions in Fig. 19.2 provide a modified approach for the initial assessment. Even time-constrained visits can include basic assessment of sexual function, which can be limited to a few specific questions. This brief screening algorithm recommends that the practitioner legitimize the importance of assessing sexual health and normalize the sexual history questions as a routine part of the interview [31]. The interviewer can then assess sexual concerns, followed by more specific questions about the patient's relationship(s) and sexual response. This approach also opens the door for future discussions.

Screening with a "Ubiquity Statement"

One study suggests that older women may be more likely to respond to a "ubiquity" screening question followed by a closed-ended question such as, "Many women who have undergone treatment for breast cancer have sexual problems, how about you?" than to a more general question [32]. The stem for ubiquity statements can

include medical, social, and life-cycle issues. The ubiquity statement and closed-ended question demonstrate that the clinician is not embarrassed and thinks that discussing sexual health is important, and simultaneously "normalizes" and "universalizes" sexual concerns for women in the patient's context. The next step is an open-ended follow-up to any acknowledgement of sexual concern such as, "Tell me [more] about it."

When a sexual problem is identified using either a direct question or ubiquity statement screening approach, the clinician should determine whether (a) the concern can be addressed during the current appointment; (b) a follow-up visit is needed to allow more time to address the concern adequately; or (c) the sexual problem is beyond physician's scope of training, and the patient should be referred to a specialist [33].

The Screening Sexual History in Patients with Cancer

In cancer patients, one can probe about sexual function when discussing treatments or procedures that may have side effects or adverse consequences affecting the woman's sexual response. The clinician can anticipate and inquire about the potential impact of an intervention on the biological, psychological, and social aspects of sexuality. Cancer has both direct and indirect effects on sexual function. For example, mastectomy results in the loss of erotic sensation from the breast. However, breast surgery may also affect sexual function indirectly via effects such as disfigurement and arm pain and swelling, and a resulting negative body image. Treatment for cancer can result in an abrupt change in sexuality, unanticipated in the women's life stage, such as premature menopause from the chemotherapy and resulting infertility and/or dyspareunia. Emotional concerns may include fear of recurrence, reluctance to initiate a new sexual relationship due to the need to disclose medical details or body changes, loneliness and sense of isolation, and mood changes resulting in depression [34]. Sensitivity to the array of possible sexual changes, psychological reactions, and their impact can be a starting point for sexual health conversations with women who have completed or are currently undergoing cancer treatment.

Developing the Narrative Thread

Once a problem is detected, the clinician can further refine it using standard communication techniques such as the narrative thread and facilitating comments. Contrary to what is recommended for the general medical interview, for sexual history gathering it may be useful to model the level of explicitness by starting with a close-ended question instead of open-ended questions. Examples include "Do you experience any difficulty with lubrication? Can you reach orgasm with your partner?" Then one can follow-up with an open-ended question such as, "Tell me more about that?" [35].

The Sexual Problem Interview

To clarify the nature of a sexual problem, the interviewer can lead a patient through a description of a typical (or last) sexual experience, using the sexual response cycle as a guide. It is important to remember that a dysfunction in one phase may actually be the result of a dysfunction in another phase (e.g., decreased lubrication may cause pain and lead to decreased sexual desire), so a problem should be characterized from its onset and as it evolves over time. Also women may not be able to identify the primary disorder, as sexual problems with desire, arousal, and orgasm tend to coexist. The clinician should also inquire about sexual pain related to and separate from arousal difficulties and decreased lubrication. It is also useful to ask specifically about overall sexual well-being and satisfaction, as sexual satisfaction in women may not be linked to orgasm.

The interviewer should determine whether the problem occurs in specific situations (situational) or is generalized, occurring in all situations including masturbation and with all partners.

The clinician should explore the nature of the nonsexual aspects of the relationship, such as affection and communication; the influence of cultural or religious mores; and sexual difficulties in the partner. Additional factors to be assessed include the biopsychosocial context, including circumstances at the onset; emotional reactions or states such as anger or unresolved resentment; the patient and partner's reaction; prior sexual functioning; and traumatic events, including emotional, physical, and sexual abuse. The interviewer can ask about specific social factors that may impact sexual expression such as self-esteem in the relationship; child-rearing responsibilities; privacy; professional demands; and conflicts regarding concerns about money, schedules, and relatives. The clinician can assess the impact of lifecycle events such as pregnancy, breastfeeding, infertility, and retirement. It is important for the clinician to assess the patient's motivation for treatment, especially if the problem is not a chief complaint. Table 19.2 summarizes some essential questions to include in a sexual problem history.

It is important not to make assumptions about the patient's sexuality or partner's gender or to assume that the relationship under discussion is the only one that the patient is having. A happily married woman may be having a heterosexual or homosexual affair, or have other sexual contacts. Therefore the interviewer may conclude with "safety net" questions such as "Do you have any other questions or concerns about sex? Are there other sexual relationships that I should know about?" [33]. The implication that the physician does not hold preconceived notions may give patients the courage to discuss a sexual concern at a subsequent visit.

Table 19.2 Essential questions to include in a sexual problem history

How does the patient describe the problem, its impact, and her distress?
How long has the problem been present?
How has the problem evolved over time?
Was the onset sudden or gradual?
Is the problem specific to a situation/partner or is it generalized?
Is the patient engaging in fantasy, self-stimulation, and/or masturbation?
Were there likely precipitating events (biologic or situational)?
Are there problems in the woman's sexual relationship(s)?
What are the relevant lifecycle issues?
Are there current life stressors that might be contributing to sexual problems?
Is there guilt, depression, or anger that is not being directly acknowledged?
Are there physical problems such as pain?
Are there problems in desire, arousal, or orgasm?
Is there a history of physical, emotional, or sexual abuse?
Does the partner have any sexual problems?

Adapted from Kingsberg and Althof [37]

Language

The interviewer should use language that is clear, explicit, and mutually understood. The physician should avoid language that is excessively technical or informal, and instead use language that the patient understands and is comfortable for the interviewer. The interviewer may also use interventions such as "Let me know if you are not sure what I am asking" or "Use your own words and I will tell you if I do not understand." The interviewer should avoid words that appear judgmental. "Adultery" may be replaced with objective, descriptive phrases such as "Do you have any other partners aside from your husband?" or "Do you have sex outside your marriage?" [36].

Establishing a rapport and putting patients at ease helps to make the environment conducive for discussion of sexual problems. If a physician is comfortable with sexual terminology, patients are more likely in turn to feel comfortable reporting their sexual concerns. Physicians may benefit by practicing the use of explicit sexual terminology in order to reduce embarrassment, hesitation in delivery, or other signs of discomfort [37].

Responding to Emotions

Skillful and caring attention to emotions promotes the therapeutic alliance, comforts and supports the patient, encourages the patient to bring

up difficult or embarrassing issues, and facilitates information gathering. Discussions about sexuality may bring up sensitive issues. The interviewer may uncover issues the patient has never discussed with anyone and which may require specific interventions, such as referral for sexual trauma. Referrals are more likely to be accepted by patients when the physician normalizes both the nature of the patient's problem and the process of referral to a specialist [37]. The practitioner can attend to a patient's discomfort by deferring sensitive issues to a subsequent visit.

Using Patient-Centered Dialog to Explore Sexual Problems

Clinicians should deepen their understanding of the meaning of any positive responses to closed-ended questions about sexual function. An effective approach is to use a directive open-ended question about the core symptoms and associated *bother* or *distress*. Closed-ended questions such as "Do you experience low sexual desire?" are essential in their function as the first step of a diagnostic interview, but closed-ended questions preclude the vital narrative about whether the patient is experiencing a distressing sexual problem worthy of the patient's and the doctor's attention and treatment. Directive open-ended questions, which "direct" the patient to a particular topic but leave the format of the patient's response "open" to the patient, are an essential component of patient-centered communication [38]. Patient-centered communication is distinguished from physician-centered communication by including consideration of the patient's psycho-social context, the emotional responses to problems, and the patient's therapeutic alliance with the clinician. An example of how to conduct an interview with a patient who has confirmed that they have a sexual problem such as decreased desire (in response to a close-ended question) would be to ask an open-ended follow-up question such as, "Tell me more about the decrease in your level of sexual desire or interest, and how it affects your life." It is likely that patients will respond with a brief but informative narrative about their problem. If their response does not clarify whether the decreased desire is generalized or situational, a specific question can follow. If the patient's response does not clarify the extent of personal distress, the clinician should ask a focused open-ended question about *bother* or *impact* on life.

Discussing Specific Sexual Practices

To better understand a sexual complaint, the practitioner may inquire about specific sexual practices and how they affect the individual and impact on the sexual relationship. Common issues needing clarification include [16]:

Masturbation: From a medical perspective, masturbation is a commonly performed and universal behavior. It is physically safe and can offer individuals practice and sexual self-esteem. It may be problematic if it is associated with excessive guilt or used compulsively to avoid intimacy.

Frequency: There is a wide range of sexual frequency, from monthly to several times daily. Partner disparities in desired frequency may result interpersonal conflict.

Fantasy: Sexual fantasies are physiologic as long as they are not associated with disturbing or intrusive thoughts, which may indicate deeper psychological issues.

Clitoral stimulation: Most women need direct stimulation manually or orally to reach orgasm. Approximately one third of women only reach orgasm through clitoral stimulation, whereas other women require vaginal penetration; and some respond to both forms of stimulation.

Sexual orientation: Sexual orientation reflects one's erotic attraction toward people of the same, opposite, or both genders. Not all women who have sex with other women give themselves a label of lesbian or bisexual, so it is best to ask about sexual activity rather than asking about a label. Since most lesbian or bisexual women have experienced discrimination (yes, including by HCPs), it is even more important to ask about the gender of sexual partners to let the patient

know that one is comfortable addressing same sex sexual practices.

Essentials of a Complete Sexual History

A thorough sexual history should include medical, reproductive, surgical, psychiatric, social, and as well as sexual information [39]. Relevant content would include past medical history, current health status, reproductive (sexually transmitted disease, contraception, pregnancy) history, menopausal status, endocrine (thyroid), and psychiatric illness (depression). A detailed medical history is recommended for all sexual dysfunctions, with particular attention to the common medical comorbidities. The predominant biological causes are neurologic, vascular, and hormonal systems impairment, structural/local tissue damage, and systemic medical illness. Current use of medicines, including prescription, over-the-counter (OTCs), supplements, and alternative medicines should also be identified. The clinician should specifically inquire about [40]:

- Medical illnesses with direct influence on the neurovascular system such as cardiovascular/cerebrovascular disease, high blood pressure, peripheral vascular disease, diabetes, and multiple sclerosis.
- Chronic medical illnesses, such as arthritis, chronic renal failure, congestive heart failure, and lower urinary tract symptoms.
- Trauma or injury.
- Lifestyle factors such as nutrition, body weight/changes, sleep.
- Smoking, alcohol, recreational drugs.
- The relationship of sexual symptoms to the institution, dosing, or cessation of a medication or substance.

Table 19.3 lists some commonly prescribed medications associated with sexual side effects.

A patient's history may not be sufficient to assess sexual function, and a physical examination and/or laboratory testing may help determine the physiologic factors involved in a sexual complaint [37, 40].

Table 19.3 Some common medications with sexual side effects [44]

Antidepressants
Antipsychotics
Benzodiazepines
Antiepileptics
Antihypertensives
Beta-blockers
Alpha-blockers
Diuretics
Cardiovascular agents
Lipid-lowering agents
Digoxin
Histamine H2-receptor blockers
Hormones
Oral contraceptives, estrogens, progestins, antiandrogens, GnRH agonists
Narcotics
Amphetamines
Steroids

Use of Questionnaires

Although a face-to-face interview is the ideal, particularly when addressing a potentially sensitive topic, sexuality questionnaires can greatly assist in the screening and diagnosis of sexual disorders [37]. Questionnaires may be used to:

- Identify or diagnose a sexual disorder.
- Assess the severity of the sexual problem.
- Measure improvement or satisfaction with treatment.
- Measure the impact of the disorder on quality of life.
- Study the impact of the disorder on the partner and his/her quality of life.

An entire chapter elsewhere in this textbook has been devoted to the questionnaires used in female sexual health assessment, and this topic is beyond the scope of this chapter.

Partner Issues

A woman's problem with sexual function may be due to or exacerbated by a partner's sexual problems. Decreased desire, erectile dysfunction, premature or delayed ejaculation in male

partners may produce frustration with sexual activity that leads to a reflexive decrease in sexual desire and responsiveness. Understanding the impact of a male partner's sexual problems requires some knowledge of those disorders. Sexual dysfunction in partners may equally affect lesbian relationships, and clinicians must guard against assuming that the patient has a heterosexual orientation regardless of the patient's marital or maternal status. Addressing sexual problems in the context of relationships should include assessment of the patient and partner's sexual practices, frequency of sexual activity, and discrepancies in desire for sex. It is also important to find out if and how the patient communicates about sexual concerns or practices with their partner [41]. Dissatisfaction with a partner or relationship may be an important cause of sexual problems and may be due to dissatisfaction with the partner as a sexual partner, or dissatisfaction about any other aspect of the relationship [42].

A common cause of stress and dissatisfaction among sexual partners is a discrepancy in the frequency of their desire for sex. Women may assess their own level of sexual desire by the extent that it matches their partner's desire for sexual activity. There is significant variation across and within cultures and across individuals independently of culture, in attitudes about accommodating the expectations of others for sexual activity. Clinicians should become aware of the variation in cultural and personal norms that affect these behaviors and seek to clarify what they are for each patient.

Cancer and its treatment may have a significant impact on partnered relationships. Women undergoing treatment for cancer may be concerned about their appearance and about changes in their level of attractiveness to their partner. While undergoing chemotherapy, a woman may become self-conscious about her hair and weight loss, and changes in body weight. Her partner may be concerned about her fragility, energy, or emotional state and avoid sex as a consequence. The partner may be concerned about being exposed to radiation or chemotherapy or fearful of being exposed to the cancer through sexual contact. Also the partner's fear of loss may lead to emotional vulnerability and avoidance of intimacy. The clinician should ask about and normalize these reactions. The interview may also provide an opportunity to the patient and partner education about the impact of cancer and its treatment on sexuality.

Empathic Delineation and Reframing Problems

Empathic sexual history taking and delineation of problems can be therapeutic. Sexual histories and discussions can reframe the problem and reorient the patient and her partner toward solutions. By conducting discussions about sexuality with female cancer patients, clinicians can begin the therapeutic process by normalizing the changes in sexual function and setting expectations for future sexual changes. Clinicians can demonstrate an optimistic attitude and offer help by providing explanations and welcoming questions [14].

The Interview as a Therapeutic Intervention

The sexual health interview can be used as an opportunity to begin the therapeutic process, even during the initial stages of information gathering. Through discussions about sexuality and the exploration of emotional concerns, women often begin to discover their own solutions and use the clinician as a sounding board for new behaviors. During the encounter, the clinician can facilitate the patient's focus on her own self-esteem and sensuality, assist the patient in clarifying the role of sexuality in her life, and redirect the patient toward ways of making sex a priority.

The P-LI-SS-IT Model

During the interview, patients can be coached in enhanced communication. The clinician may suggest the patient involve her partner. The P-LI-SS-IT

model is a widely recognized stepwise approach to the sexual counseling that provides behavioral and psychological techniques easily integrated in general practice [43]:

- (P) Permission: patients are given permission to discuss their problems and emotions and to explore new solutions.
- (LI) Limited Information: the practitioner may educate the patient about sexual physiology or suggest educational resources such as literature, videos, and erotica.
- (SS) Specific Suggestions might include more tailored approaches designed to improve sexual and emotional communication such as the sensate focus exercises, masturbation, Kegel exercises, technical advice regarding sexual positions, and the use of lubricants or dilators.
- (IT) Intensive Therapy may involve referral for individual therapy to deal with intrapsychic issues or couples therapy to improve communication or address conflict.

Conclusions

Sexual concerns, complaints, problems, and dysfunctions are common and emerging in increasing frequency in women with cancer, as more attention in being directed toward detection of these clinical issues. While clinicians and patients are reluctant to initiate and conduct conversations about sexuality, patients and their partners welcome these opportunities. They are grateful for the clinician's willingness to listen and highly appreciative of the clinician's investment in their well-being and quality of life. There are effective screening and assessment approaches that the clinician can learn and employ in the evaluation of sexual complaints and diagnosis of sexual dysfunctions. Sexual health conversations can build trust, strengthen the clinician–patient relationship, and increase patient satisfaction and engagement in care.

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Chapter 20
Communication About Sexuality and Cancer

Susan Carr

Keywords Communication • Barriers • Language • Families • Partners

Introduction

"Communication does not depend on syntax, or eloquence, or rhetoric or articulation, but on the emotional context in which the message is being heard" (Edwin H Friedman).

Sexuality is inherent in everyone in some form or another, and the way an individual will choose to express or not express their sexuality will probably differ at various stages in their life. Having a diagnosis of a potentially life threatening disease, no matter what the prognosis, has a major effect on any individual. Besides any physical impact on sex from either the cancer or its treatments, the emotional impact can be intense, and it is this emotional impact which can have a profound effect on the individual's sexuality and sexual behaviour and comfort.

The prevalence of sexual problems in men and women with cancer has long been recognised, with between 40 and 100% of all patients with cancer having problems of a sexual nature at some point in their lives [1]. Commonly reported problems in people with cancer are erectile dysfunction (ED) for men and loss of libido and vaginal dryness for women [2]. Despite this evidence, however, few cancer patients recall discussing sexual risks before or after treatment [3] and there continues to be a major gap in patient satisfaction in the way this is dealt with within the cancer journey.

The frequent surreptitious nature of these problems presents a challenge to clinicians. Good communication between the patient and their clinician remains the basis of the ability to diagnose and treat the sexual difficulty.

Background Prevalence of Non-Communication

Women with gynaecological cancers have as expected, a high prevalence of sexual problems. Evidence shows that sex is rarely discussed with these women. Despite recognising that sex was an important issue, only 25% of UK doctors in one recent study and 20% of nurses would discuss sex with their ovarian cancer patients. [4]. Despite recognising that discussions on sexuality were part of their job, 98% of cancer clinicians in Finland spoke to less than 50% of their patients about the topic [5]. Long-term survivors of vaginal and cervical cancer managed to maintain the same rate of sexual activity as the general population despite having higher sexual morbidity, however, their medical care in regard to sexual function following cancer diagnosis was lower than their overall cancer care [6]. Women with breast cancer, in particular, those undergoing chemotherapy, develop ongoing sexual problems early after therapy and their information

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needs are extensive [7]. In men with prostate cancer, sexual function is the second most important issue after survival. In this group, the patients' needs for appropriate and accurate information in making treatment choices remain largely unmet [8]. As many as one-third of people with head and neck cancers experience problems with sexuality and intimacy. The loss of libido found commonly after laryngeal and hypopharyngeal surgery [9] and a lack of relevant sexual information given to these patients and their carers has been noted [10]. An extensive review of the unmet supportive care needs of cancer patients highlighted spirituality, communication and sexuality as the domains which were the least frequently investigated [11].

Who Should Communicate?

It has been stated that patients wish their doctors and nurses to communicate with them about sex, yet commonly there are mismatched expectations between patients and health professionals, leading to overall unmet patient needs [12, 13]. It is important that whomever initiates discussions about sex with a patient should be properly trained and thus, knowledgeable about and comfortable with the topic. They must not only be cognizant of the physical side of sex, but should acknowledge and empathise with the emotional aspects.

Many professionals feel comfortable with an organic disease that they can understand and treat. It makes them feel in control. Loss of libido, however, has no physiological markers and has a large psychogenic element. Just acknowledging and listening to the problem, however, and referring patients for psychosexual therapy if appropriate can let the patient know that their distress has been recognised. Oncology nurses are often the first-line healthcare professionals to recognise and address sexual issues with the patient [14], and even more so with sexual minority groups [15]. This, however, should not absolve the physician from at least approaching the issue and acknowledging its importance. Until human sexuality becomes part of core undergraduate teaching, this situation is likely to continue.

Barriers to Communication

The ability to communicate in a clinical setting depends on many variables ranging from the attitudes and emotional state of the individuals trying to communicate, to the physical environment in which this communication is taking place.

Attitudes of Staff

Often cited as a major problem is the attitude of health professionals to discussions about cancer and sex. Sex is often "medicalised" and health professionals concentrate on discussion of any physiological disruption to sexual function and reproduction [12, 13]. It is always easier to talk about organic disease which is potentially amenable to creams, tablets or surgery, than emotional problems which will only respond to psychodynamic treatment. It is recognised, however, that clinicians in busy oncology clinics have little time in which to discuss sexual morbidity and it seems only reasonable that cancer centres recognise this and adjust their clinic programmes appropriately. Centres of cancer excellence should show leadership in this area.

It is easy and dangerous to make assumptions about patients, especially about something as private, personal and variable as sex. Commonly young healthcare workers assume anyone much older than themselves is unlikely to be sexually interested or active, but increasing evidence demonstrates that sexual interest exists well into the 70s and beyond [6]. General practitioners do not address sex proactively with older people [16], and despite evidence that older people are sexually active, and do have problems, these problems are not discussed by their physician [6].

As well as age, assumptions are made about sexuality depending on the patients' culture and partnership status, as well as disease status [12, 13]. It is worthwhile asking direct questions such as, "Do you have a sexual partner?" and "Are they male or female?" and "Do you have any

problem with sex?" before any discussions take place. When asked these questions directly some patients will respond. Even those who decline to answer will gain from these questions that that particular clinic is a place where one can discuss sexual issues, and they may take that opportunity later in their treatment journey.

Many staff have strong religious beliefs which make it difficult for them to enter into sexual discussions with patients, especially those whose value systems differ dramatically from their own. If communication about sex cannot be done in a dispassionate and non-judgemental manner, it could potentially cause more harm than good, and is best done by professionals who are well trained, and comfortable with the topic. Nonetheless, all staff responsible for the care of the cancer patient should at least have a basic training in this area so that referral to more specialised practitioners can occur.

Communicating with Patients

Patients want help with their sexual problems. They are often overwhelmed in the initial stages of cancer diagnosis with a mixture of fear of the unknown and concerns about survival. They may be more concerned about the impact of diagnosis on their family and friends and are unwilling to address anxieties about sex at that point even if they are thinking about it. Patients have said that they are too embarrassed to mention the topic of sex with their health care team, as they feel it may be regarded as "trivial" in the context of everything else that is happening. People find it difficult to talk about sexual concerns anyway, however some patients feel that the cancer diagnosis empowered them to talk about things that they might have felt were otherwise taboo.

A good way of initiating discussion about sex is to administer a simple patient questionnaire with relevant questions. This can trigger the patient to participate in discussion of sexual matters [17]. If the questionnaire is given to all cancer patients, then staff do not have to make subjective judgements, or jump to wrong conclusions about anyone's sexual behaviour. This gets over daily barriers such as age, cultural and maybe ethnic differences between the patient and clinician.

Gender differences in sexual information needs for cancer patients is another variable factor. Men traditionally find it harder to express their feelings. A study in Sweden described this barrier as comprising five separate domains, including barriers to talking, seeking healthcare and the masculinity barrier itself [18]. Single men with non-seminomatous testicular cancer are more likely to experience sexual problems than married men with the same diagnosis [19]. Sexual dysfunction in men with prostate cancer may not only affect performance, but also sexual intimacy, everyday interactions with women, sexual fantasies and self-perceptions of masculinity [20]. These issues are hard to elicit in consultation, but can be sensitively addressed. After haemopoietic stem cell transplantation, however, women appear to be more troubled by sexual dysfunction than men [21].

Sexual and relationship problems which are longstanding may be thrown into focus by the cancer diagnosis. There may be severe underlying problems such as a background of emotional deprivation. Both childhood and adult emotional abuse and adult sexual abuse are all associated with higher rates of sexual dysfunction [22]. An in-depth examination of the emotional reactions to a sexual problem may bring these issues to the fore. Depending on the patients' emotional state, they may or may not choose to disclose the problem, but will be more likely to if an appropriate prompt is given or a direct question is asked.

Communication with Partners

The impact on sexual partners of cancer victims is enormous with 76% of partners of non-reproductive site cancers and 84% of partners of a reproductive site cancer reporting an impact on their sexual relationship [23]. People go through a gamut of complex and conflicting emotions when caring for their sexual partner who has a

cancer diagnosis. Issues of self-blame, grief, sadness and anger arise and are added to fear, and sadly sometimes leads to rejection of the partner. There is a change of role from lover to carer, and all this is added to the physical and emotional fragility of the cancer sufferer themselves. In these circumstances, it can be difficult to communicate. It has been reported that less than 20% of the partners of cancer patients were able to re-negotiate sexuality within their relationship [23]. Difficulties were found in communicating sexually, particularly if there had been communication problems before the cancer. A major problem was the unwillingness and inability to consider alternatives to penetrative sex [24]. Even simple strategies like suggesting the use of appropriate literature or visual materials can open a patient's/partner's minds to different, but equally satisfying means of sexual pleasure. Fertility is of course closely linked to the penile penetrative experience for many women, and is a major cause for distress [25], so if relevant the sexual problem should be addressed in this context.

Communication with Families

The families of people of cancer always become involved in some way with the patients' cancer journey. They may experience similar feelings to the patient, coupled with a feeling of helplessness in the face of an overwhelming diagnosis. In a close family, communication may become a problem if they wish to become over involved. In issues of sexuality, it is particularly important to allow the cancer sufferer complete privacy in talking about sex, unless they specifically wish otherwise. Well wishing children, family and friends often become unwitting participants in discussions about the patients' bodily functions, however in order to maintain the patients' dignity, sexual discussions should be confined to private discussion. Thus, the current recommendation that support persons should always attend consultations with the patient needs to be re-evaluated in this context.

The issue of sexuality in cancer with young people can be problematic in relation to communication and the family. There is a tendency of families of young people with cancer to become over concerned and protective. Many cultures are uncomfortable about communicating about sex with young people, and cancer makes it more complex. A young person with cancer has the myriad of sexual, body image and self-esteem issues of adolescence to contend with concomitantly [26]. Being able to speak to the young person alone about these issues, if the patient wishes, can be very helpful.

At the other end of the spectrum, many older people are newly sexually active. Several studies have reported people over 70 being sexually active. In Sweden, the proportion of women over 70 having sex has increased [27] and 24% of over 70s were having sex more than twice a month [28]. In a German sample of 8,000 men, age 30–80, 71.3% of the older sample reported regular sexual activity [29].

Language Barriers

Although the majority of patients will be culturally and linguistically attuned to the healthcare setting in which they find themselves, there is always a substantial minority of patients who have different needs in relation to communication about sexuality and cancer.

If someone is not accustomed to talking about sex, and cannot speak the clinic language fluently, it will be no easier for them to do so in a cancer setting, unless there are culturally sensitive advocates to facilitate this. Many cancer sufferers of different ethnic backgrounds will bring family members to interpret at their general consultations, yet this can be a strong inhibitor to discuss sex especially if it is a child or some other non-partner translating for them. If, however, a good translator is present in whom the patient has confidence in both their comprehension and discretion, sexual discussions and even sexual therapy can be very helpful to the patient. The use of interpreters is widespread in most

medical facilities, however the interpreter may be skilled in translating, but may be completely unaware of sexual language, and be unable to interpret nuances in meaning.

Individuals with physical or learning disability should equally have their communication needs carefully catered for. Many of the local self-help organisations offer superb help in the form of communication tools for their users, and should be consulted if any problems. In many areas, social workers are primed to link in with these organisations, and will help facilitate communication as part of their work. Especially in regard to minority groups with cancer, a multidisciplinary approach is more likely to meet their access and information needs.

Communication with LGBT Individuals

Gay men and lesbian and bisexual women and transsexuals are also at risk of cancer and may find sexual discussion difficult. More than 50% of lesbian women do not disclose their sexual orientation to their general practitioner as they are worried about a negative reaction, and are thus unable to enter meaningful dialogue about sexual matters in the clinical setting. Although they may adapt better sexually to the sequelae of cancer than heterosexuals, they still find problems obtaining relevant information on sex and medical support [30]. Even when lesbian-specific information is provided it may not be relevant to all [31]. Men who have sex with men may not disclose their sexual orientation, particularly if they are married and do not wish their wife to know, and therefore are reluctant to discuss sexual issues. In the UK, a study of general practitioners showed that non-hetero-sexual orientation formed a barrier to addressing sexual health issues for almost half of the sample [32]. Homophobic attitudes were also found in a minority of practitioners. Many clinicians admit to ignorance about minority sexuality, and although wanting to help are inhibited in the discussion by their own lack of knowledge.

Transsexuals are mainly concerned with how they are received in the clinical setting and how they are addressed. A male-to-female transperson is known as a transwoman, and should be referred to as "she" and a female-to-male as a transman, who should be addressed as "he". If all patients are treated with respect, and listened to about sexual matters, then no problems should arise. The onus, to open up the opportunity for disclosure of sexual orientation, however, is on the providers, not the patient [33].

Ethnicity

Sexuality is one of the most fascinating aspects of the human lifespan, and is the subject of endless diverse debates around the globe. One's attitude to sexuality is heavily dependent on background culture, religion, culture, family and peers, local laws, social circumstance, age and opportunity.

This means that, as far as possible, these diverse factors also need to be taken into account when dealing with sexuality and cancer. Only 21% of a widespread Asian population with sexual problems sought medical help, partly due to economic and partly for socio-cultural reasons [34]. Aboriginal and Torres Straight Islanders in Australia will not talk about sex, even with a local support worker, and women of many religious backgrounds find sex a taboo area. Conversely in some cultures the woman's sexuality is the subject of open discussion within the family, especially around reproduction, however, it is not known how cancer alters this discourse.

Many women round the globe have experienced Female Genital Mutilation, and although often able to achieve orgasm, they also experience sexual problems [35]. There are clear guidelines on clinical and obstetric care for such women, however sexual issues are only vaguely mentioned (RCOG Guidelines 2010). These women rarely present at a sexual medicine clinic, despite their need for help. It may be that in the cancer setting, within a trusted team it is possible to address some of these concerns. Males from ethnically diverse backgrounds may be unable to

express their sexual difficulties because of the tremendous shame in "losing their manhood", and suffer such devastating problems in silence. All minority groups may need more specific sexuality information delivered in a way which is suitable for that particular patient, using gender-specific culturally aware staff.

In developing countries, cancer patients have many unmet communication needs [36], and it may be that, as in the developed world, minor changes in the organisation of clinics and clearer communication strategies will be of enormous help.

Disability

Individuals with physical, sensory or learning disabilities find it hard to be recognised as sexual individuals, and in many "enlightened" societies have had to fight for their full sexual rights. Communication for these individuals may be difficult in relation to everyday matters. If, however their communication needs are sensitively met overall, then discussion on sexuality in relation to their cancer should be able to take place. Many of the self-help and patient advocate organisations will provide expert assistance, and can be consulted. In this, as any situation, the patient may wish their advocate to remain with them whilst talking about sex, and the patients' wishes should be respected. Physical access is important, however greater amounts of time is usually needed in clinic to deal with the consultation effectively and sensitively.

Barriers Related to Location

The clinical physical environment may form an enormous barrier to communication. Much hospital design is so focused on clinical utility that it forgets the autonomy and dignity of a patient. If one is fit and well, one generally would not choose to share sleeping quarters and toilet facilities with complete strangers, sometimes of mixed gender. Nor would someone choose to be wheeled along a public corridor in nightclothes or operating room garb. Privacy of communication is often sadly a victim of bad planning also. A curtain round a bed in a ward is no barrier to sound, and a room with other people present can be a powerful inhibitor to talking about sex. A large window may enhance the light in a room, but not if it looks directly onto another's bed, thus negating the feelings of privacy. Many cancer consultations are carried out in a teaching environment. The patient may be quite agreeable to this in general, but may find it harder to discuss sexual issues with students present, especially if they are decades younger than themselves, or even the primary clinician. Even a room with reasonable sound proofing may not be the right setting if the clinician is clearly anxious to get on with seeing his next patient, and does not have the time to talk. Time is very important to patients. Patients describe clinician time-related attitudes as crucial to their experience of the consultation [37]. Sometimes it is not the actual time spent, but the feeling that the patient will be given as much time as they need, without pressure to hurry, which can be equally beneficial.

Space, privacy and time are all essential for good communication, but sadly, what seem like mere basics are seemingly unattainable luxuries in some clinical settings.

There has been some discussion about the patient's bed itself as being an inhibitor of sexuality, especially in the palliative phase. It has been suggested that the replacement of the patient's own bed at home by a hospital bed, to ease nursing care, is an area which is important to the patient, but which nurses find hard to approach in discussion [38]. When patients are in a palliative care setting in a hospital, the partner often has to utilise a chair or temporary bedding. Some enlightened units, however, have introduced double beds in the hospital, in order to permit the patient to remain comforted by their partner at the end of their life. Sexuality in the palliative phase is one of the most difficult areas of discussion in cancer care, however, it may be important to the patient and should be addressed [39].

Clinician Education

It used to be thought that the ability to communicate well was an inborn attribute, and it is still the case that some individuals will always have the charisma, empathy and knowledge to communicate appropriately even in difficult circumstances. It is now well recognised, however, that communication skills, particularly in a professional setting, can be effectively taught and enhance patient care. Although 90% of clinicians recognised that communication about sex was important to their patient, 94% felt they were poorly trained and were unlikely to have discussions around sexual difficulties with their patients [40]. The issue of lack of training is frequently highlighted, especially in dispelling myths about sexuality and cancer. Nurses who are traditionally more likely to address sexual issues with cancer patients also need education [41]. Cancer physicians' attitudes and beliefs towards psychosocial issues improved after they had completed communication skills training [42]. This training used behavioural, affective and cognitive components and produced potentially more effective interviewing styles. A Cochrane review of communication skills training for healthcare professionals, however, concluded that training programmes produced changes in some areas of communication skills but not others; however, training appeared to encourage the patients to express more emotion in their face-to-face consultations.

As well as developing good communication skills, the clinician should be well educated in sexual problems, and be confident enough to permit discussion without personal feelings of embarrassment or ignorance. It is sufficient to encourage and allow disclosure, and then refer to a specialist sexual problems clinic, or make an appointment at a more suitable time and place. Clinicians do not need to be expert in this field, indeed, an ability to handle the initial consultation is all that is required.

Although it has been widely documented that nurses are more likely to communicate with patients over sexual issues, both undergraduate and graduate sexual medicine education is poorly co-ordinated even in highly medically developed countries. Good standardised teaching programmes are necessary to bridge the gap between developments in the field, patients' needs and clinician skills [43].

Patient Information

Patients often express needs for information about sex in relation to their cancer. They wish this written information early in their cancer management, even if they do not want to use it until later. They want to know if their sexual function will be affected by pain or discomfort, or if it may impact negatively on their cancer and its treatment. They may suffer loss of libido, in what was a previously happy sexual relationship, and wish to talk about it. Much good information is available as written leaflets, books, TV, radio and websites, and these can be utilised by the cancer centres together with the patient. As patients are reluctant for many reasons to initiate discussions on sex, various communication tools have been used to facilitate this disclosure and discussion. Use of the Screening Inventory of Psychosocial problems (SIPP) in patients receiving radiotherapy was thought to facilitate discussion on social and sexual issues and prevent under diagnosis of psychosocial problems [44]. Another study used a standard Quality of Life questionnaire, but concluded that individual assessment alongside standard questionnaires was needed to facilitate discussion on individual non-medical matters such as sexuality [45]. A combined brief psychosexual intervention was used with mastectomy patients and their partners, the patients reported improvements in depression and anxiety as well as ability to communicate their desire [46] (Table 20.1).

Table 20.1 Useful self-help websites

http://www.macmillan.org.uk
http://www.cancer.org
http://www.cancersupportivecare.com
http://www.oncolink.com
http://www.cancer.gov (NCI)
http://www.sexualhealthaustralia.com
http://www.mautnerproject.org

Information to Public

Remarkably, in this era of modern mass communication, where sex is used as a commodity in almost every area of profit making, both legal and illegal, there is still a significant divide between patient information needs on the subject and the provision of this information in healthcare settings. The gap is often filled by superb patient help organisations such as Cancer Backup in UK, the Cancer Council in Australia and the American Cancer Society in the USA, who supply information geared to the consumer. These organisations have provided lifelines to patients, making accurate and client-centred information accessible around the clock. In some countries these organisations are government backed, and in others, they have charitable status. Everyone with cancer has as much right to accurate information about help with their sexual issues, as with any other aspect of their disease, and these organisations are an important part of the multidisciplinary approach to communication about the disease.

Research

It is interesting that death as a topic is more easily dealt with than discussions on sexuality, which is a complex and powerful life force. Over the last few years, fortunately, there has been a marked increase in studies relating to different aspects of cancer and sexuality. These studies have recognised the importance of the topic to the patient, and have raised the issue within the clinical community [47]. Some critical views on current research have highlighted more areas for investigation. Knowing the prevalence of a condition is essential to helping to understand and deal with it, yet it has been proposed that the varying discrepant reports on prevalence of female sexual difficulties may be due to study design (Hayes 2008). Sexual vulnerabilities in both men and women have been noted but even in relation to the common cancers, research is limited. In men with prostate cancer, research on the sexual outcomes of the men and their partners in a cultural context is scarce (Wittman 2009). Women suffer increasing sexual vulnerability with increasing episodes of HPV. Despite this, in women with HPV-related warts and intraepithelial HPV-related lesions research on the sexual impact is still scarce (Graziottin 2009).

Conclusions

Most people with cancer still feel their sexual health needs are not being met adequately. Few cancer patients recall discussing sexual risk before choosing treatment options, or being offered treatment for sexual problems after cancer therapy [3]. There is lack of communication by professionals and lack of appropriate accessible information on cancer and sexual issues, or where it exists, it is not being appropriately distributed. Communication about sex should also recognise that sex is pleasurable and can enhance the lives of willing participants and bring much joy and comfort to cancer sufferers. There has been an upsurge in awareness and interest in the topic of sexuality over the last few years, however, a continuing drive is needed by clinicians and patients in order to push these needs higher up the cancer management agenda.

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Chapter 21
Validated Questionnaires in Female Sexual Function Assessment

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Keywords Questionnaires • Psychometrics • Validation • Validity • FSFI • SVQ • DISF • DSFI • BSFI-W • GRISS • CSFQ • MSFQ • GMSEX • ISS • PSSI • FSDS • SSS-W

Introduction

Cancers and their treatments are associated with significant sexual dysfunction in both genders [1], but female cancer patients are significantly less likely than males to seek or receive treatment for their sexual concerns [2]. One study found that even though the majority of health care providers on oncology teams thought their patients would experience a sexual problem arising from treatment or advancement of the disease, only a quarter of oncologists and a fifth of nurses discussed these concerns with their patients. The health care professionals cited lack of knowledge about diagnosis and treatment as a large component of the barrier in addressing their patient's sexual dysfunction [3]. Crucial to closing this gap in the diagnosis and treatment of female sexual dysfunction is the development and validation of psychometrically sound instruments for diagnosing dysfunctions and monitoring sexual symptoms.

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To this end, there is currently available a number of well-established instruments for assessing sexual function and satisfaction in women. In this chapter, we review the relative strengths and weaknesses of nine measures of sexual function and five measures of sexual satisfaction/distress for which the psychometric properties are well established. Where available, we provide information on the use of these measures in female cancer patients. We review measures of sexual function and satisfaction separately given recent findings suggesting sexual satisfaction in women is a particularly complex, multifaceted construct that is separate from sexual functioning [4–6].

Using Psychometrics to Evaluate an Instrument

When choosing an appropriate measure, one must consider what is known about that measure's psychometric properties, or the characteristics of the measure that contribute to its validity and reliability. A reliable measure has very little to no measurement error; any variation in measurements reflects true variation in the population. Reliability can be compared across instruments with reliability coefficients that range from 0 (measurements are entirely due to error) to 1 (measurements are entirely free from error). There are two kinds of reliability that are of particular interest for self-report FSD instruments. *Internal consistency* refers to the degree to which items are endorsed

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together, and reflects how well an instrument (or a factor of an instrument) captures one specific construct. *Test–retest reliability* refers to the degree to which the same input (the same testing conditions in the same population) will consistently replicate the same output (the same measurement). *Test–retest reliability* is generally measured using repeated administrations of an instrument in the same sample over the course of 2–4 week intervals. In the case of clinician-rated instruments, one must also consider *inter-rater reliability* – the degree to which there is agreement between clinicians on outcome measures.

Validity relates to an instrument's accuracy in measuring what it is thought to measure. The most commonly used index of validity is *face validity*, or the extent to which the items of an instrument appear to address the construct of interest. Related is *convergent validity*, which refers to how closely the results of an instrument are to other already established measure of the same (or very similar) construct. *Divergent validity*, on the other hand, refers to the dissociation of the instrument's scores from measures of related but theoretically different constructs. For example, a measure of self-reported lubrication should be convergent with measures of genital throbbing or heat but divergent with measures of marital satisfaction. Finally, *discriminant validity* pertains to how well an instrument can identify a particular population. In the case of FSD instruments, discriminant validity generally refers to whether or not a measure can differentiate between clinical and nonclinical populations. Establishing *discriminant validity* is often an ongoing process, as the generalizability of the instrument's properties requires reevaluation for each new population of interest.

In addition to evaluating the overall reliability and validity of an assessment questionnaire, clinicians and researchers selecting an instrument for assessing sexual function and satisfaction in cancer populations might also consider whether the measure has been used in the cancer population of interest, and whether it has been validated in a cancer population, or only in a noncancer population. Below we review publicly available measures of sexual function and satisfaction that have demonstrated acceptable reliability and validity.

Female Sexual Function Assessment Instruments (Tables 21.1–21.4)

Sexual Activity Questionnaire (SAQ)

The Sexual Activity Questionnaire (SAQ) [7] is a 14-item self-report inventory which assesses the level of sexual activity, reasons for current sexual inactivity, and sexual functioning. It was designed specifically for use in clinical trials in cancer populations. One element of the SAQ which is unique amongst the measures reviewed in this chapter is a section assessing reasons for the lack of sexual activity, which offers a list of reasons pertaining to the patient ("too tired") as well as his/her partner ("my partner is not interested in sex"). The sexual functioning section has three subscales supported by factor analyses: pleasure (including items assessing sexual desire and satisfaction), discomfort (including items assessing problems of sexual arousal and pain), and habit (assessing changes in sexual frequency). Notably missing from the sexual functioning section are items assessing orgasm or aspects of arousal other than vaginal lubrication. Validation of the SAQ was conducted in a sample of 528 women (447 with high risk for breast cancer and 81 with low risk; age range 35–65 years) recruited for a clinical trial of tamoxifen [7]. The validation study established 2-week test–retest reliability and internal consistency in the good to excellent range, and discriminant validity in differentiating pre- and postmenopausal women on the sexual activity subscale and discomfort factor of the sexual functioning subscales. Norms and standardized percentile scores are available for a community sample of 1,165 women (age range 20–69 years) [8]. Face validity was established in a group of 638 women with gynecological disorders; compliance and response rates ranged from 77 to 82%, with the lowest compliance in the oldest group of women. The SAQ takes approximately 5–10 min to administer, and is available in English and Norwegian [8]. Norms have also been established in lesbian women with recent cancer diagnoses [9].

Table 21.1 Measurement characteristics for indices of female sexual functioning

Inventory name	# Items	Standardization sample	Administration time/modality	Domains measured
SAQ	14	447 with high risk for breast cancer and 81 with low risk (35–65 years)	10 min Self-report Women only	Sexual activity/reasons for inactivity, sexual pleasure, sexual discomfort
SVQ	27	257 women with cervical cancer (23–80 years)	Unknown administration time Self-report Women only	Sexual functioning, partner's sexual problems, body image, vaginal changes
BISF-W	22	225 healthy women (20–55 years); 104 surgically menopausal women with impaired sexual function (21–55 years)	15–20 min Self-report Women only	Thoughts/desire, arousal, frequency of sexual activity, receptivity, pleasure/orgasm, relationship satisfaction, problems affecting sexuality
CSFQ	35	122 male and female medical students (22–35 years) and 33 psychiatry residents (25–43 years)	15–20 min Interview Male and female versions	Sexual pleasure, sexual desire/frequency, sexual desire/interest, arousal, orgasm
DISF/DISF-SR	25	399 community members (19–69 years)	10–15 min Interview and self-report Male and female versions	Sexual cognition and fantasy, arousal, sexual behavior and experience, orgasm, sexual drive, and relationship
FSFI	19	131 normal women (21–68 years); 128 women with FSAD (21–69 years)	10–15 min Self-report Female only	Desire, arousal, lubrication, orgasm, satisfaction, pain
GRISS	28	88 sex therapy clients (males and females)	15–20 min Self-report Male and female versions	Anorgasmia, vaginismus, impotence, premature ejaculation, avoidance, dissatisfaction, nonsensuality, infrequency, noncommunication
DSFI	254	230 male and female college students (mean age: 32 years)	>30 min Self-report Male and female versions	Information, experiences, drive, attitudes, psychological symptoms, affect balance, gender role definition, fantasy, body image, sexual satisfaction
MFSQ	19	364 women (18–26 years)	10–15 min Self-report Female only	Sexual interest, satisfaction with sexual activity frequency, vaginal lubrication, sex partners, orgasm

Table 21.2 Measurement characteristics for indices of female sexual satisfaction

Inventory name	# Items	Standardization sample	Administration time/modality	Domains measured
GMSEX	5	99 undergraduates in long-term romantic relationships	Unknown administration time Self-report Male and female	Sexual satisfaction
ISS	25	100 men and women seeking treatment for relationship problems (mean age: 32.7 years)	5–7 min Self-report Male and female	Sexual satisfaction
PSSI	24	275 undergraduate women (17–24 years)	Unknown administration time Self-report Female only	General sexual satisfaction, satisfaction with partner
FSDS	12	60 nurses without sexual problems; 18 female patients with FSD (mean age: 48 years)	Unknown administration time Self-report Female only	Frequency, intensity
SSS-W	30	181 women in romantic relationships (18–56 years)	5–10 min Self-report Female only	Contentment, communication, compatibility, relational concern, personal concern

The strengths of the SAQ include items that assess the individual and partner's sexual dysfunction or disinterest, reasons for sexual inactivity, and changes in habitual level of sexual frequency. Weaknesses include a lack of items assessing orgasm functioning, a definition of arousal limited to lubrication, and an unknown level of construct validity.

Use in Cancer Populations

Of all of the assessment instruments reviewed here, the SAQ is the most widely used in cancer research, with dozens of studies published utilizing the measure in various gynecological cancer populations. Generally, the SAQ identifies about half of all cancer populations – both patients and survivors – as sexually inactive. Most studies using the SAQ indicate greater sexual dysfunction (higher discomfort and lower pleasure scores) in cancer populations than for controls.

In the breast cancer literature, there are norms available for patients receiving tamoxifen, chemotherapy, a combination, or none of these treatments [10], as well as survivors of a wide age range (25–51 years), broken into groups [11]. The SAQ has been shown to be sensitive to changes in sexual activity and pleasure following high dose and conventional chemotherapy for breast cancer, both in the short term (6 months) and longer term (5 years) [12]. Norms have also been established for women at high risk for breast cancer who received prophylactic mastectomies, both pre- and postmenopausal and with and without reconstruction [13], and the sexual pleasure dimension has been shown to differentiate between women who received breast reconstruction from those who did not [14]. While some studies have suggested that the SAQ is sensitive to changes in sexual pleasure following prophylactic mastectomies [15], others have suggested no difference in SAQ scores between women who did and did not accept surgery [16]. The SAQ did not detect any treatment-related changes in sexual functioning in a trial of venlafaxine and clonidine for treatment of hot flashes in breast cancer patients [17].

Among women with ovarian cancer, norms have been published for populations who are and are not receiving treatment [18] as well as survivors of ovarian germ cell tumors [19].

Table 21.3 Reliability coefficients and validity correlations for sexual functioning indices

Inventory	Test-retest reliability	Internal consistency reliability	Concurrent validity	Divergent validity	Discriminant validity	Clinical cut-offs
SAQ	0.65–1.00	0.97–0.99	N/A	N/A	Cancer from noncancer populations; patients who are and are not receiving treatments for cancer	N/A
SVQ	N/A	0.46–1.00	$R = 0.52$–1.00 to expert observer scores	N/A	Cancer patients from noncancer patients	N/A
BISF-W	0.68–0.78	0.39–0.83 −0.08–0.72	$R = 0.46$–0.69	N/A	N/A	N/A
CSFQ	0.45–1.00	0.64–0.80	$R = 0.42$–0.76 CSFQ subscale to comparable subscales of DISF	N/A	Depressed from nondepressed patients	N/A
DISF	0.80–0.90	0.74–0.80	N/A	N/A	Sexually functional from dysfunctional	N/A
FSFI	0.79–0.88	0.89–0.97	N/A	$R = 0.53/0.22$ to marital adjustment for control and FSAD groups, respectively	FSAD, FOD, and HSDD from controls	26.55
GRISS	0.47–0.82	0.61–0.83	$R = 0.56$; female total score to therapists ratings of problem severity	N/A	Sexual treatment seeking from medical treatment seeking	N/A
DSFI	0.58–0.96	0.60–0.97	N/A	N/A	N/A	N/A
MFSQ	0.69–0.95	0.74	N/A	N/A	Premenopausal from postmenopausal and oral contraceptive users from nonusers	N/A

Table 21.4 Reliability coefficients and validity correlations for sexual satisfaction indices

Inventory	Test-retest reliability	Internal consistency reliability	Concurrent validity	Divergent validity	Discriminant validity	Clinical cut-offs
GMSEX	0.78–0.84	0.90–0.96	$R = 0.63$ GMSEX to ISS	Relationship of GMSEX (sexual satisfaction) to GMREL (relational satisfaction): $R = .50$	N/A	N/A
ISS	0.93	0.92	N/A	More effective than Index of Marital Satisfaction at differentiating between women with and without FSD ($R = .76$ vs. $R = .52$, respectively)	Individuals with sexual problems from controls	13
PSSI	N/A	0.92	$R = 0.68/0.37$ PSSI to ISS/orgasm consistency	N/A	N/A	N/A
FSDS	0.80–0.92	0.86–0.90	N/A	$R = 0.59/0.58$ FSDS to measure of depression/negative affect	FSD from controls	15
SSS-W	0.58–0.79	0.74–0.9	$R = 0.22$–0.70; SSS-W subscales to satisfaction scale of the FSFI	Relationship between subscales and Marital Adjustment Test range from $R = .19$ (personal concern) to $R = .57$ (communication)	FSD from controls	N/A

The sexual activity and pleasure domains have been shown to differentiate between community participants and survivors of ovarian germ cell tumors [20] as well as epithelial cancers [21]. Like in the breast cancer literature, it has been shown that scores on the sexual pleasure and discomfort domains of the SAQ can differentiate between women who underwent prophylactic salpingo-oophorectomy from those simply receiving screenings for ovarian cancer [22], although these effects may drop out after 6 months postsurgery [23]. The sexual activity domain does not appear to differentiate between women who have undergone oophorectomy and those who have not [22]. Similarly, SAQ activity domain scores are not significantly different between women who did and did not go on hormone replacement therapy (HRT) following oophorectomy [24].

The SAQ norms for long-term cervical cancer survivors have been published [25, 26]. Some reports demonstrate that the sexual pleasure and discomfort domains can differentiate cervical cancer survivors from matched controls [26] while others suggest only the discomfort domain differs between the groups [25]. There appears to be no difference between 1-year postsurgery SAQ scores of women who received subtotal or total hysterectomies [27]. Also, there is no difference in 2-year postsurgery SAQ scores between women who received either hysterectomy or uterine artery embolization [28].

Sexual Function – Vaginal Changes Questionnaire (SVQ)

The Sexual Function – Vaginal Changes Questionnaire (SVQ) [29] is a self-report inventory with 20 core items that measure current sexual functioning and 7 additional items which can be used to assess changes in functioning after cancer diagnosis. The measure was designed to supplement the SAQ in assessing orgasmic and vaginal problems following treatments for gynecological cancers. Validation was conducted in a sample of 257 women with cervical cancer (age range 23–80 years); in this sample, internal consistency was good, and qualitative data suggested that the patients interpreted the items as they were intended. The measure demonstrated discriminant validity in differentiating women with cervical cancer from age-matched controls [30]. Item-level norms for women with and without cervical cancer are available [31]. To date, the measure is only available in English. The approximate time of administration has not been reported.

The relative strengths of the SVQ are its inclusion of specific items relating to vaginal changes and its public availability. Its relative weakness is a lack of research regarding its validity and test–retest reliability.

Use in Cancer Populations

As noted above, the SVQ has been used mainly to assess sexual functioning in women with cervical cancer. One study found that SVQ scores were significantly associated with time since diagnosis and negative sexual self-schema [30]. Another study found that although patients who had received hysterectomies initially reported significantly lower sexual interest scores on the SVQ than did age-matched controls, this difference abated after a year [32]. However, in another longitudinal study, patients with recurrent or persistent cervical cancer reported significant worsening of all SVQ-assessed domains of sexual functioning over the course of 2 years [31].

The Female Sexual Function Index (FSFI)

The Female Sexual Function Index (FSFI) [33] is a 19-item self-report measure with six statistically and theoretically supported factors as well as a total global score. The factors are as follows: desire (2 items), arousal (4 items), lubrication (4 times), orgasm (3 items), satisfaction (3 items), and pain (3 items). The original validation study by Rosen et al. [33] was performed in a sample of 131 sexually healthy control women (age

range 21–68 years) and 128 age-matched women (age range 21–69 years) with diagnosed female sexual arousal disorder (FSAD). This study established the reliability of the FSFI in both healthy controls and sexually dysfunctional patients, with good levels of internal consistency both at the factor and total score levels and strong 2–4 week test–retest reliability. It also established divergent validity with weak correlations to a test of marital satisfaction, the Locke-Wallace Marital Adjustment Test. Further studies have also shown that the FSFI has discriminant validity in differentiating sexually healthy controls and women with FSAD [33], female orgasmic disorder (FOD) [34], hypoactive desire disorder (HSDD) [34], and vulvodynia [35]; norms in all of these populations are available at the factor and total score level. The FSFI has an established clinical cutoff score of ≤26.55 [36]. Norms have also been established in a community sample of gay women [37].

The FSFI takes approximately 15 min to administer, and is available on the web at www.fsfi-questionnaire.com. Translated versions of the FSFI have been validated in Spanish [38], Chinese [39], French [40], Italian [41], Portuguese [42], German [43], Korean [44], Malay [45], Turkish [46], and Dutch [47].

The relative strengths of the FSFI are a wide base of research from independent research teams supporting its reliability and validity, wide use in the sexual health literature, established clinical norms and cutoffs, and many publicly validated translations.

Use in Cancer Populations

The FSFI has been used in a number of cancer populations, with published norms for most of the gynecological cancers. Frumovitz et al. [48] established norms for cervical cancer patients who received radiation treatment and those who had radical hysterectomies; they further found that radiation patients reported significantly lower FSFI scores than do those who underwent hysterectomies and healthy controls, who did not differ significantly from each other. Speer et al. [49] similarly established norms for breast cancer survivors and found that survivors did not differ from historical FSAD patients. A more recent study has established norms in breast cancer survivors who did and did not receive chemotherapy [50]. Furthermore, Brotto et al. [51] showed that the FSFI was sensitive to treatment-related changes for a psychoeducational intervention for sexual dysfunctional in women with gynecological cancer. Published norms are also available for women with rectal cancer [52] and sexually active and inactive women with leukemia or Hodgkin's disease [53].

Derogatis Interview for Sexual Functioning (DISF/DISF-SR)

The Derogatis Interview for Sexual Functioning (DISF) [54] is a 25-item measure that is available both as a semistructured interview and a self-report form. In addition to the global summary score, there are five domains supported by factor analysis: sexual cognition/fantasy (5 items), sexual arousal (5 items), sexual behavior/experience (5 items), orgasm (6 items), and sexual drive/relationship (4 items). Both versions of the DISF have good internal consistency and 1-week test–retest reliability; the interview version has good to excellent inter-rater reliability [54]. Although norms for sexual dysfunctional women are not currently available, community sample norms in both genders have been published for the DISF and DISF-SR. These norms have been standardized into T-scores for a large community sample ($n = 399$ with an age range of 19–64) with a mean of 50 and a standard deviation of 10; as 90% of sexually healthy participants scored above a T-score of 63, this is taken to be the normalcy cutoff [54].

The DISF/DISF-SR takes approximately 15 min to administer and is available in a number of translations including French, German, Finnish, Polish [55], Danish, Dutch, Italian, Spanish, and Norwegian. The DISF is copyrighted and thus available exclusively by purchase through Clinical Psychometric Research, Inc.

The relative strengths of the DISF and DISF-SR are a standardized scoring system that allows comparison of individual profiles to a norm and to itself over time, three separate levels of interpretable data (item, domain, and global composite), and flexibility of both self-report and interview forms. The latter may be of particular use among researchers and clinicians working in populations where the rate of literacy is low (or unknown). Its relative weakness is its proprietary nature, which necessitates purchase of both the measure and its scoring system.

Use in Cancer Populations

As the DISF uses a standardized scoring system, studies using the DISF allow direct comparison between cancer patients and the normative population. Marks et al. [56] followed men and women with a mixed group of cancers (majority leukemia) before and after receiving bone marrow transplants (BMT). The authors found that about half of the patients reported clinically significant sexual dysfunction pre-BMT (i.e., DISF scores below 63). After the treatments, one third of patients reported a significant increase in sexual function (of 10 points, or one standard deviation) but an equal reported equally significant decreases in functioning; thus, the overall population change was nonsignificant. In another longitudinal study, male and female lung cancer patients receiving either chemotherapy alone or chemotherapy plus radiation therapy were followed for 4 months. All but three of the patients had DISF scores below the norm (below 50) at baseline and there was a nonsignificant trend towards decreasing over the three time points. The two treatment groups did not differ significantly from each other, but women reported significantly lower sexual functioning than did the men [57].

A recent clinical trial of a clitoral therapy device (the Eros device) for irradiated cancer patients used both the FSFI and DISF to measure intervention-related changes [58]. The two measures complemented each other's strengths and weaknesses: while FSFI allowed the authors to mark participants as clinical or nonclinical based on the clinical cutoff, the Derogatis Sexual Functioning Inventory (DSFI) allowed the authors to track individual standardized profiles using the percentile scores (i.e., observe which participants improved most within a group of individuals all expected to improve). The authors observed significant improvement in all of the subscales of the DSFI as well as a group trend towards normalcy (i.e., mean T-scores near 63); and as the patients reported a mean FSFI score of greater than the clinical cutoff, the authors were able to confirm their nonclinical status.

Derogatis Sexual Functioning Inventory (DSFI)

The DSFI [59] is a broad measure of ten domains relevant to sexual function, including sexual attitudes, sexual knowledge, past and current sexual activity or behavior, types and level of fantasy, sexual drive, gender role definition, affective balance, psychological symptoms, body image and satisfaction, for a total of 254 items. Due to its length, the measure is rarely used in full solely to measure sexual functioning; however, researchers may use specific domains to track constructs of interest such as changes in sexual activity from previous behaviors. Internal consistencies of individual domains have been shown to be in the acceptable to good range, as is the 1-week test–retest reliability [59]. The global score has divergent validity with weak correlations to the Locke-Wallace Marital Adjustment Test and Dyadic Adjustment Scale [60]. Norms for a community sample of sexually healthy women ($n = 143$, mean age of 32 years) are available for all subscales, as are norms for women with anorgasmia [61]. The sexual drive and satisfaction subscales have been shown to differentiate diabetic women from matched controls [62]; similarly, the satisfaction subscale has been shown to differentiate women with spinal chord injuries from a sexually healthy population [63].

The DSFI takes about half an hour to complete in its entirety, and is available in French [64], Chinese [65], Greek [66], and Finnish [67] language translations. Like the DISF, the DSFI is a proprietary measure available through Clinical Psychometric Research, Inc.

The relative strengths of the DSFI are its long history (and thus broad base of research utilizing the measure), and the wide variety of subscales that offer a comprehensive assessment of sexual function and related constructs. The relative weaknesses include a length that may be prohibitive in some settings and its proprietary nature.

Use in Cancer Populations

As noted above, research using the DSFI most often uses one or a few subscales of interest. One of the most comprehensive uses of the DSFI in cancer patients was conducted in breast cancer patients who were receiving chemotherapy or other treatments. In this study, scores for the patients receiving chemotherapy on the body image, affect, psychological symptoms, sexual drive, and sexual satisfaction subscales were significantly lower than those in other treatments [68]. Current sexual activity subscale norms have been established in women who have received mastectomies with and without reconstruction [69]; a similar report established sexual activity norms in mastectomy patients with and without sexual partners [70]. The activity and satisfaction subscales were used to assess the differences between breast cancer patients who were disease free and those who had experienced recurrences: while there were no significant differences between groups on sexual satisfaction or frequency of kissing, the recurrence group reported significantly lower intercourse frequency [71]. In a related study, the satisfaction subscale in women who were 5-year disease free survivors was not significantly different from never-ill age-matched controls [72]. Findings on the body image subscale in cancer populations are mixed, with some reports suggesting cancer patients score significantly lower than healthy women [73] while others find no difference [74].

Brief Index of Sexual Functioning – Women (BISF-W)

The Brief Index of Sexual Functioning – Women (BISF-W) [75] includes 22 items assessing sexual functioning and satisfaction in women. The first validation study was conducted in a sample of 269 women (age range of 20–73) and established 1-month test–retest reliability and convergent validity with the DSFI [59]. The original version was found to have three statistically supported factors: sexual interest/desire, activity, and satisfaction [75]; however, a new conceptually based scoring procedure has been developed which allows the BISF-W to be used more easily in clinical trials [76]. In addition to the total score, this new scoring algorithm has seven domains, including sexual thoughts/desire, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasm, relationship satisfaction, and problems affecting sexual function. Of these, some domains have internal consistencies that are in the acceptable range (e.g., desire) while others proved to be relatively poor (e.g., arousal). Norms for the total score, as well as the seven domains of the new scoring system, have been published for sexually healthy women with and without regular sex partners [76].

The BISF-W takes 15–20 min to complete. Translations exist for Korean [77], Italian [78], German [79], and French [80]. The relative strength of this measure includes a long history and detailed system of seven domains; the relative weaknesses include lack of information on validity of the new scoring system as well as poor reliability in some domains.

Use in Cancer Populations

Despite its wide use in sexuality research as a whole, there is relatively little work using the BISF-W in cancer populations. Using the new scoring system, Mazer et al. [76] established norms for the BISF-W in women who had undergone cancer surgery which induced early menopause (salpingo-oophorectomy) and found that

these surgically menopausal women reported lower functioning than sexually healthy women, both in composite scores and in separate domains. Shifren et al. [81] found that in a group of oophorectomized women, two of the seven sexuality domains of the BISF-W as well as the total composite score demonstrated sensitivity to treatment-related changes of transdermal testosterone treatments vs. placebo. A similar study conducted among Korean women who were posthysterectomy and who received HRTs revealed lower scores of sexual problems on the BISF-W than those who did not receive HRT [82]. A recent trial of a couples-focused coping intervention in early stage breast or gynecological cancer patients and their partners demonstrated that the Sexual Intimacy domain of the BISF-W was sensitive to intervention-related changes; however, this was not also true of any of the other domains nor the total score [83]. Included in the report on this trial are baseline norms for a mixed group of breast and gynecological cancer patients.

Changes in Sexual Functioning Questionnaire (CSFQ)

The Changes in Sexual Functioning Questionnaire (CSFQ) [84] is a clinician administered structured interview with 35 items that capture changes in sexual functioning related to illness, medication, or treatments. There are five domains in the CSFQ, including sexual desire (frequency; 2 items), sexual desire (interest; 3 items), sexual pleasure (1 item), sexual arousal (3 items), and orgasm (3 items), with additional items regarding degree and extent of change in sexual functioning over time as well as the possible causes of the changes. Each domain, as well as the total score, has been shown to have discriminant validity in differentiating clinically depressed patients and nonclinical controls [85]. The standardization sample for the CSFQ was 122 medical students (68 men and 54 women of an age range of 22–35 years) and 33 psychiatry residents (17 men and 16 women with an age range of 25–43 years). In these samples, internal consistency and both 1-week and 1-month test–retest reliability of the CSFQ were good. Furthermore, the CSFQ has proved to have convergent validity the *Derogatis Index of Sexual Function* (*DISF*) [85]. While there are norms for depressed patients and the standardization sample [85], there are not currently norms published for women with diagnosed FSD.

The CSFQ takes approximately 20 min to administer and is easy to score. Publicly available translations include Spanish [86] and Chinese [87], with many more available through www.proqolid.org. There is also a validated short form available, the CSFQ-14 [88]; however, due to its more recent development, little validation research is currently available.

The relative strengths of the CSFQ are a focus on changes in sexual function which differentiate long-standing sexual problems from those that arise out of illness or treatment, available norms for depressed populations, flexibility of self-report and interview versions, and a wide research base in the psychopharmacological literature base. The relative weakness is the unknown level of validity in using the CSFQ as a diagnostic tool for sexual dysfunction.

Use in Cancer Populations

The CSFQ has been used in efficacy studies measuring the effects of interventions for sexual dysfunction following cancer treatments such as radiation or surgery. Norms are available as baseline (i.e., presexual health intervention but postcancer treatment) scores for patients in a mixed group of several cancers [89, 90]. The treatment outcome literature using the CSFQ in cancer populations is mixed, with some studies reporting changes in CSFQ scores after interventions such as group sexual therapy [89] and others reporting no changes following treatments such as transdermal testosterone [90] or estrogen replacement therapy [91].

Golombok-Rust Inventory of Sexual Satisfaction (GRISS)

Despite its name, the Golombok-Rust Inventory of Sexual Satisfaction (GRISS) is primarily a measure of sexual functioning. It was the product of collaboration at a sexual health clinic "think tank" and was designed to assess both a (heterosexual) couple's relationship quality and each individual partner's sexual functioning. The GRISS has 56 items (28 items for males and 28 for women) that fall into 12 domains (5 for women, 5 for men, and 2 common to both genders). It is possible to transform the individual domains to stanine (ranked order) scores to plot profiles of sexual functioning. These transformations are normed to a clinical sample but can also be used in nonclinical populations. A global score can be computed for both the couple and the individual. The seven domains in the female version of the GRISS are anorgasmia (4 items), vaginismus (4 items), avoidance (4 items), nonsensuality (4 items), dissatisfaction (4 items), frequency of sexual contact (4 items), and noncommunication (4 items). The original validation was conducted on a sample of 88 clients from sex therapy clinics (i.e., 88 men and women presenting together in a clinical setting): in this sample, internal consistency of each domain and the global measure were acceptable to good. The factor analysis supporting the domains has also been conducted in a nonclinical sample [92]. Test–retest reliabilities were calculated from a different sample of 41 couples in sex or marital therapy: even with significant changes over the course of therapy, the reliability of the GRISS was still good for most domains (with the exception of dissatisfaction) [93]. Discriminant validity has been established with the five female domains differentiating between sexually functional ($n = 30$) and dysfunctional ($n = 42$) women [92]. The GRISS is sensitive to treatment-related changes in sexual functioning in a study of 30 couples receiving sex therapy; also in this sample, the convergent validity between blind clinician ratings and GRISS scores was acceptable to good [92].

The GRISS takes approximately 15 min to administer, and is available in Dutch [94–96], Turkish [94], and Chinese [97]. The GRISS is a proprietary measure available through Psychcorp, a subsidiary of Pearson Assessments.

Strengths of the GRISS include a broad base of research on its validity and reliability and potential for use as a measure for both a couple and each individual. Its relative weaknesses include some outdated language in the items and its proprietary nature.

Use in Cancer Populations

The GRISS was used to investigate an educational intervention to protect sexual function of intestinal cancer patients who were to receive permanent stoma. The GRISS scores in the control group indicated a slow decline in sexual function over time, while in the intervention group, there were no changes in the satisfaction, avoidance, and anorgasmia subscales (as well as the total scores), indicating that sexual function in these domains had been preserved [98]. The GRISS was also used to investigate sexual function in breast cancer patients who had undergone mastectomies with and without breast reconstruction. Although the GRISS norms for both groups were lower than healthy controls, this difference was not statistically significant [99].

McCoy Female Sexuality Questionnaire (MSFQ)

The McCoy Female Sexuality Questionnaire (MSFQ) [100] is a 19-item self-report inventory developed to track longitudinal changes in women's sexual functioning due to menopause. The first twelve questions assess general sexuality and interest; the final seven questions assess functioning during heterosexual intercourse. While the items assess separate domains of functioning, it has been validated only at the item and total score level. Reliability was established in a student sample of 318 women (age range 17–70

years); internal consistency was good and 2-week test–retest reliability was acceptable to good [101]. The MFSQ has been shown to reliably differentiate between pre- and postmenopausal women [102] and oral contraceptive users and nonusers [100], and is sensitive to hormonal treatment induced changes in sexual functioning [103–105]. A short-form version, the Personal Experiences Questionnaire (PEQ), has been adapted from nine questions from the MFSQ [106, 107]. The PEQ was validated in a community sample of 438 women (age range 45–55 years); in this sample, the internal consistency within factors was poor (with some Cronbach's alpha coefficients as low as 0.38) but consistency for the overall scale was adequate [108]. In a separate study, the PEQ demonstrated discriminant validity in differentiating women presenting for treatment at sex therapy or psychiatric clinics and women at family planning clinics; convergent validity was also found with high correlations to the relevant domains of the DISF-SR [106].

The MSFQ takes about 10 min to complete, and has been validated in Swedish [103], Norwegian and Dutch [104], French [105], and Italian [109]. The relative strengths of the MSFQ are its adaptability to use in women who have not experienced sexual intercourse (i.e., using only the first twelve items) and the availability of a validated short form. Its weaknesses include low reliability of some items in the short form and lack of separate validated factors.

Use in Cancer Populations

The MSFQ has been used in cancer populations, to track changes in sexual functioning due to hormonal changes, either from treatment for cancer (e.g., after surgical menopause) or hormone replacement treatments. In the former case, several studies have followed women who received hysterectomy and/or oophorectomy pre- and postsurgery. One study showed that 1-year postsurgery, women who had undergone hysterectomy reported significantly lower functioning in two items of the MSFQ (sexual enjoyment and coital frequency) as well as the total score; however, for women who had undergone both hysterectomy and oophorectomy, scores at 1-year follow-up did not differ significantly from presurgery scores [110]. A follow-up study found that although androgen levels in both groups had declined, this decline was not associated with scores on the MSFQ [111]. On the other hand, an intervention study investigating the effects of androgen and estrogen replacement therapies on sexual function of hysterectomy and oophorectomy patients found opposite results: the authors found that over a 24-week intervention, as the women's serum testosterone significantly increased, so did their MSFQ scores [112]. In a study conducted among women who underwent either abdominal or laparoscopic hysterectomies, MSFQ scores after a 1-year follow-up did not differ between groups [113].

Other Measures of Female Sexual Functioning

There are a number of other measures of female sexual functioning available; however at the present time there is not adequate research to assess their utility in cancer populations. Examples include the Brief HSDD Screener [114], the Decreased Sexual Desire Screener [115], the Sexual Interest Desire Inventory [116], the Profile of Female Sexual Functioning [117], and the Gynaecologic Leiden Questionnaire [118]. Of interest is the Gynaecologic Leiden Questionnaire, which was developed to measure the sexual functioning of female cancer patients.

Sexual Satisfaction Assessment Instruments

Sexual satisfaction is generally understood as an individual's affective response to the subjective evaluation of his or her sexual experiences; hence, its distinction from sexual function per se.

Additionally, while little research has been done on the relationship between sexual satisfaction and sexual distress, recently experts in the field of human sexuality have suggested that these constructs are not necessarily opposite poles on the same continuum, but may instead be independent factors [119, 120]. In other words, distress might not simply be the absence of satisfaction, or satisfaction the absence of distress. While few studies on female sexual dysfunction have included measures of sexual distress [121], the DSM-IV-TR guidelines require either marked distress or interpersonal difficulty as prerequisites to a diagnosis of sexual dysfunction [122]. Sexual distress has recently been measured as a distinct construct in a number of studies [121, 123, 124] and validated measures of sexual distress [120, 125] are available. This distinction between satisfaction and distress should be considered when deciding precisely which variables are of interest in any particular study. Researchers focusing on patients' general sexual well-being would likely include measures of sexual satisfaction whereas those focusing on diagnosable sexual dysfunction (sexual difficulties with resultant personal distress as per DSM-IV-TR criteria) may be better served by a scale measuring sexual distress specifically.

The most common method of assessing sexual satisfaction is with a single self-report item that asks participants to rate how satisfying they find sexual activity "in general" or within some specified time frame. Similarly, sexual distress is often assessed with a single item such as "During the past 4 weeks, how much distress or worry has you're your own sexuality caused you?" [123]. Single-item measures are limited in that they are rarely independently validated, and they are less reliable than multi-item scales because lone items are more likely to be skipped or misread by participants and are less resilient to day-to-day fluctuations in responding. Also, the range of responses possible for a single item leads to a restricted variance in scores, and most traditional statistical techniques (regression and ANOVA) assume the presence of a normally distributed, continuous outcome variable.

Sexual satisfaction is also commonly assessed using subscales within measures of sexual functioning. While these subscales may avoid some of the problems inherent in single-item measures, their validity may be compromised by the fact that, while full-scale scores are often validated against relevant external criteria, this is rarely the case for specific subscale scores. As such, claiming that a satisfaction subscale from within a measure of functioning is a validated measure of sexual satisfaction may be inaccurate. Sexual distress, being a recently described construct, is rarely assessed in this way.

Below, we describe five multi-item, validated and reliable measures of sexual satisfaction or distress and summarize the minimal research that has been conducted using these measures in cancer populations.

The Global Measure of Sexual Satisfaction (GMSEX)

The Global Measure of Sexual Satisfaction (GMSEX) [126] is a 5-item self-report measure of sexual satisfaction meant to measure one's overall satisfaction with the sexual aspects of a relationship. The GMSEX was developed as an outcome measure for the interpersonal exchange model of sexual satisfaction using a sample of 52 female and 47 male undergraduate students in long-term romantic relationships (duration 3–36 months). Norms are available in the initial validation study. Scores on the GMSEX are related to multiple indicators of sexual and relational functioning including relative balance of sexual costs and rewards [127] and relationship satisfaction [128]. Internal consistency and test–retest reliabilities are within the acceptable range. The GMSEX takes less than 5 min to administer. Unpublished data from use with breast cancer survivors is available from the scale's authors.

The GMSEX's strengths are that it is reliable, valid, very brief, and shows no overlap with measures of sexual functioning. Its limitations are that it is one-dimensional (with no measure of distress), has not been used with

clinical populations, and assumes that the participant is in a stable romantic relationship and, thus, cannot assess sexual satisfaction in single women.

The Index of Sexual Satisfaction (ISS)

The Index of Sexual Satisfaction (ISS) [129] is made up of 25 self-report items and provides a single sexual satisfaction score. The ISS was developed using a sample of 100 men and women (mean age of 32.7 years) seeking treatment for relationship problems. The scale, with norms, is not available for public use, but may be purchased through its authors. Scores on the ISS are related to martial satisfaction and general contentment. The ISS can reliably discriminate between individuals judged by therapists to have and not have sexual problems. Internal consistency and test–retest reliabilities are within the acceptable range. Divergent validity has been established using the Index of Marital Satisfaction [130] and the Sexual Attitude Scale [129, 131]. The ISS was more effective at differentiating between patients with and without sexual problems than either the Index of Marital Satisfaction or the Sexual Attitude Scale. This suggests that the ISS is tapping sexual satisfaction specifically, and does so more precisely than scales of different, but related constructs (martial satisfaction and sexual attitudes). The ISS takes approximately 5–7 min to administer. The scale has been used to measure satisfaction in patients with polycystic ovary syndrome [132].

The strengths of the ISS are that it is reliable, valid, and brief; norms are available; and clinical cut-off points have been established. Its limitations are that it is one-dimensional, scoring procedures and norms are not publicly available, some items overlap with sexual functioning, and it makes no differentiation between satisfaction and distress. Additionally, it assumes that the participants are in a romantic relationship.

The Pinney Sexual Satisfaction Inventory (PSSI)

The Pinney Sexual Satisfaction Inventory (PSSI) [133] is a self-report measure of female sexual satisfaction that includes 24 items and provides scores on two domains of satisfaction as well as a total score. The domains assessed have been confirmed using factor analyses and are general sexual satisfaction (14 items) and satisfaction with partner (10 items). The PSSI was developed on a female sample of 275 women in an introduction to psychology course (age range 17–24 years). Ninety-seven percent of these women were single. Norms for the subscale and full-scale scores can be computed using the initial validation study. The PSSI is related to other established measure of sexual satisfaction, orgasm consistency, and frequency of intercourse. Internal consistency and test–retest reliabilities are within the acceptable range. The administration time of the PSSI has not been reported. To our knowledge, the PSSI has not been used with a cancer population.

The strengths of the PSSI are that it is reliable, valid, and brief; norms are available; it assesses two distinct components of satisfaction; and that it can be used by participants not currently in romantic relationships. Its limitations are that it has not been used in clinical populations, some items overlap with sexual functioning, and it makes no differentiation between satisfaction and distress.

The Female Sexual Distress Scale (FSDS)

The Female Sexual Distress Scale (FSDS) [125] includes 12 self-report items and provides scores on two domains of sexual distress as well as a total score. The domains assessed are frequency of distress (6 items) and intensity of distress (6 items). Factor analysis has shown that scores on the FSDS represent a single underlying factor. The FSDS was developed on a female sample of

60 nurses with no reported sexual problems and 18 patients with a variety of sexual problems (mean age of 48 years). Community norms are available in the initial validation study. The FSDS has been shown to reliably discriminate women with sexual problems from control patients on each of domain scores as well as the full-scale score. Internal consistency and test–retest reliabilities are within the acceptable range. Divergent validity has been established using measures of somatization, depression, and negative affect. Correlations between the FSDS and these measures were moderate in magnitude (0.28, 0.59, and 0.58 for somatization, depression, and negative affect, respectively). These relationships demonstrate that scores on the scale do not solely reflect these related but conceptually different factors. The administration time of the FSDS has not been reported. The scale has been used to measure changes in sexual distress in response to cancer treatment [51].

The FSDS's strengths are that it is reliable, valid, and brief; norms are available; clinical cut-offs are established; it is available in multiple languages; it clearly differentiates between satisfaction and distress (measuring distress only); it does not assume the participant is in a romantic relationship; and there is minimal overlap with measures of sexual functioning. Its limitation is that it measures only sexual distress (as opposed to a broader conceptualization of sexual satisfaction).

The Sexual Satisfaction Scale for Women (SSS-W)

The Sexual Satisfaction Scale for Women (SSS-W) [120] is a 30-item self-report measure of female sexual satisfaction that provides scores on three domains of sexual satisfaction and two of sexual distress, as well as a total score. The domains assessed have been confirmed using factor analyses and include contentment, communication, compatibility, relational concern, and personal concern (each with 6 items). The SSS-W was developed on a female sample of 79 normal controls (age range 18–53 years) and 102 participants who met DSM-IV-TR criteria for female sexual dysfunction (age range 18–56 years). Norms are available for control and women diagnosed with sexual dysfunction at the item level, the domain level, and the full-scale score in the initial validation study. The SSS-W full-scale score and each of the domain scores have been shown to reliably discriminate between women with and without sexual dysfunction. Internal consistency and test–retest reliabilities are within the acceptable range. Divergent validity has been established using the *Locke-Wallace Marital Adjustment Test*. Correlations between the SSS-W subscales and the Locke-Wallace were moderate in magnitude, with only the relational domains showing a significant relationship. This shows that the SSS-W measures sexual satisfaction specifically, and not the related construct of marital satisfaction. The SSS-W takes approximately 5–10 min to administer. To our knowledge, the SSS-W has not been used with a cancer population.

The SSS-W's strengths are that it is reliable, valid, and brief; norms are available; it is multifaceted; there is minimal overlap with sexual functioning; and it clearly differentiates and measures both satisfaction and distress. Its limitation is that it requires participants to be in a romantic relationship.

Summary

This chapter has provided a review of 9 measures of sexual function and 5 measures of sexual satisfaction. All of the measures reviewed have acceptable reliability and validity for assessment in women. Most of the sexual functioning measures reviewed have been used extensively in research among cancer populations. Only 2 of the 5 measures of sexual satisfaction/distress (the GMSEX and the ISS) have been used for assessment among women cancer patients. Which of these questionnaires should be selected for use for a particular study will necessarily depend on the specific sexual domains of interest (e.g., desire, arousal, orgasm, pain, satisfaction), the amount of time available for participant

assessment (the scales range from 5 to 254 items), and the hypotheses and goals of the study. In the last case, if the goals include a comprehensive examination of sexual functioning among cancer patients, then the best measures would include the GRISS and the DSFI. If the goal includes measuring treatment outcomes, then appropriate measures would include the CSFQ, MSFQ, and BISF-W. If it were necessary to use the measure as a diagnostic tool, the FSFI would be well suited. And finally, if the goal included comparing results to literature on other cancers, the best measure might be the SAQ, which has a broad base of previous cancer research, or the DISF/DISF-SR, which has a standardized scoring system. Regardless of the measure used, however, it is important to note that these instruments can only offer one piece of a larger context of health and sexuality: no amount of research on a measure's psychometric properties can allow it to fully capture the complex story of women's sexual experiences during and after a battle with cancer.

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Chapter 22
Validated Questionnaires in Male Sexual Function Assessment

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Introduction

Self-administered questionnaires and symptom scales are valuable adjuncts to clinical practice in sexual medicine and are an important part of high quality research. Despite their value in identifying and evaluating sexual dysfunction, screening tools and questionnaires should *never* substitute for a thorough sexual, medical, and psychosocial history. For patients with multiple sexual dysfunction symptoms following cancer diagnosis or treatment (e.g., ED and low libido), further evaluation of these symptoms is *always* recommended prior to initiating therapy for cancer or sexual dysfunction. Whenever possible, the temporal association or causal relationship between the symptoms should be assessed. The *sexual, medical* and *psychosocial* history is an essential element in the basic evaluation and should be obtained in *all patients* presenting with complaints of sexual dysfunction. The essential components of *sexual function assessment* in the male should always include: erectile response (onset, duration, progression, severity of the problem, nocturnal/morning erections, self-stimulatory and visual erotic-induced erections), altered sexual desire, ejaculation, orgasm, sexually-related genital pain disorders, and partner sexual function, if available.

The patient's psychological state should also be assessed in every case, with special attention to symptoms of anxiety or depression; past and present partner relationships; and medical comorbidities and treatments (including drugs and surgery). A critical aspect of assessment is the identification of patient's needs and expectations, personal priorities and treatment references, which may be significantly influenced, in turn, by cultural, social, ethnic, and religious perspectives. Additionally, patient education is necessary in fostering a therapeutic relationship, facilitating patient–physician communication, and enhancing treatment compliance. Lastly, partner participation may be influenced by cultural and social expectations, as well as patient needs and preferences.

Symptoms Scales and Questionnaires

Validated symptom scales and self-administered questionnaires may assist the clinician in recognizing and diagnosing the sexual problem. These measures may permit patients to acknowledge the problem and to *initiate* a clinical discussion with their health provider. Sexual function symptom scales should be used

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routinely to assess functional level (e.g., ability to respond, level of interest) and to determine the impact of therapy. Scales and questionnaires are also a valuable tool in clinical trials and outcomes research on male sexual function. The most frequently used type of instrument is the self-administered questionnaire. These questionnaires should be systematically developed with input from experts in the field and patients experiencing difficulties with sexual function and then tested to insure that they meet specific psychometric properties. The most fundamental requirements for psychometric validity include *reliability* and *validity.* Reliability refers to the consistency or replicability of data, while validity reflects the degree to which an instrument or scale measures what it intends or claims to measure. Two essential indicators of validity for measures of sexual function are: sensitivity to diagnostic status (e.g., functional vs. dysfunctional) and sensitivity to treatment change. Both are essential features of any scale which is designed to serve as a diagnostic and/or efficacy measure in either clinical or research settings. For a more detailed description of measurement development and validation procedures, please see the FDA Guidelines for Patient Reported Outcomes [1].

There are a number of validated symptom scales that assess male sexual function. These scales assess a range of topics which include: male sexual dysfunction, couple's and partner satisfaction, and sexual quality of life or well-being measures. This chapter is not meant to review all of the published scales on male sexual dysfunction, but will review the scales that the authors thought were most suitable as determined by the frequency of use of the scale and appropriate psychometric properties. Most of the scales described below are well-established and widely used in research or clinical settings. In all, we have reviewed 14 scales, and placed them in the following categories: Comprehensive Male Sexual Dysfunction Scales, Delayed Ejaculation Scales, Premature Ejaculation Scales, Treatment Satisfaction Scales, Sexual Quality of Life Scales, and Cancer Specific Scales/Validation Data in Cancer Patients.

Comprehensive Male Sexual Dysfunction Scales

Golombok Rust Inventory of Sexual Satisfaction

The Golombok Rust Inventory of Sexual Satisfaction (GRISS) is a 56-item (28 items for women and 28 items for men) self-report instrument designed to assess the existence and severity of sexual problems among sexually active individuals and heterosexual couples [2]. It is designed to assess each individual partner's function and the overall relationship. For assessment of individuals the men's and women's items can be presented as two separate forms. The GRISS is comprised of 12 domain scores, 5 for women, 5 for men and 2 scores common to both. An aggregate total score for each respondent is also used to summarize the quality of relationship and sexual functioning in the couple. Domains pertaining to men include premature ejaculation (four items), impotence (four items), avoidance (four items), nonsensuality (four items), and dissatisfaction (four items). Equivalent domains pertaining to women include anorgasmia (four items), vaginismus (four items), avoidance (four items), nonsensuality (four items), and dissatisfaction (four items). The two domains common to both women and men are frequency of sexual contact (four items) and noncommunication (four items).

This instrument was designed for use with sex therapy clients and was originally standardized using 44 heterosexual couples (88 individuals) seeking marital or sex therapy. A transformation key allows couples to see their scores plotted on a profile provided for the couple as part of therapy. It takes approximately 15 min to complete, and it is designed for use with heterosexual sex therapy clients.

Internal consistency of the subscales was acceptably high and ranged from 0.61 to 0.83. Test–retest assessment involved a comparison of scores from both pre- and posttherapy for 41 of the couples. Test–retest calculations for women ranged from 0.47 to 0.82. Women in therapy showed higher rates of dysfunction across subscales

compared to the control sample of general practitioner patients. A Dutch translated version of GRISS showed a similar factor structure to that of the English version, and demonstrated reasonably high internal consistency for the each of the subscales. The GRISS has demonstrated utility in establishing lowered sexual functioning among women with obsessive–compulsive disorder and psychiatric comorbidity among women identified as having FSD using scales from the GRISS.

Norms are available from the development sample of therapy clients as well as for a comparison nonclinical sample of 59 general practitioner patients. It is available in Dutch and English.

International Index of Erectile Function

The International Index of Erectile Function (IIEF) is a widely-used, 15-item self-report inventory developed by Rosen and colleagues [3, 4] to provide a brief, standardized measure of erectile function and capacity. It measures five domains of sexual function in men. The IIEF was developed in conjunction with the clinical trial program for sildenafil, and has since served as a major endpoint in over 50 clinical trials. The principal domains of the IIEF were identified through literature search, review of existing instruments, and interviews with patients suffering from erectile dysfunction. The IIEF represents quality of male sexual function in terms of five domain scores: *erectile function, orgasmic function, sexual desire, sexual satisfaction, and overall satisfaction.* The IIEF does not yield a total score.

Both internal consistency (0.73–0.95) and test–retest reliabilities (0.64–0.84) are superior for the scale, and there is factor analytic confirmation of the principal domains. Sensitivity and specificity are very good, and concurrent validation against other comparable measures has been demonstrated. Discriminative validity has been well established in comparisons of functional vs. dysfunctional samples, and sensitivity to therapeutic change has been consistently shown within the context of clinical trials of sildenafil and other treatments for ED. A 5-item brief form of the IIEF termed the Sexual Health Inventory for Men (SHIM) has also been developed and validated, along with a diagnostic classification and an ED severity scale [5]. A systematic review of more than 60 studies found the IIEF scale to be highly robust in different ethnic and geographic populations, as well as sensitive to treatment effects across a variety of treatment agents. The evidence base for the scale has been rated A1 by the third International Consultation on Sexual Medicine.

Delayed Ejaculation Scales-Male Anorgasmia

Male Sexual Health Questionnaire

The Male Sexual Health Questionnaire (MSHQ) was developed by Rosen et al. [6]. It is a 25-item validated questionnaire to measure specific aspects of ejaculation in older men. The MSHQ, which includes independent domains for *ejaculation* (seven items), *erection* (three items), and *sexual satisfaction* (six items), provides a more in-depth assessment of ejaculatory function and sexual satisfaction than the IIEF. The *ejaculation domain* of the MSHQ assesses loss of ejaculation, delayed ejaculation, the force of the ejaculation, the amount of semen ejaculated, pleasure associated with ejaculation, pain/discomfort during ejaculation, and the bother associated with ejaculation. A four-item MSHQ-EjD Short Form, with three ejaculatory function items and one bother item, has also been psychometrically validated for the assessment of EjD in clinical and research settings [6].

In psychometric validation studies, the three domains of the 25-item MSHQ demonstrated a high degree of internal consistency (0.81–0.90), rest–retest reliability (0.86–0.88), and construct validity, together with the ability to differentiate between men with LUTS and sexual dysfunction and healthy men. The three ejaculatory function items of the MSHQ-EjD Short Form maintain reliability and construct validity for assessing EjD in heterosexual, bisexual, and gay men [7].

Premature Ejaculation Measures

Several premature ejaculation measures have been described in the literature, although only a small number have undergone extensive psychometric testing and validation. Currently, there are two questionnaires that meet most of the criteria for test development and validation: The Premature Ejaculation Profile (PEP) and the Index of Premature Ejaculation (IPE). A third brief diagnostic measure (Premature Ejaculation Diagnostic Tool [PEDT]) has also been developed, and is available for clinical use [8].

Premature Ejaculation Profile

A four-item, self-report measure of premature ejaculation have been described by Patrick et al. [9]. The PEP is comprised of single-item constructs of: (1) perceived control over ejaculation; (2) satisfaction with sexual intercourse; (3) personal distress related to ejaculation, and (4) interpersonal difficulty related to ejaculation. Each of the four individual items is assessed on a five-point scale, which are averaged to provide an index PE score. The measure has been used in observational studies and clinical trials of premature ejaculation [10]. It has also been recommended for clinical use in evaluating the subjective components of the disorder. Validation studies have been performed in comparison to stop-watch measures of intravaginal latency and other PRO measures of sexual function and distress.

Psychometric evaluation was conducted in both large-scale observational studies and clinical trials conducted for dapoxetine (a centrally acting, agent for treatment of PE) [9]. Test–retest reliability was reported as Intra Class Correlations (ICC), which ranged from 0.66 for perceived control to 0.80 for the overall PE index score in the US observational study. The measure showed adequate known groups validity in comparing men with PE to non-PE controls. As predicted, men with IELT of 0–2 min showed significantly poorer scale scores than men above 2 min ($p<0.001$). Sensitivity to change analyses was also conducted.

Index of Premature Ejaculation

The IPE was developed by Althof et al. [11]. It is a 10-item self-administered questionnaire designed to evaluate sexual satisfaction, control, and distress in men with premature ejaculation. It was developed over four stages: item pool development, initial psychometric analyses, patient interviews, and final psychometric analyses.

The IPE contains three-factor analytically-derived domains: control, sexual satisfaction, and distress. All three domains have shown excellent internal consistency and reliability, as well as showing good known groups validity between men with and without PE. Convergent validity against IELT was also strong for all three domains [control ($r=0.75$); sexual satisfaction ($r=0.60$), and distress ($r=0.68$)]. Treatment sensitivity was yet to be determined.

Premature Ejaculation Diagnostic Tool

The previous two measures (PEP, IPE) are available for use as treatment change or outcome measures of PE treatment. The PEDT was developed and is available only in the form of a screening questionnaire [9]. This questionnaire is a brief, 5-item measure used to screen men for potential presence of PE based on DSM-IV-TR criteria of lack of control, frequency, minimal stimulation, distress, and interpersonal difficulty.

Internal consistency (Cronbach's alpha = 0.71) and reliability (ICC = 0.73) were good. Importantly known-groups validity was strong when comparing men with time-defined PE (IELTs ≤2 min in 70% of coital attempts) and those with self-reported no PE. A score of ≥11 would suggest presence of PE and men scoring 9 or 10 are likely to have PE and are recommended

for further assessment. This scoring system has shown good convergent validity with clinical expert diagnosis of PE (k-statistic = 0.80).

Treatment Satisfaction Scales

Treatment Satisfaction Scale

The Treatment Satisfaction Scale (TSS) is a sexual quality of life measure developed by Kubin et al. [12] for use in treatment outcome studies of male sexual dysfunction. The scale provides a comprehensive assessment of sexual satisfaction of men with ED, and their partners and to assess sequential measurements over time to evaluate satisfaction with treatment [12, 13]. It is a multifaceted measure of patients' and partners' satisfaction with their sexual life relating to erectile dysfunction and intended for prospective use.

The TSS has four modules: unmedicated patient (12 items), medicated patient (19 items), unmedicated partner (12 items), and medicated partner (18 items). All TSS modules have these domains: spontaneity, quality of erection, quality of ejaculation, quality of orgasm, sexual pleasure, and confidence. The medicated patient and partner modules have these domains: reliability of treatment, convenience, treatment efficacy, conformity to treatment expectations, overall satisfaction, and intentions for continued use of the particular drug.

The TSS baseline "unmedicated" and "medicated" modules have 63% item-congruence. The medicated patient and partner modules of the TSS comprise 95% identical items and the unmedicated patient and partner modules comprise 100% identical items. This multidimensional scale has good internal consistency, reliability, and concurrent validity with the IIEF [12]. Specifically, all multiitem scales (satisfaction with erectile function, sexual confidence, and satisfaction with medication) had Cronbach's alphas above 0.70 at baseline and follow-up. Furthermore, all patient TSS domains were significantly correlated with three domains of the IIEF (erectile function, intercourse satisfaction, and overall satisfaction) and there was a significant correlation between men's IIEF-erectile function results and the six-partner TSS domains [13]. The TSS scales were able to discriminate between four ED severity groups, and between responders and nonresponders to treatment; all patient and partner TSS scales were responsive (sensitive to change) for the respondents.

Erectile Dysfunction Inventory for Treatment and Satisfaction

The Erectile Dysfunction Inventory for Treatment and Satisfaction (EDITS) scale was developed by Althof et al. [14]. It is a multidimensional scale to assess male treatment satisfaction following ED therapy, and which explores the impact of patient and partner's satisfaction on treatment continuation. The Patient EDITS version consists of 11 items, scored from 0 (no satisfaction or dissatisfaction) to 4 (high satisfaction) and measuring overall satisfaction, degree to which treatment met expectations, likelihood of treatment continuation, ease of use, satisfaction with onset of action, satisfaction with duration of action, impact of treatment on sexual confidence, partner satisfaction with treatment, how the partner felt about the patients continuing with treatment by patient self-report), naturalness of erections and naturalness of erection hardness. The Partner version of the EDITS consists of five items assessing overall satisfaction, degree to which treatment met expectations, how treatment affected the partner's sense of sexual desirability, partner satisfaction with duration of action, and how the partner feels about the patients continuing to use the treatment. The EDITS score is calculated by multiplying the mean EDITS score by 25 resulting in a treatment satisfaction range of 0 (extremely dissatisfied) to 100 (extremely satisfied).

Scores on the Patient EDITS and the Partner EDITS were normally distributed with internal consistencies of 0.90 and 0.76 respectively. The Patient EDITS has an internal consistency of 0.90 and a test–retest reliability of 0.98.

The Partner EDITS has an internal constancy of 0.76 and a test–retest reliability of 0.83. The EDITS has also shown sensitivity to change.

Psychological and Interpersonal Relationship Scale

The Psychological and Interpersonal Relationship Scale (PAIRS) scale was developed by Swindle et al. [15, 16] to assess broad psychosocial outcomes associated with erectile dysfunction and its treatment. Items were generated based on literature review, focus groups, interviews with patients and partners, market research and consultation with clinicians. Of the 47 items initially developed, 23 were retained to form three domains: Sexual Self-Confidence (six items), Spontaneity (nine items), and Time Concerns (eight items).

Four studies were completed to psychometrically validate the PAIRS. Factor analysis elicited the three-domain structure and, convergent and divergent validity hypotheses were confirmed. Discriminant validity was also demonstrated with scores across all three domains being statistically significantly different between men with ED and those with no ED. Reliability was assessed using Pearson's correlation coefficient and showed adequate results: Time concerns ($r=0.63$), Spontaneity ($r=0.66$), and Sexual Self-confidence ($r=0.77$). In addition, strong internal consistency across the studies and domains was shown (α: 0.73–0.97). Responsiveness of the measure to treatment effect was also shown.

Sexual Quality of Life Scales

Sexual Life Quality Questionnaire

The Sexual Life Quality Questionnaire (SLQQ) was developed by Woodward et al. [17]. It is a validated, multidimensional questionnaire that consists of two domains: (1) sexual quality of life (SQoL) (10 items) and (2) treatment satisfaction (6 items). The SQoL domain compares the current sexual experience of the subjects or his partner with their individual experience prior to the onset of the subject's erectile dysfunction. Scores on each item can range from −4 to 4, with 0 indicating no change from before the onset of erectile dysfunction, negative numbers denoting worse outcomes, and positive scores indicating better outcome.

The SLQQ is an adequate measure of treatment satisfaction as shown by a high correlation with response to a question asking about their likelihood of continuing the treatment ($r=0.89$). The SLQQ is also responsive and able to detect changes in sexual quality of life [199]. For the quality of life domain, Cronbach's alpha was 0.97 for patients and 0.98 for partners. For the treatment satisfaction domain, Cronbach's alpha was 0.85 for patients and 0.87 for partners respectively.

Self-Esteem and Relationship Questionnaire

The Self-Esteem and Relationship (SEAR) questionnaire was developed by [18] to assess impact of erectile dysfunction on men's self-esteem and sexual relationship. A total of 86 items were developed via focus groups, interviews with medical specialists and literature review. Validation of the measure resulted in 14 items, which form two domains: Sexual Relationship Satisfaction (eight items) and Confidence (six items), the latter domain consisting of two sub-domains of Self-Esteem (four items), and Overall Relationship Satisfaction (two items).

Factor analysis was used to determine the most appropriate structuring for the SEAR. The Psychological General Well-Being measure and the SF36 were used to demonstrate the convergent and divergent validity of the SEAR. The SEAR discriminates well not only between men with diagnosed ED and age-matched controls but also across levels of self-reported ED severity. Internal consistency was high for the domains and sub-domains of the SEAR (α, 0.76–0.93), as was reliability (ICC, 0.57–0.79). The SEAR has been used in a number of clinical trials,

which has demonstrated its sensitivity to treatment effect and allowed the definition of a minimal clinically meaningful improvement (approximately ten points across the domains/sub-domains). For an overview of the SEAR, see [19, 18] and Symonds et al. [8].

Sexual Quality of Life: Male

The Sexual Quality of Life measure for Men (SQOL-M) was developed by Abraham et al. [20] for or use in men with either premature ejaculation or erectile dysfunction to assess impact of these conditions on men's self-esteem, relationship, and emotional well-being. The item pool was taken from the Sexual Quality of Life measure for Females (SQOL-F – see below) after confirmation from experts, a review of the literature and interviews with men with either ED or PE that the items were applicable to men. Factor analysis and item–total correlations showed that 11 items, as a total score, of the 18 items were most pertinent to men.

The reliability and validity of the SQOL-M was confirmed in both men with ED and PE. Internal consistency ranged from 0.87 to 0.93 and test–retest reliability ranged from 0.77 to 0.79. Convergent validity with the IIEF-Overall satisfaction domain for men with ED and IPE-satisfaction and distress domains for men with PE was confirmed. Highly significant differences were shown between men without sexual dysfunction compared to those with ED or PE, or as a combined sexual dysfunction group.

Cancer-Specific Scales and Validation Data in Cancer Patients

Expanded Prostate Cancer Index Composite/UCLA Prostate Cancer Index

The Expanded Prostate Cancer Index Composite (EPIC) is an expanded 50-item version of the UCLA-PCI 20-item questionnaire [21, 22]. The EPIC added items to the UCLA-PCI to assess broader issues of quality of life in men who had received treatment for prostate cancer. Although both of these scales include items which are not directly related to sexual functioning (e.g., urinary symptoms, bowl symptoms, or hormone domains), both scales assess sexual function in men with prostate cancer, and were developed from feedback from prostate cancer patients. The UCLA-PCI contains an eight-item sexual function scale and a one-item sexual bother scale. The sexual function scale asks about sexual desire, the quality and frequency of erections, frequency of intercourse, and overall sexual function. The sexual bother question asks "how big of a problem has getting and maintaining an erection been" for the subjects. The EPIC expanded the UCLA-PCI sexual function scale by one item making it nine items, and the additional question focused on frequency of "sexual activity." The EPIC expanded the UCLA-PCI sexual bother scale by three items, making it a four-item scale. The additional questions focused on "how big of a problem" the patient is experiencing with sexual desire, achieving an orgasm, and sexual function (or lack of sexual function). Both of these scales invite the respondent to assess these items over the past 4 weeks.

These scales from both the UCLA-PCI and the EPIC have been shown to have adequate psychometric properties. The Cronbach's alpha for the UCLA-PCI sexual function scale was 0.93, with the test–retest reliability of 0.92. The single question sexual bother scale of the UCLA-PCI demonstrated a test–retest reliability of 0.70. There is no Cronbach's alpha for a one-item scale. All items of the UCLA-PCI sexual function scale had a factor loading of >0.59 on the sexual function factor. Likewise, the EPIC scale also produced good internal consistency and test–retest reliability. The Cronbach's alpha for the sexual function scale was 0.92 and for the sexual bother scale the Cronbach's alpha was 0.84. The test–retest reliability of the sexual function and sexual bother scales were 0.90 and 0.78, and both scales demonstrated good discriminate validity with general cancer quality of life scales.

Validation of Scales in a Cancer Population

Few scales have validation information specifically in cancer patients. The EPIC and UCLA-PCI have the advantage of being validated specifically in cancer patients as these scales were developed with input from and for use in men with prostate cancer. However, the other scales mentioned in this chapter were not developed specifically for cancer patients, and as a result, many lack the needed validation in this population. Although this may seem like an insignificant aspect, specific questions in these scales may need to be phrased differently for cancer patients. For example, since men who have had a radical prostatectomy will no longer ejaculate during an orgasm, any question from the scales discussed in this chapter that ask about "ejaculation" as opposed to "orgasm" will not be appropriate for men postradical prostatectomy. As such, it is important to review the validation information of each of these scales in cancer patients. It is also important to make the distinction between scales that have been used in cancer patients, developed or validated specifically in cancer patients. Many scales have been used in assessing sexual function in cancer patients and results have been reported, however if there is no formal validation data demonstrating that the scale is appropriate for this population, the results of these studies should be judged as preliminary or exploratory, and in need of replication with an instrument validated specifically in this population.

Currently, the EPIC and the UCLA-PCI measures are the only measures with published validation data specifically in cancer patients. However, these scales limitations as noted above.

Summary and Conclusions

Self-administered questionnaires and symptom scales are an important component of assessment in both research and clinical settings. The instruments for assessing male sexual function reviewed in this chapter are for the most part, contemporary measures that have been developed according to standard psychometric principles and practices. The measurement constructs these scales and questionnaire are designed to operationalize tend to be consistent with the acknowledged elements of sexual dysfunction in men.

Despite major advantages of these measures in efficiency and quantitation of measurement, it should be noted that these scales also have their limitations. First, these measures provide information only on the current level of sexual function and cannot substitute for a detailed sexual or medical history. Furthermore, the scales and questionnaires do not provide information regarding specific etiology or comorbid medical or psychiatric conditions. These again need to be assessed in the context of a detailed medical and psychosocial history. Second, some individuals experience discomfort or embarrassment while completing questionnaires, or may experience language or comprehension difficulties. Steps should be taken to ensure privacy and confidentiality and to assist the patient with comprehension when necessary. Finally, and as noted above, the use of questionnaires or symptom scales should never be used as an alternative or substitute for direct inquiry or face-to-face clinical interaction with the patient.

As the field continues to evolve and development, new questionnaires will undoubtedly be developed and disseminated. It is incumbent on clinicians and researchers to be aware of these developments in the future.

Appendix

Medical, Psychosocial, and Sexual Assessment Questionnaire

Please answer the following questions about your overall sexual function in the past 3 months:

Erection

(a) Chronology
- When was the last time you had a satisfactory erection?
- Was the onset of your problem gradual or sudden?
- When was your last normal erection?
- Do you have morning or night-time erections?
- On a scale of 1–5 rate your rigidity during sex?
- With sexual stimulation can you initiate an erection?
- With sexual stimulation can you maintain an erection?

(b) Qualify
- Is your erectile dysfunction partner or situational specific?
- Do you lose erection before penetration, or before climax?
- Do you have to concentrate to maintain an erection?
- Is there a significant bend in your penis?
- Do you have pain with erection?
- Are there any sexual positions that are difficult for you?

Libido/Interest

- Do you still look forward to sex?
- Do you still enjoy sexual activity?
- Do you fantasize about sex?
- Do you have sexual dreams?
- Are you easily sexually aroused (turned on)?
- Do you have a strong sex drive?

Ejaculation/Orgasm/Satisfaction

- Are you able to ejaculate when you have sex?
- Are you able to ejaculate when you masturbate?
- If you have a problem with ejaculating, is it:
  - You ejaculate before you want to?
  - You ejaculate before your partner wants you to?
  - You take too long to ejaculate?
  - You feel that nothing comes out?
- Do you have pain with ejaculation?
- Do you see blood in your ejaculation?
- Do you have difficulty reaching orgasm?
- Do you find your orgasm satisfying?
- What percentage of sexual attempts are satisfactory to your partner?

Satisfaction

- Are you satisfied with your sexual function? Yes/No
  - If No, please continue:
- How long have you been dissatisfied with your sexual function?
  - 3 Months 6 Months 1 Year 2 Years Over
- What effect, if any, has your sexual problem had on your partner relationship/s?
  - Little or no effect Moderate effect big effect
- What is the most likely reason/s for your sexual problem
  - Medical illness or surgery
  - Prescription medications
  - Stress or relationship problems
  - Don't know

Previous Consultations

- Have you consulted a physician or counselor for your sexual problems?
- If yes, what type of physician or counselor have you consulted (check all that apply):
  - General practitioner
  - Urologist
  - Other specialist
  - Counselor or psychologist

- Are you taking any medication or receiving medical treatment for your sexual problem? If yes, what medical or other nonmedical treatments are you using?
- How effective has the treatment been?
  - Not at all effective
  - Somewhat effective
  - Very effective
- The problem with your sexual function concerns: (check one or more)
  - Problems with little or no interest in sex
  - Problems with erection
  - Problems ejaculating too early during sexual activity
  - Problems taking too long, or not being able to ejaculate or have orgasm
  - Problems with pain during sex
  - Problems with penile curvature during erection
  - Other
- Which problem is most bothersome
- (Circle) 1 2 3 4 5 6 7

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Chapter 23
Evaluation of the Female with Sexual Dysfunction

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Keywords Examination • laboratory testing • Hormones • Testosterone • Sonography • Vuvloscopy • Plethysmography • FMRI

Examination of the Female Cancer Patient

The evaluation of a patient with sexual issues begins with a detailed medical history. Speaking generally allows the provider to initiate a discussion on sexual function using screening questions aimed at encouraging honest discussion about potentially revealing and perhaps embarrassing information. Using open-ended questions (e.g., "Is there anything else you want to talk about?") can often be the key to broach sensitive issues. In the event the patient does not introduce the topic, more detailed questioning to assess sexual health may be required (e.g., "Are you having any problems with sexual arousal, desire, or orgasm?").

For women who complain of sexual difficulties, the relation of the concern to a cancer diagnosis or treatment is particularly relevant. Eliciting information regarding onset, duration, location, triggers, quality, characteristics, and associated symptoms of sexual pain is important because the symptoms that exist may be heightened due to her cancer. However, if sexual symptoms predated oncologic treatment, a search for other noncancer-related etiologies is warranted. Multiple conditions may induce sexual problems, thus their identification and treatment is critical in the formulation of an effective treatment plan. For example, arthritis, diabetes, and/or underlying genital infections may be associated with pain with vaginal penetration. In addition, a history of prior sexual trauma, such as rape or abuse, may require the utilization of a provider with mental or sexual health expertise.

Symptoms can also develop after cancer's onset. In particular, certain treatments (e.g., surgery, radiotherapy [RT], medications) can lead to dyspareunia. For some patients, genital pain with light touch can be encountered following radiation to the pelvis, breasts, or anogenital area. Pain with vaginal penetration can be due to prior pelvic surgery or pelvic radiation, which can shorten and/or scar the vaginal vault leading to a decrease in elasticity. In addition, chemotherapy and endocrine therapies, which cause ovarian failure, may lead to vaginal dryness due to change in the hormonal milieu affecting the hormone receptors in that area.

Beyond a detailed history, a review of medications is required. Most drug classes can affect the sexual response cycle and cause sexual problems. For example, antidepressants and antihypertensive medications can change sexual desire, arousal, and orgasm. In addition, decreases in arousal and desire can lead to decreased vaginal lubrication and vice versa, potentially contributing

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to a vicious cycle of pain and sexual issues. Health care providers should consult sexual pharmacology resources to help them identify a potentially offending agent(s). Illicit drug use, alcohol consumption, and the presence of herbal supplements are also important aspects to assess, because they can impact sexual function.

The social history should include an exploration of relationship(s) in women with cancer. Many health care providers wrongly assume that their cancer patients are involved in heterosexual relationships. However, same-sex relationships are equally impacted by cancer, and patients who are single are also impacted in the dating world. Thus, all forms and questioning should be gender and culturally neutral. A medical history should be followed by a careful physical examination. For women, this includes a thorough vaginal and pelvic examination. Detailed examination of both external and internal genitalia is important. The vulva should be inspected for ulcers, lesions, fissures, or ulcerations. If palpation of the vestibule elicits pain, the diagnosis of provoked vestibulodynia should be considered. The examination should proceed with the insertion of a finger into the vaginal vault and attention to the tone of pelvic musculature. Often penetration of the vault may elicit involuntary contraction of the muscles, which can point toward a diagnosis of vaginismus. In addition, palpation of the urethra can be performed. If tenderness is elicited, urethritis should enter into the differential.

A speculum examination provides direct visualization of the vaginal mucosa, cervical os or vaginal cuff in the case of a patient with a prior hysterectomy. It is notable that patients with vaginismus may not tolerate a normal adult-sized speculum, and the use of a pediatric speculum may become necessary. Atrophy, dryness, and fissuring of the vaginal walls can be seen and evaluated, while areas of bleeding, nodularity or abnormal appearance should be noted. Finally, a bimanual examination is important to assess the pelvis and surrounding structures. Tenderness elicited with abdominopelvic palpation may point to an extravaginal etiology, such as endometriosis, adnexal lesion(s), or gastrointestinal pathology. Tenderness involving the rectovaginal septum may point toward adhesions as an etiology. Finally, fullness at the rectovaginal septum should raise the suspicion of ascites and if unexplained, aspiration should be considered to rule out infection or malignancy.

The initial evaluation should include a consideration for laboratory work, although it is not entirely necessary. Although the majority of a diagnosis can be obtained through a thorough history and physical examination, laboratory studies are necessary to rule out or confirm the involvement of other illnesses that can contribute to sexual issues. For example, a complete blood count can rule out underlying anemia as a cause of chronic fatigue or excessive pallor. Tests of lipid profiles and fasting glucose are often indicated. Endocrinopathies that may impact on sexual responses will be discussed below

Specialized Testing for the Sexual Health Assessment

A clinical examination of the urogenital tissues revealing signs of atrophy should be followed by an acid/base test with pH paper to assess the vaginal environment. Patients with vaginitis often have elevated levels of pH. A vaginal cytological smear can be used as an adjunct to exclude other causes of vaginal complaints such as candidiasis, bacterial vaginitis, trichamoniasis or other sexually transmitted infections that can interfere with normal vaginal flora (e.g., gonorrhea, chlamydia). Finally, an office-based wet mount and whiff test are fast adjuncts that can help to exclude underlying or compounding infectious etiology.

Laboratory Testing

As previously stated, many sexual complaints can be due to underlying conditions such as anemia, thyroid disease, dyslipidemia, metabolic disorders, and hormonal imbalances. Tests to confirm these diagnoses should be based upon patients' complaint(s), history and physical examination. Commonly ordered studies to be considered include, but are not limited to: complete blood count, thyroid panel, liver function tests, fasting lipid profile, fasting prolactin, adrenal precursors (e.g., DHEA, DHEAS), and/or sex steroids

(e.g., estrone, estradiol, progesterone, testosterone, and sex hormone binding globulin). The utility of many of the laboratory tests has come into question as there is some concern regarding reliability and normative values for women across the life cycle [1]. There have been reported normative values for testosterone in women across the life cycle. Blood tests are expensive and many sexual health care experts question their utility in clinical practice. For example, testosterone testing still remains controversial because the optimal methods to measure testosterone have yet to be established [2]. Some authors do not advocate measuring testosterone since the extent to which testosterone influences the sexual response cycle also remains to be elucidated. In spite of the controversy, there do exist double-blind placebo-controlled data concerning the use of testosterone in women with hypoactive sexual desire disorder who have had bilateral oophorectomy and who have had estrogen replacement. Efficacy data reveal significant sexual health benefits in terms of sexual interest, sexual arousal, orgasmic function, and overall satisfaction.

Sonography

If a clinical examination yields suspicion of anatomical pathology, further investigation with a pelvic or transvaginal sonogram should be considered. Uterine enlargement, adnexal fullness or abdominal masses can contribute to the development of sexual complaints, thus visualization of the pelvic anatomy to rule out underlying structural pathology may be useful. Clitoral ultrasound can also be performed. It allows for the visualization of the clitoris in three planes: cross section, sagittal section, and coronal section. A well-trained ultrasonographer may be able to follow the entire clitoris by dragging the probe along one same plane. Blood vessels can also be assessed with this method.

Advanced Testing

While advanced specialized testing for female sexual problems remains experimental in many cases and is used in the clinical research setting, it can be included in the assessment when other methods do not yield the information needed to make a proper diagnosis or treatment plan. Thus, the following modalities are sometimes used to assist in this task:

Vulvoscopy

Vulvoscopy is the examination of the vulvar and surrounding structures with magnification to rule out underlying vulvar pathology. It has been gaining popularity for the assessment of dyspareunia and other introital pain syndromes. A solution of acetic acid is applied onto the vulvar tissues and then the tissues, including the labia majora and minora, are examined for underlying pathological changes. This can include cobble stoning, neovascularization, acetowhite changes or punctuations which can suggest lichen sclerosis, metaplasia, dysplasia or neoplasia. Thus, any anatomical changes of clinical suspicion that are visualized should be biopsied and sent for microscopic evaluation by an experienced dermatopathologist.

Vaginal Photoplethysmography

Photoplethysmography allows for the objective measurement of blood flow to a particular body part, such as the vagina or clitoris. Unfortunately, there is much variance in test results due to movement during measurement. Formalized assessment algorithms are being developed to combat this issue, but further research is needed in this area [3, 4].

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging consists of a series of images used primarily in research settings to measure changes in blood flow to the central nervous system during specific activities. There is growing body of data illustrating neurobiological influences of brain function and their

implications on female sexual functioning. Brain imaging studies are helpful in attempting to delineate brain structures, neuromodulators, and hormonal influences that maybe involved in the cycle of female sexual response [5].

Quantitative Sensory Testing

Quantitative sensory testing is repeatable and a valid descriptor of sensory state that are used to assess sensory function for other neuropathies. One example is biothesiometry which allows for controlled administration vibration or thermal change to the pelvic musculature and floor structure to define a sensory threshold by indicating onset of perceived sensation. Age-corrected normograms for thresholds of vibratory and thermal sensations for the clitoris and vagina have been reported.

Perinometry

Perinometry may also be helpful in the assessment of the pelvic floor musculature. A shealthed probe is placed within the vagina and then the patient is asked to contract her musculature. The rise in change of pressure is recorded and one can assess for high or low pelvic tone dysfunctions.

Psychosexual Assessment After Cancer Diagnosis and Treatment

Sexual concerns are distressing complications for couples during the diagnostic, treatment, and survivorship phases of cancer. Several physiologic and psychological factors that are specific to oncology patients can negatively impact sexual health and functioning. Body image concerns resulting from extensive surgical procedures, radiation, and/or chemotherapy may present a psychological barrier to intimacy. Partner conflicts and relationship miscommunications can be severe, debilitating, and painful. Sexual problems often have an acute onset, appearing shortly after treatment ends or when the couple attempts to resume sexual activity. Many couples report that sadness emerges when they attempt to resume sex, leaving them vulnerable to sexual dysfunction and a sense of sexual inadequacy. For patients who find that sexual expression is impossible, uncomfortable or less fulfilling, the change may threaten the integrity of their relationships, limiting this source of social support [6]. Among women who survive a breast or gynecologic malignancy, sexual dysfunction incidences range from 30 to 100%. Researchers such as Barni and Mondin suggest that changes in desire or interest are estimated to occur in 23.4–64%; arousal/lubrication concerns in 20.5–48%; orgasmic concerns in 16–36%; dyspareunia concerns in 35.4–38%, and vaginismus in 18% of survivors [7].

Surgical Considerations

Surgery alters structural anatomy and can compromise the neurovascular integrity related to sexual responsiveness. It is important to identify the connection between the site(s) of the surgery and the significance that certain body parts played prior to cancer, and to elucidate if a previous source of erotic pleasure has been altered during the surgical process. After the surgical removal or alteration of a part of the body so intrinsically linked with femininity, assessment of body image issues is critical. It is important to address her feelings about the cosmetic result of her surgery as it related to her feelings of attractiveness and desirability. Schover and colleagues examined the impact of breast surgery on sexual functioning and concluded that conservative operative procedures and/or reconstruction play only minor roles in sexual functioning. Women who undergo immediate reconstruction after mastectomy may be more likely to be satisfied with cosmetic/esthetic results and less likely to feel loss with

respect to sexual attractiveness. However, at long-term follow-up, women who had and had not undergone breast reconstruction did not differ with respect to coital frequency, ease of orgasm, or overall sexual satisfaction [8].

Radiation Therapy Considerations

Radiation therapy can cause skin damage, severe fatigue, alopecia, diarrhea, nausea, and vomiting. Many radiation-induced symptoms contribute to general malaise. They may also impact the sexual response cycle, most commonly, sexual interest or libido. Psychologically, some patients and/or their partners fear the myth of being "radioactive." Some patients experience a pervasive feeling "being tired and sick" during the entire radiation experience, such that they are unlikely to consider sex play. Partner may feel helpless during this time and unaccustomed to seeing their active partner overcome by malaise [9].

Chemotherapy Considerations

For up to 40% of women who receive chemotherapy as adjuvant cancer treatment, the onset of menopause can be an unexpected and unwelcome occurrence. Menopausal symptoms, including hot flashes, night sweats, interrupted sleep patterns, and vaginal dryness, can happen quickly and may lead to irritability and mood destabilization. Vulvar and vaginal tissue can become thin with diminished elasticity. This can contribute bothersome introital irritation during the day, and dyspareunia with attempts to self pleasure or engage in partner sex play. In addition, weight gain can be a common scenario after undergoing chemotherapy. This can contribute to an altered body image and feeling "not sexy anymore." Research by Goodwin and colleagues suggest a mean overall weight gain of 1.6 kg, with an average gain of 2.5 kg, in newly diagnosed breast cancer patients receiving chemotherapy. The exact mechanism for this common side effect is unclear [10].

Hormone Therapy Considerations

After chemotherapy and radiation therapy, many women with breast cancer are started on hormonal treatments, such as aromatase inhibitors. The purpose of this medication is to halt the conversion of circulating androgens to estrogen, thus diminishing the body's exposure to estrogen to decrease the risk of recurrence or a second breast cancer. Many women on hormonal treatments complain of exacerbation of vulvar vaginal dryness, dyspareunia, and loss of sexual desire (superseding what they experienced as a result of chemotherapy-induced menopause). Attempts at sexual activity may result in prohibitive pain and active vaginal bleeding.

Sexuality and Relationship Considerations

The literature supports that many women adapt well after they learn of a cancer diagnosis. However, there is a subset of women who report continued anxiety, depression, and concerns regarding body image, the fear of recurrence, posttraumatic stress disorder, and sexual problems even after their cancer treatment are completed. Women may link prior negative sexual experiences, past sexual behavior (e.g., promiscuity, extra marital affairs, sexually transmitted infections) to their cancer diagnosis. Women may verbalize that they feel "older" and less desirable. This distress can be significant, and affect sexual desire, arousal, satisfaction, and sexual pain, equal to or more so than lowered hormonal levels as in natural menopause.

Other Psychological Considerations

The dynamics of intimate relationships can change in several ways after cancer diagnosis and treatment. Survivors may feel an acute impact on their roles as caregivers and/or wage earners. This can directly impact family or partner dynamics,

and can create marital and financial tension. Single women who are cancer survivors may also concern about negotiating new relationship paradigms, timing of diagnosis disclosure during dating, and sexual rejection which hinders intimate relationships.

Issues of Sexuality

Assessment, diagnosis, and treatment of sexual concerns are the shared responsibility of several professionals, including the medical, surgical, oncologic, psychobehavioral, and sexual medicine care teams. Careful attention must be directed to coordinate the goals of medical and behavioral specialists and to evaluate social support networks and coping styles. A crucial step in assessing a woman's complaints of altered sexuality and distress is to identify her "baseline or normal" sexual patterns. This includes desire for self-stimulation, incidence of erotic night-time dreams, spontaneous sexual thoughts during the day, and desire for sex with her partner. Despite the common complaint of lack of sexual desire, survivors often express a "need to be desired" by their partner. Feeling desired helps to maintain sexual self-esteem and facilitate the posttreatment return to intimacy. Most women resume some form of sexual behavior after treatment, even if it is uncomfortable, less arousing or if they are not sexually motivated to do so. This may be as a result of fear of abandonment or as a means of maintaining much needed emotional support and connection through a difficult time. Regardless of the motivation, women frequently look to their medical and mental health care providers to assist them in the task of regaining desire and sexual comfort.

Conclusions

The diagnosis of cancer and the subsequent treatment can profoundly affect the way in which a woman functions psychologically and physically as a sexual being. Interventions to improve sexual desire and overall sexual life after cancer include: comprehensive psychosexual assessment, education, counseling, pharmaceuticals, and behavioral strategies. The ultimate goal of these therapies is to maximize sexual desire and comfort while minimizing patient risk. These results can be better understanding, negotiation of expectations, heightened desire, diminished pain, and rekindling of the loving spark between a cancer survivor and her partner.

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Chapter 24
Evaluation of Male Sexual Dysfunction

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Keywords Examination • Questionnaires • Testosterone • Sonography • Duplex Doppler ultrasound • Office injection

Male Sexual Dysfunctions and Cancer Survivors

The management of male sexual dysfunction and specifically erectile dysfunction (ED) has seen major changes in each decade since the 1970s thanks to the discovery that a papaverine injection could produce erection, the NIH Consensus Statement which defined ED in 1992, advances in minimally invasive diagnostics, and the development of orally effective erectogenic class of drugs, the phosphodiesterase type-5 inhibitors (PDE-5 Inhs). As a result the health care professionals most frequently consulted have also changed from the psychologists to the urologists and now to the primary care clinicians (PCC), who are the most frequent prescribers of the PDE-5 Inhs. The evaluation and management of male sexual dysfunctions may come under the purview of many different providers besides PCCs including cardiology, urology, endocrinology, psychiatry, psychology, and neurology and allied health care professionals. Unfortunately, many providers are reluctant to ask patients about sexual health. Identification of sexual dysfunctions has been hampered by traditional and difficult to overcome barriers: embarrassment, lack of expertise in sexual history taking, concerns about the safety of ED treatments, and lack of time. Studies have documented both patient and physician misconceptions [1]. A public opinion poll of 500 U.S. adults suggested that 85% of patients would be willing to talk with their physicians if they had a sexual problem, but 71% did not think their physicians would be responsive or helpful; 68% were concerned that their physicians would be embarrassed [2]. In the United States, 5-year overall cancer survival rates for patients diagnosed between 1996 and 2003 were 65%, with an estimated 11.1 million cancer survivors [3]. The Institute of Medicine has addressed posttreatment needs for cancer survivors. The IOM in its report *From Cancer Patient to Cancer Survivor: Lost in Transition* emphasized both quality of life issues and the role PCCs must play in the long-term care of survivors [4]. Future care plans for cancer survivors must directly address sexual dysfunctions. There are long-term physical and psychological factors that significantly impact sexual function in cancer survivors. For the male patient, these include ED, ejaculatory dysfunction, loss of desire/arousal, infertility, pain, changes in body image, depression, and anxiety. Numerous studies have documented sexual dysfunctions in cancer survivors. Twenty to 30% of breast cancer survivors, 80% of prostate cancer survivors, 37% of Hodgkin's survivors, and 58% of head and neck cancer survivors describe sexual difficulties as a result of their

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cancer therapies [5–8]. Park et al. [9] surveyed physicians associated with a North American medical school with respect to sexual function in cancer survivors. Of the 277 respondents, 88% acknowledged that they were "somewhat/very" comfortable providing care to adult cancer survivors; only 46% reported that they were "somewhat/very" likely to initiate conversation about sexual dysfunction, and 62% of internists "never/rarely" addressed sexual dysfunction in cancer survivors. In this study unlike others, "lack of time" was not considered a barrier by respondents, but an internist's perceived lack of preparation and training were associated with avoiding conversations about sexual dysfunctions. Given the significant prevalence of sexual dysfunctions among cancer survivors, the severity of those dysfunctions and the lack of specific training in sexual health – the ultimate resource for cancer survivors seeking assessment and care may reside in the office of specialists and in cancer centers. Huyghe et al. [10] conducted a needs assessment survey to justify establishing a reproductive health clinic at UT M.D. Anderson Cancer Center in Houston, Texas. They surveyed patients who had received therapies for cancer at M.D. Anderson (800 patients); response rates were 29% for men and 26% for women. They noted that most sexual problems were related to cancer treatments; in men 49% reported "having trouble getting and or keeping a firm erection" as a new problem after cancer, with only 12% reporting ED "before and after cancer." Orgasmic or ejaculatory dysfunction (have trouble reaching orgasm or climax is very weak) was reported by 30% of men as a new problem after cancer and in 9% as a problem before and after cancer. At time of cancer diagnosis 80% of men were sexually active (by retrospective recall) and 60% remained active at the time of survey. There were a variety of reasons cited for becoming sexually inactive highlighting the complexities of sexual dysfunctions and the interplay of patient and partner factors: 27% of males cited lack of a sexual partner vs. 51% of female cancer survivors. Women were more likely to have lost desire than men (34% vs. 13%). Women were more likely to describe feeling unattractive than men (28% vs. 16%). ED or ill health (64%) was the primary reasons for men becoming sexually inactive. At least a third of patients under age 50 would have liked a consultation for fertility before initiating cancer therapies. The M.D. Anderson group has rightly concluded that reproductive and sexual health needs are largely unmet for cancer survivors and that embedding that expertise within cancer centers would provide education, research, and best practice standards for cancer patients.

Changing Paradigms in the Evaluation of Erectile Dysfunction

In the era when the treatment of ED consisted of the penile prosthesis or psychotherapy, nocturnal penile tumescence (NPT) monitoring in a sleep laboratory and the penile/brachial artery pressure indices were the most commonly utilized tests for differential diagnosis; the single goal was to make certain that a penile prosthesis would not be wrongly implanted in the patient with "psychogenic" ED. The era of penile injection brought about refinements in penile testing such as duplex ultrasonography and pharmacologic cavernosometry and cavernosography. The RigiScan® (Timm Medical Technologies, Inc.), a computerized device for monitoring penile tumescence and rigidity, was developed for outpatient testing to rule out psychogenic ED and remains a standard in medico-legal investigations. The widespread use and abuse of these tests led to the introduction of a goal-directed approach, devised to conserve health care dollars and minimize patient morbidity from excessive testing [11]. Evaluation was based on a thorough medical and psychosexual history and a focused physical examination with limited laboratory testing. The goal-directed approach emphasized the role of patient education, physician/patient dialog, and the need to consider the patient's preferences in making diagnostic and treatment decisions; at this time urologists were the main health care providers in ED.

The First International Consultation on Erectile Dysfunction, convened in Paris in July of 1999, and was co-sponsored by the World Health Organization, International Consultation

on Urological Diseases, American Urological Association (AUA), and Société Internationale d'Urologie. Recommendations, as with each subsequent consultation, were peer reviewed through open public presentation, debate, and commentary. *ED was redefined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance* [12]. The evaluation and treatment algorithms were similar to those in the goal-directed approach. The consultants emphasized that ED is a symptom of many underlying medical conditions and that treatment requires the direct involvement of a physician. Four years later, the Second International Consultation on Sexual Medicine (ICSM) made additional recommendations. The approach to the evaluation and management of ED was restructured on the basis of patient-centered and evidence-based principles [13]. The dominant model in medicine has been the "disease-centered," in this model of care the patient has a passive role. In contrast, patient-centered approach consciously adopts the patient's perspective and respects his or her ideas, expectations, and values, as "the physician tries to enter the patient's world, to see the illness through the patient's eyes" [14]. Evidence-based evaluation implies that physicians should be guided in their decision making by the findings from controlled research, which heavily weights recommendations based on randomized, double-blind, placebo-controlled clinical trials. Patients vary in their preference for information and involvement in the decision-making process, and for this reason the ICSM recommended the management of male sexual dysfunctions be flexible and respectful of patient/partner needs. Strong consideration should be given to the evidence basis for diagnostic evaluations. Costly or invasive procedures should not be recommended in the absence of supporting evidence of their applicability. The algorithms recommended by the 2004 ICSM for the diagnosis and treatment of ED are shown in Fig. 24.1 [15].

At the most recent ICSM (Paris 2009) a unified management approach to evaluating and treating sexual problems in both men and women was adopted [16]. The recommendations for clinical evaluation of men and women with sexual dysfunctions are summarized in a five-step algorithm (ISCM-5), Fig. 24.2. The first step includes mandatory medical, sexual, and psychosocial history. A focused physical examination is highly recommended. Step 2 is interpretation of findings and the determination of the need for specialized testing. The ICSM recommends that applied diagnostic procedures have both supporting evidence for their utility in a specific case of sexual dysfunction and be held to a set of defined goals (Table 24.1). Step 3 encompasses

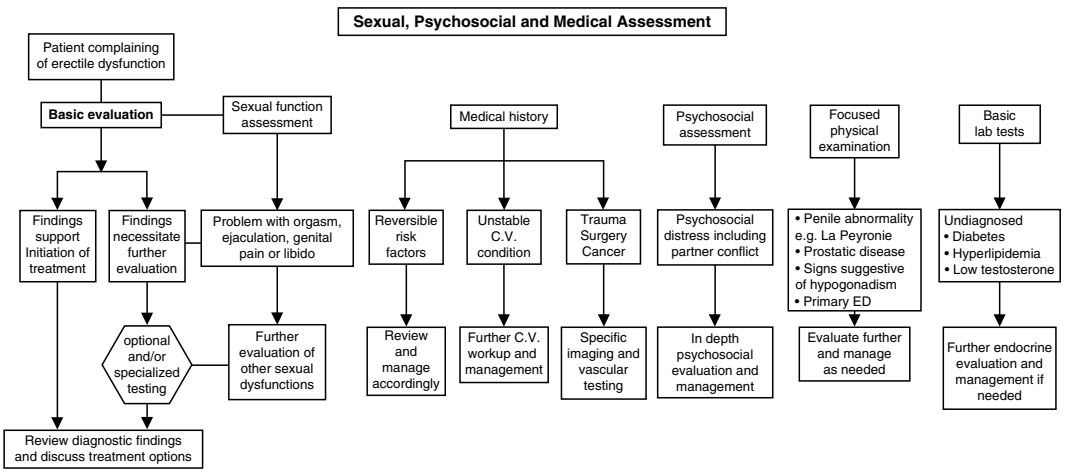

Fig. 24.1 International Consultation on Sexual Medicine (ICSM) algorithm for the evaluation of male sexual dysfunctions (modified from Rosen et al. [13])

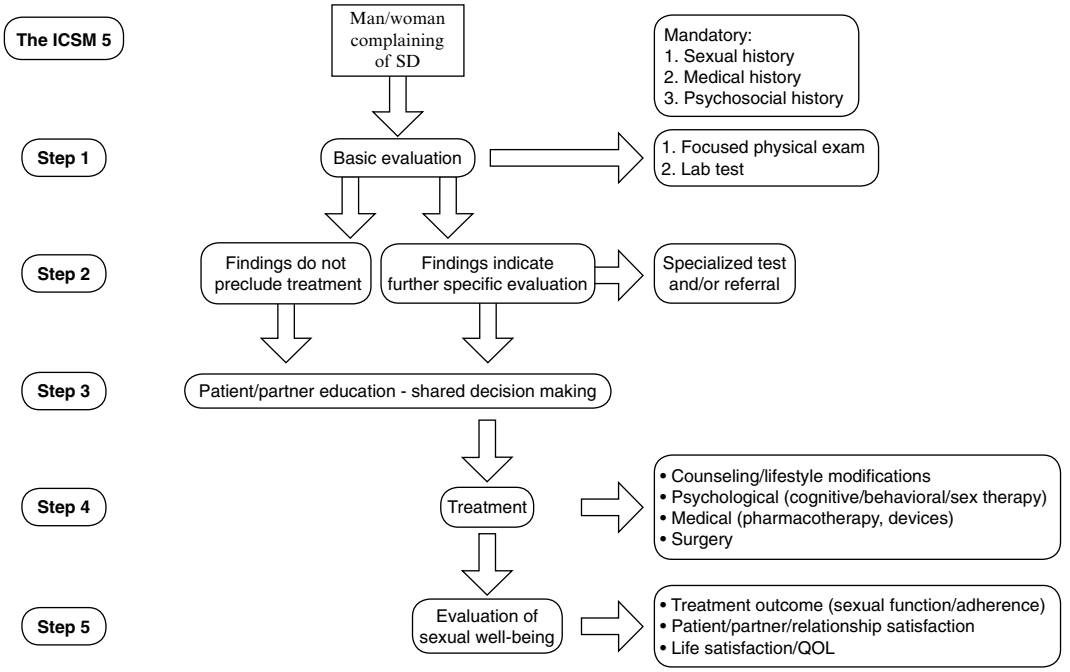

Fig. 24.2 ICSM-5 stepwise diagnostic and treatment algorithm for sexual dysfunctions in men and women [16]

Table 24.1 The goals of diagnostic procedures

Increase certainty about presence/absence of disease
Define disease severity
Monitor clinical course
Assess prognosis, risk, or stage within a diagnosis
Plan treatment

Adapted from [16]

Table 24.2 Brief Sexual Symptom Checklist for Men (BSSC-M)

1.	Are you satisfied with your sexual function? Yes/No
2.	How long have you been dissatisfied with your sexual function?
3a.	The problem(s) with your sexual function is: (mark one or more)
	1. Problem with little or no interest in sex
	2. Problem with erection
	3. Problem ejaculating too early during sexual activity
	4. Problem taking too long, or not being able to ejaculate or have orgasm
	5. Problem with pain during sex
	6. Problem with penile curvature during erection
	7. Other
3b.	Which problem is most bothersome?
4.	Would you like to talk about it with your doctor? Yes/No

Open resource International Consultation on Sexual Medicine 2009 in [16]

patient/partner education as sexual dysfunctions are often confused. At this step the identification and distinction of biological findings are used to determine the degree to which the dysfunction is deemed organic and these include anatomic (postsurgical or trauma), vascular, neurogenic, hormonal, and drug related. Step 4 is the development of a mutually agreed upon course of treatment(s). Step 5 calls for follow-up. A successful outcome requires both restoration of sexual function and improvement in patient's sense of well-being. To identify sexual problems in both men and women, the 2009 ICSM developed two sets of screening checklists: the Brief Sexual Symptom Checklist for Men (BSSC-M) and the Women (BSSC-W), Table 24.2. The screeners are offered as an adjunction to the sexual history and have not been validated. Nonetheless, they are brief and should identify patients with sexual problems presenting to primary care offices.

Questionnaires and Sexual Function Symptom Scores

Prior to the 1998 many male sexual function profiles and ED questionnaires were developed [17–20]. The aim of these questionnaires was to differentiate psychogenic from organic ED. More recently, a variety of self-report measures assessing the levels of male sexual function or dysfunction have been described. Self-administered questionnaires (SAQs) have seen their greatest use in clinical trials. SAQs provide quantifiable efficacy endpoints for drug trials; they quantify sexual interest, performance, and satisfaction. Those most commonly referenced include the International Index of Erectile Function (IIEF) by Rosen et al. [21], the Brief Male Sexual Function Inventory (BMSFI) by O'Leary et al. [22], and the Erectile Dysfunction Inventory for Treatment Satisfaction (EDITS) by Althof et al. [23]. Other self-report measures include the Derogatis Sexual Function Inventory (245 items) [24] and the Center for Marital and Sexual Health Questionnaire (18 items) [25].

The BMSFI instrument covers sexual drive (2 items), erection (3 items), ejaculation (2 items), perceptions of problems in each area (3 items), and overall satisfaction (1 item). The EDITS questionnaire supplies efficacy endpoints that permit drug companies to tabulate pre- and posttreatment responses in ways that, although subjectively based, provide quantifiable data for U.S. Food and Drug Administration (FDA) reviews. The IIEF is the most widely used SAQ, and it is statistically validated in many languages. It is composed of 15 items which address and quantify five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction [21]. In the hope of providing physicians with a "checklist" on erectile function that could be used in an office setting, an abridged 5-item version of the IIEF-15 was developed, the Sexual Health Inventory for Men (SHIM) in which 4 items are taken from the erectile function domain [26]. The fifth item addresses sexual intercourse satisfaction; it was chosen to reflect the central element in the NIH Consensus Panel [27] definition of ED, which ties erectile function to satisfaction: "maintain erection of sufficient rigidity and duration to permit satisfactory sexual performance." Both the IIEF and the SHIM use a five-point Likert-type scale. The most important difference between the IIEF-15 and the SHIM is that the latter asks patients to self-assess erectile function and satisfaction over the past 6 months, a more clinically relevant time frame than 4 weeks (IIEF). ED severity is classified into five categories based on a SHIM score of 1–25: severe (5–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25), Table 24.3. These contemporary questionnaires measure erectile quality and successful coitus but do a poor job assessing psychosocial domains of ED. The Self-Esteem And Relationship questionnaire (SEAR) addresses emotional well-being (self-esteem, sexual relationship satisfaction, sexual satisfaction) of the patient impacted by ED [28].

Table 24.3 Sexual Health Inventory for Men (SHIM)

How do you rate your confidence that you could get and keep an erection?
When you had erection with sexual stimulation, how often were your erections hard enough for penetration?
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
When you attempted sexual intercourse, how often was it satisfactory for you?

Adapted from [26]

Questionnaires and Cancer Survivors

Research on cancer survivors and sexual function outcomes would be well served by greater reliance on structured, validated self-report measures. Cross sectional and longitudinal studies of colorectal cancer survivors have noted that the

overall health-related quality of life after treatment is good, but at the same time acknowledged both men and women report declines in sexual activity and significantly worsening sexual function. Donovan et al. [29] in a review of sexual function in men and women treated for colorectal cancer concluded that "published studies investigating sexual dysfunction after colorectal cancer treatment generally have been limited conceptually and methodologically." An estimated 60,000 men undergo radical prostatectomy each year in the United States [30]. ED following prostatectomy is well studied and has been linked to age, coronary artery disease, diabetes mellitus, quality of preoperative erections, frequency of intercourse, hypertension, neurovascular bundle preservation, and surgeon experience. Even this extensive literature is encumbered by flaws in methodology [31]. Walz et al. [32] conducted multinational study using the IIEF to assess baseline erectile function in 1,134 men undergoing free prostate cancer screening. They found that one in two men participating in prostate cancer awareness events was affected by ED [32]. The high prevalence of ED in this prostate cancer screening cohort suggests the importance of pretreatment baseline sexual function assessments and the specific role for validated self-report measures.

From a practical standpoint, sexual self-report measures are noninvasive, inexpensive, require limited expertise, and provide an organized adjunct to the clinical interview. These measures by their nature rely on self-assessment. Self-report measures can contribute to our appreciation of the epidemiology and impact of ED, but they do not enhance our understanding of pathophysiology of ED. Blander et al. [33] demonstrated that SAQs do not differentiate among the various causes of ED (arterial, venous, or mixed vascular), and evidence-based assessments (diagnostic tests) still have a role in evaluating complex patients. In clinical practice, a good case history, preferably taken from both partners, physical examination, and proper laboratory studies still form the cornerstone in the evaluation of MSD.

Medical, Sexual, and Psychosocial History

Initial assessment of a male sexual problem includes a detailed medical, sexual, and psychosocial history. Checklists may be helpful in the recognition and initial evaluation of a sexual problem, but they should not be substituted for a detailed sexual history. The physician should always be attentive to both the intrapersonal and interpersonal aspects of sexual dysfunction. Careful attention should be paid to both the style and the content of the initial evaluation. Overall, the clinician should maintain an attitude of comfort and flexibility throughout the evaluation process [13].

Medical History

The goals of medical history taking are (1) to evaluate the potential role of underlying medical conditions and comorbidities, (2) to differentiate between potential organic and psychogenic causes, and (3) to assess the potential role of medication (some may cause or contribute to the patient's sexual difficulties; some, like nitrates, may be contraindications for specific treatments, like phosphodiesterase inhibitors). ED is a disorder with multiple comorbidities and risk factors. The degree of ED strongly correlates with the severity of existing cardiovascular disease. New clinical evidence suggests that ED is even a harbinger of symptomatic coronary heart disease, with several years lead time. Therefore, missing an opportunity to identify and treat ED likely means missing the opportunity to prevent significant cardiovascular morbidity for male patients [34–36].

The examiner should begin with a medical history, explaining the risk factors for ED, before addressing sexual problems, and the patients will feel more at ease talking about cardiovascular health and providing a list of medications. Medical history may reveal causes or comorbidities such as cardiovascular

disease (hypertension, atherosclerosis, or hyperlipidemia), diabetes mellitus, and depression (Table 24.4). New research suggests that ED is prevalent among men with the metabolic syndrome [37], which includes the presence of at least three of the following findings: waist circumference greater than 102 cm, triglycerides >150 mg/L (1.69 mmol/L), HDL cholesterol less than 40 mg/L (1.04 mmol/L), blood pressure greater than 130/85 mmHg, and fasting glucose greater than 110 mg/L (6.1 mmol/L). Additional risk factors include smoking, pelvic/perineal/penile trauma, neurologic disease, endocrinopathy, prescription/recreational drug use, and alcohol abuse. Related dysfunctions may be overlapping or simply confused by the patient who claims ED (e.g., premature ejaculation, Peyronie's disease, difficulty reaching climax, lack of sexual interest, and psychosexual relationship problems). Taking a history of cancer therapies (colo-rectal surgery, prostatectomy, cystectomy, pelvic radiation, partial penectomy, pelvic radiotherapy, brachytherapy, and chemotherapy) will often yield significant insights. Radical pelvic surgery (e.g., prostatectomy, abdominoperineal resection) is well known to be associated with ED [38, 39].

Table 24.4 Comorbidities and risk factors for erectile dysfunction

Age >50 years
Hypertension
Hyperlipidemia
Diabetes mellitus
Depression
Cigarette smoking
Hypogonadism
Metabolic syndrome (at least three of the following)
Abdominal obesity
Elevated triglycerides
Reduced high density lipoprotein cholesterol
High blood pressure
High fasting glucose
Lower urinary tract symptoms (secondary to benign prostatic hypertrophy)

*Emerging risk factors are inflammatory biomarkers, psychological stress, and recreational drug use

Sexual History

A comprehensive sexual history is essential to confirm the diagnosis as well as to evaluate the patient's overall sexual function. Ideally, the interview should be conducted face to face. Attention should be paid to the setting, in particular the need for privacy and confidentiality, and the clinician should make every effort to ensure the patient's trust, comfort, and openness. The objective is to elicit the sexual history in a nonthreatening and permissive manner; initiating such a dialog facilitates patient candor. The doctor and patient should have the opportunity to discuss matters privately, but interviewing the partner for corroboration of the history and assessment of mutual goals is no less important. If the patient presents with his partner, this goal is easily achieved; the physician may take the opportunity of the physical examination to inquire in private whether the patient has other specific concerns he was reluctant to share in the presence of his partner.

Sexual history taking should be aimed at ascertaining the severity, onset, and duration of the problem. Critical elements are alterations in erectile function, sexual desire, ejaculation, orgasm, presence of genital pain, and lifestyle factors (sexual orientation, presence of spouse or partner, and quality of the relationship). It is necessary to determine whether the presenting complaint is ED or ejaculatory dysfunction especially since both are common complaints of men aged 50–80, as demonstrated by Rosen et al. [40] in the Multinational Study of the Aging Male (MSAM-7). The MSAM-7 study also demonstrated that lower urinary tract symptom severity was statistically and positively associated with ED. Independent of age, the severity of LUTS was associated with greater likelihood and severity of ED. The interviewer should also obtain information about the presence and quality of noncoital erections (masturbatory, nocturnal, or morning). If the patient complains of decreased arousal, one should attempt to determine if this occurred before or after the development of ED. After the interview the clinician should have a clear

concept of the primary sexual problem, and which aspects of the sexual response cycle (desire, erection, ejaculation, or orgasm) may be involved [13].

Psychosexual History for the Nonmental Health Professional

A psychosocial assessment is essential. The nonmental health professional can initiate the evaluation of psychosexual dysfunctions by following some simple principles. Given the interpersonal context of sexual problems, the physician should carefully assess the patient's past and present relationships. Sexual dysfunction may affect the patient's self-esteem and coping ability, as well as social relationships. The physician should not assume that every patient is involved in a monogamous, heterosexual relationship. Relationship problems are invariably associated with sexual dysfunctions [41, 42]. Hartmann [43] suggests that the psychosexual interview be structured: (1) current sexual problem and its history, (2) deeper causes of sexual dysfunction, (3) the relationship, and (4) psychiatric symptoms. Immediate causes that should be brought out by the interviewer include fear of failure and performance anxiety. Widowers, typically confront both complex psychological issues and organic para-aging phenomena. On the one hand, there is a host of anxiety provoking issues: dating, new partners, unresolved mourning/guilt, and missing/longing for their lifelong partner. On the other hand, these men are because of their age, at risk for ED. They may need for more intense stimulation to erect and achieve climax. Remote and "deeper" causes of psychogenic ED include unresolved parental attachments, sexual identity, sexual trauma, and cultural–religious issues [44, 45] and these will require specialized referral. The clinician must address the patient's expectations. Often unrealistic expectations are placed on ED treatments: restoration of erections will increase the frequency of intercourse, make partners more interested in sex, cure marital problems, or make a person more loveable.

Just this one dialog with the male patient may reveal anxieties, unrealistic expectations, depression, marital strife, or partner problems – any of one of which is indication for specialized referral to a mental health professional. In addition, questions should be asked about other relevant aspects of the patient's life, including occupational status, financial security, family life, and social support. In many cases, organic and psychogenic factors often coexist, particularly in individuals or couples with long-standing or chronic sexual dysfunction. Table 24.5 highlights aspects of the patient's history that may be useful in differentiating between organic and psychologic ED [46]. The concluding observation to make is that partners are not always present when the male patient presents for evaluation. Perelman [47] has strongly advocated for "partner cooperation" to one of the goals for therapy, not "partner attendance." Regardless of whether the partner attends the office visit, the likelihood of treatment success is greatest for men who have cooperative partners. The final step of the ICSM-5 algorithm calls for evaluation of sexual well-being after

Table 24.5 Differentiating between psychogenic and organic ED

Characteristic	Organic	Psychogenic
Onset	Gradual[a]	Acute
Circumstances	Global	Situational
Course	Constant	Varying
Noncoital erection	Poor	Rigid
Organic risk factors	Present	Variable
Psychosexual problem	Secondary	Long history
Partner problem	Secondary	At onset
Anxiety and fear	Secondary	Primary

[a]In the male cancer survivor or trauma victim, the onset of organic sexual dysfunction may be acute. The sexual history should focus on prediagnosis and posttherapy sexual function (cancer surgery, radiotherapy, or chemotherapy)

Modified from Hengeveld [46]

treatment, and this requires an assessment of relationship satisfaction to define the outcome of interventions.

Physical Examination

The physical examination is an essential component of sexual dysfunction evaluation, although in many cases of male sexual dysfunction it will not specify the etiology. The ICSM 2009 five-step algorithm highly recommends physical examination of men and women with sexual complaints. Especially for the male patient complaining of ED, the examination may be revealing (e.g., decreased peripheral pulses, penile plaques, phimosis, testicular atrophy, suspicion of prostate cancer). For the male cancer survivor, the examination may document treatment-specific findings (e.g., abdominal stoma, radiation changes to skin of the genitalia, incontinence, penile fibrosis, absent testicles, absent rectum, loss of hair, gynecomastia). The exam should include a general screening for medical risk factors or comorbidities, such as body habitus and blood pressure. Depending on the details of the history, examination may require greater focus on assessment of the cardiovascular, neurologic, and genital systems. For the adolescent cancer survivor, this means particular focus on the genitalia and secondary sex characteristics. Evaluation of sexual and genital development may occasionally reveal an obvious cause (e.g., hypospadius, micropenis, chordee, Peyronie's plaque). Patients with certain genetic syndromes, such as Kallmann's or Klinefelter's, may present with obvious physical signs of hypogonadism or a distinctive body habitus. Patients with degenerative neurologic disorders or diabetes may show evidence of peripheral neuropathy. Testing for genital and perineal sensation and the bulbocavernosus reflex (BCR) is useful in assessing possible neurogenic ED and ejaculatory dysfunctions [13]. Seftel [48] notes that the physical examination should include a general screening to corroborate the sexual history and recommends a checklist which can be followed by both PCCs and specialists (Table 24.6).

Table 24.6 Physical examination checklist for MSD

Body habitus
Waist circumference
Suprapubic fat pad (buried penis)
Gynecomastia
Hair distribution
Cardiovascular
Blood pressure, heart rate
Femoral and peripheral pulses
Edema: lower extremity or genital
Genital area
Penis: size, fibrosis, plaques, warts
Glans/Foreskin: balanitis, phimosis, skin lesions
Testicles: presence, size, consistency, tenderness
Hydrocele/Spermatocele/Varicocele
Inguinal hernia
Rectum: anal tone, stricture, hemorrhoids, warts, bleeding
Prostate: size, consistency, tenderness, induration
Lower extremity strength and coordination

Laboratory Testing

Recommended laboratory tests for men with sexual problems typically include fasting glucose, fasting lipids, and hormonal profiles. These tests are performed primarily to identify or confirm specific causes (e.g., hypogonadism) or to assess the role of medical comorbidities (e.g., diabetes, hyperlipidemia), Table 24.7. The laboratory investigation may identify treatable conditions or previously undetected medical illnesses that may contribute directly to ED. Additional laboratory tests (e.g., thyroid function) may be performed at the discretion of the physician based on the medical history and clinician's judgment. Prostate-specific antigen (PSA) may be measured in patients (as per physician's screening protocol); however, the age at which screening with PSA should begin and end remains controversial. The AUA and the AUA

Table 24.7 Laboratory testing to be considered in MSD

Testosterone assay
Fasting glucose
HbA1c (for men with diabetes mellitus)
Lipid profile
Prostate-specific antigen (PSA) (as per American Urological Association (AUA) guidelines)
For all men considering testosterone treatment

Foundation believe that early detection of and risk assessment for prostate cancer should be offered to asymptomatic men 40 years of age or older who have a life expectancy of at least 10 years. Men who wish to be screened should have both a PSA test and a digital rectal exam (DRE) (see http://www.auanet.org Policy Statements: Early Detection of Prostate Cancer, April 2009). Most guidelines concur that PSA should be measured in men at risk (digital rectal abnormality, family history of prostate cancer). From the standpoint of ED/MSD management, a PSA should be obtained if testosterone replacement therapy is anticipated [13].

Hormonal Evaluation

In male sexual dysfunctions, most endocrinopathies (e.g., complaints of low libido, lack of arousal, arousal disorder, difficulty reaching climax, loss of morning erections) center around androgen levels, specifically testosterone (T). Historically, hypogonadism as a cause of ED was thought to be rare, but recent data support a significant increase in hypogonadism with aging. The interrelationships among hypogonadism, depression, and ED are now recognized. Recent investigations linking low T to the risks of metabolic syndrome and diabetes mellitus have compelled international and European guidelines to recommend measuring serum T in men with diabetes, obesity, and symptoms that suggest low T [49]. Each of these points underscores the importance of an endocrine evaluation. The decrease or absence of hormonal secretion from the gonads in men is traditionally referred to as hypogonadism. More contemporary designations attempt to acknowledge aging as the primary cause of declining androgens: androgen deficiency of the aging male (ADAM), partial androgen deficiency of the aging male (PADAM), hypoandrogenism, symptomatic late-onset hypogonadism (SLOH). "Andropause" is a popular term but regarded by most specialists as inappropriate for the male condition.

Testosterone is normally produced in men at a rate of 4–8 mg/day (~0.24 mol/day), occurring in a pulsatile manner [50]. The diurnal pattern has a peak level in the early morning and a nadir in the evening. Testosterone can be converted to dihydrotestosterone (DHT) within androgen target cells (skin, liver, prostate, and other organs) that contain the enzyme 5α-reductase [51]. Testosterone is also metabolized to estradiol by the aromatase enzyme complex in brain, fat, liver, and the testes [51]. In normal men, 2% of testosterone is unbound (free testosterone) and 30% is bound to sex hormone–binding globulin (SHBG) [52,53]. The remainder is bound with lower affinity to albumin and other serum proteins. Free testosterone and albumin-bound portions make up the bioavailable testosterone fraction. The relative concentrations of these carrier proteins (SHBG and albumin) modulate androgen bioavailability. The synthesis of SHBG by the liver is downregulated by androgens and upregulated by estrogens. SHBG has a higher affinity for testosterone than for estradiol, and changes in SHBG concentration change or amplify the hormonal milieu. Elevated estrogens, thyroid hormone, and aging each variably increase serum SHBG levels and decrease bioavailable testosterone. Exogenous androgens, growth hormone, and obesity depress SHBG levels and increase the free testosterone levels.

Serum Evaluations and the Choice of an Assay: The most biologically relevant measure of T should be the unbound or free fraction, but commercial assays for free T are inconsistent and have been considered invalid by some investigators. The best indicator of bioavailable T is free T + albumin-bound T. A formula can be found on the Web site of the International Society for the Study for the Aging Male (http://www.issam.ch). Once the values of total testosterone

and SHBG are entered, the calculator automatically indicates the bioavailable testosterone. In men with serious liver disease or hypoalbuminemia, it may be appropriate to enter the serum albumin value for the calculation (http://www.issam.ch/freetesto.htm).

Serum Testosterone Range: Wide individual variability in the threshold of serum testosterone below which impairment of androgen-dependent processes becomes evident makes both diagnosis and treatment difficult. *The 2007 Endocrine Society position paper characterizes a serum total T <200 ng/dL (6.9 nmol/L) as diagnostic of hypogonadism; 200–320 ng/dL (11.1 nmol/L) as equivocal, and > 320 ng/dL (11.1 nmol/L) as normal* [54]. Circadian rhythm of testosterone levels should be considered in measuring serum testosterone; blood should be drawn between 8:00 and 11:00 am. For screening, a total testosterone determination is usually adequate. If the testosterone level is below or at the low limit of normal, it should be confirmed with a second determination together with assessment of luteinizing hormone (LH) and prolactin. In an older man, the diagnostic lines are not as clearly defined since the amplitude of diurnal variation is less, strategically this means less variation between morning and early afternoon levels. One or more of the following serum laboratory values may be required to diagnose hormone deficiencies: (1) total/free/bioavailable testosterone, (2) SHBG, (3) LH, and (4) follicle-stimulating hormone (FSH). *Hypogonadism is defined as "primary" – testicular when T is low and LH and FSH are high. Hypogonadism is defined as "secondary" – pituitary/hypothalamic when T is low and LH and FSH are low or normal*.

Hyperprolactinemia: The very low prevalence of hyperprolactinemia does not justify routine screening of prolactin in men with ED [55, 56]. It has been recommended to determine prolactin only in men with low serum testosterone or low sexual desire. Buvat and Lemaire [57] showed that serum prolactin levels drawn only in ED patients with low T levels would have missed 6/12 hyperprolactinemias and 3/7 pituitary tumors. In a study by Johri et al. [58], determining serum prolactin only in ED patients with a score less than 3 in the Sexual Desire Domain of the IIEF would have missed 50% of the cases of hyperprolactinemia. Buvat [59] has recommended that, by restricting the serum prolactin determination to men with low sexual desire, gynecomastia, or serum testosterone less than 4 ng/mL, more than half of the laboratory determinations need not have been done in their ED patients; one of ten marked cases of hyperprolactinemia would have been missed, but none of the six pituitary tumors. Finally, any man with a confirmed diagnosis of hyperprolactinemia (non-drug-induced, not stress induced and not secondary to renal insufficiency) should undergo investigation of the hypothalamic-pituitary area (with magnetic resonance imaging) to rule out the presence of a tumor responsible for the hyperprolactinemia.

Cancer Survivors and Gonadal Status

A high incidence of hypogonadism has been reported in young cancer survivors age 25–45 years; patients were treated for nonhormone-dependent cancers: lymphoma, germ cell, leukemia, gastrointestinal, brain, sarcoma, and skin [60]. Others have described fatigue, depression, and anxiety specifically among testicular cancer survivors [61]. Testicular germ cell cancer is a common malignancy in men between the ages of 20 and 40 years. Survivors with gonadal dysfunction have a low quality of life [62]. For survivors treated with retroperitoneal lymph node dissection, there is a high risk of ejaculatory dysfunction, and for those men treated with radiotherapy, ED has been reported [63]. Ebberhard et al. [64] compared 129 testicular germ cell cancer patients, 3–5 years posttreatment to an age-matched cohort of 916 men (age 18–54 years) each of whom had completed an epidemiological study on sexual life in Sweden. They noted that survivors of testicular cancer were more likely to report both manifest low sexual desire (4% vs. 2%) and manifest ED (12% vs. 3%) compared to controls. Sexual dysfunctions are also evident in young men treated

for other malignancies. A recent cross-sectional observation study of 176 male cancer survivors and 213 male controls age 25–45 was undertaken at the Clinical Oncology Unit of University of Sheffield, United Kingdom [65]. The investigators noted that young male cancer survivors report marked impairment of quality of life, energy, and quality of sexual functioning; each of which was exacerbated in survivors with androgen deficiency. They concluded that young cancer survivors appeared less strong, energetic, physically fit, and have suboptimal function compared to age-matched controls. Interestingly, psychological distress was not elevated, self-esteem was normal, and relationships were not impaired compared to controls. *These investigations argue both for testosterone screening in cancer survivors and reflect the complex relationship between testosterone health and sexual well-being.*

Review of Findings

Results of the initial evaluation should be reviewed with the patient, and partner if available, before initiating therapy or recommending advanced diagnostics (*ICSM-5, step four*). This review is an opportunity to educate patients on the anatomy and physiology of sexual function, summarize findings from the history/physical examination, and define for the patient his sexual dysfunction. Modifiable risk factors (e.g., stress, marital conflict, cigarette smoking, alcohol/drug abuse, obesity) should be addressed. The potential role of prescription drugs, including psychotropic and cardiovascular agents, or other iatrogenic causes of sexual dysfunction (e.g., cancer therapies) should be discussed.

Specialist Consultation and Referral

With the advent of effective oral treatment for ED, PCCs currently manage the majority of cases of male sexual dysfunction. However, either the patient or PCC may wish to consult a specialist for further diagnostic evaluation (Table 24.8). In accordance with the principles of the ICSM 2009 [16], patients (and partners where possible) should be included in the decision making. Patients should be fully informed of the cost and potential risks of additional procedures, as well as the potential benefits and evidence supporting their use. Generally, accepted indications for specialized evaluation are failure of first-line therapies, Peyronie's disease, primary ED, history of pelvic/perineal trauma, cancer surgery, or radiotherapy.

Table 24.8 Clinical signs and symptoms of hypogonadism

Sexual
Diminished libido (decreased sexual arousal)
Loss of morning erections
Difficulty reaching climax (delayed ejaculation, anorgasmia)
Suboptimal response to oral PDE-5 inhibitor therapies
Physical
Decreased testicle volume
Gynecomastia
Fatigue
Decreased bone mineral density
Decreased lean muscle mass
Increased central obesity
Anemia
Psychosexual
Depression
Impaired memory and cognition
Decreased vitality, energy, sense of well-being

Advances in the understanding of erectile physiology and improvements in technology have greatly increased our ability to define the types of ED (neurogenic, psychogenic, and vasculogenic). The goal of a specialized evaluation is to define the etiology and severity of ED, usually in cases where empiric therapy with a PDE-5 Inh has failed or is contraindicated. Confirmatory testing is not mandatory; a physician may pursue further empiric treatments beyond PDE-5 Inhs, but the patient should have the option of a comprehensive evaluation. Three or four decades of experience is available with several tests: combined intracavernous injection (ICI) and stimulation (CIS), pharmaco-penile duplex Doppler ultrasound (PDDU), dynamic infusion cavernosometry

and cavernosography (DICC), selective pudendal arteriography, and NPT.

There remains much controversy as to the indications and relative value of testing in the assessment of ED. The diagnostics for other male sexual dysfunctions are largely questionnaire based (hypoactive sexual desire and ejaculatory dysfunctions). Advanced diagnostics for ED are in the domain of those urologists who have specialty expertise in male sexual dysfunctions. Table 24.9 lists available diagnostics for ED and the quality of evidence supporting each. The tests commonly utilized in the office are (a) pharmacotesting with ICI followed by genital self-stimulation or audiovisual sexual stimulation (AVSS), (b) pharmacotesting with oral PDE-5 Inh with or without injection, and (c) PDDU. NPT and rigidity remains an effective tool but is not routinely done by the urologist. NPT has seen continued use in medico-legal assessments, in drug trials as proof of postulate "nocturnal erectile quality does improve compared to placebo with agent X," and to assess return of normal nocturnal erections following trauma or cancer operations. Selective internal pudendal arteriography was extremely popular in the 1980s performed in select men considering penile vascular bypass operation (e.g., ED following severe pelvic trauma). Currently, there is a resurgence of interest in this technique, secondary to a clinical trial *Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with Sub-Optimal Response to PDE-5 Inhibitors* (Medtronic).

Table 24.9 Evidence-based tests for ED and grades of recommendation

Test	Recommendation[a]
Vascular	
Intracavernous injection (ICI) pharmacotesting	B
Pharmaco-penile duplex Doppler ultrasound (PDDU)	B
Dynamic infusion cavernosometry and cavernosography (DICC)	B
Pudendal arteriography	C
CT angiography	D
MRI angiography	D
Infrared spectrophotometry	D
Radioisotope penography	D
Audiovisual Sexual Stimulation (AVSS)	
Independent or jointly with vascular testing	C
With or without: pharmacologic stimulation (oral PDE-5 Inhs or ICI)	C
Neurophysiologic	
Nocturnal penile tumescence and rigidity (NPTR)	B
Erectionmeter/rigidometer	D
Biothesiometry (vibratory thresholds)	C
Dorsal nerve conduction velocity	C
Bulbocavernosus reflex (BCR) latency	B
Plethysmography/electrobioimpedance	D
Corpus cavernosum electromyography (CC-EMG)	C
MRI or PET scanning of brain (during AVSS)	D

[a]Grades of recommendation:

A: At least one meta-analysis, systematic review, or randomized controlled trial with a very low level of bias and directly applicable to the target population

B: A body of evidence including high-quality systematic reviews of case control or cohort studies directly applicable to the target population and demonstrating overall consistency of results

C: A body of evidence including well-conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal, directly applicable to the target population, with overall consistency of results

D: Nonanalytic studies (e.g., case reports, case series, and expert opinion)

Modified from Rosen et al. [13] and Harbour and Miller [109]

Vascular Evaluations of Erectile Dysfunction

A penile vascular evaluation is aimed at differentiating and quantifying the two pathologies responsible for ED: arterial insufficiency and veno-occlusive dysfunction. Several tests are available (Table 24.9): intracavernous pharmacotesting, pharmacopenile duplex Doppler ultrasound, DICC, selective internal pudendal arteriography, computer tomographic angiography, and magnetic resonance angiography.

First-Line Evaluation of Penile Blood Flow

Intracavernous Injection and Stimulation: ICI is a pharmacotest which requires ICI of a vasodilator or a combination of vasodilators, followed by genital self-stimulation or AVSS, and assessment of the erection by an observer [66,67]. This screening test is the most commonly performed office diagnostic procedure for ED. It allows the clinician to bypass potential neurologic and hormonal influences, and evaluate the vascular status of the penis directly. Several injectable vasodilators have been used (Table 24.10), including papaverine alone, alprostadil alone, a combination of papaverine and phentolamine (Bimix), or a mixture of all three of these agents (Trimix). The technique involves injecting the medication through a $^{5}/_{8}$-in. needle (27–29 gauge) into the corpus cavernosum. The erectile response is evaluated for onset, rigidity, and duration. Alprostadil has become the agent of choice for diagnostic procedures because of a lower incidence of prolonged erection. In patients suspected of neurogenic ED (following prostatectomy or colorectal anal surgery), Bimix may be preferential because the incidence of painful erections is lower. One in five neurologically intact men will complain of an ache in the penis following Alprostadil injection. A normal CIS response (rigid erection) rules out cavernous venous occlusive dysfunction. ICI may be normal (rigid erection) but false-negative, in as many as 20% of patients with borderline arterial inflow (when normal is defined as >35 cm/s peak systolic flow on Doppler ultrasound, and borderline is defined as 25–35 cm/s, [68]). A false-positive test (partial erection when there is no underlying vascular pathology) may occur because of patient anxiety, needle phobia, or inadequate dosage. Before injection, the patient should be informed about the purpose, alternatives, risks, and benefits of the test. He should not leave the office until the penis becomes flaccid spontaneously or detumescence is induced by injection of a diluted phenylephrine solution.

Second-Line Evaluations of Penile Blood Flow

Penile Doppler Sonography

This is a specialized test requiring thorough knowledge of erection hemodynamics and penile sonographic anatomy. This diagnostic test is indicated when a patient has failed first-line ED therapy with an oral PDE-5 Inh drug, or meets other criteria outlined for specialized referral (see Table 24.11). *The penile blood flow study or PDDU consists in vasoactive penile stimulant followed by genital self-stimulation or AVSS and blood flow assessment by color duplex Doppler*

Table 24.10 Common intracavernous agents used in diagnostic testing and therapy

Drug [supplied concentrations]	Dose range	Advantages
Papaverine [30 mg/mL]	30–60 mg	Low cost
Papaverine [30 mg/mL] + Phentolamine [5 mg powder]	0.1–1 mL	More potent than papaverine alone
Alprostadil [10–20–40 mcg/mL]	1–20 mcg	Metabolized in penis; Priapism rare
Papaverine + Phentolamine + Alprostadil	0.1–1.0 mL	Most potent; highest risk priapism

Table 24.11 Indication for specialized diagnostics and referral

Patient request
Treatment failure
Primary ED (poorly sustained erections, life-long)
Anatomic penile deformities
Peyronie's disease
Congenital: hypospadias, chordee
Trauma
Phimosis
Short penis, buried penis
Pelvic/perineal trauma
Priapism
Complex endocrinopathy
Complex psychosexual disorder
Relationship problems
Complex vascular problems
Complex neurologic problems
Cancer survivor (postchemotherapy, radiation, surgery)
Medical–legal evaluation

Modified from Broderick [110]

ultrasound. PDDU provides an objective, minimally invasive evaluation of penile hemodynamics. In color-coded duplex ultrasound, the direction of the blood flow is designated with red (toward the probe) or blue (away from the probe), making the identification of the small cavernous vessels and recording of blood flow easier [69–71]. The aim of PDDU is to assess changes in spectral waveform from the cavernous arteries in a step-like manner following ICI of a vascular stimulant (Table 24.10). The ultrasound probe consists of high-resolution (7–10 MHz) real-time ultrasonography and color pulsed Doppler, which enables the examiner to visualize the dorsal and cavernous arteries selectively and to track dynamic penile blood flow changes associated with the various phases of erection. Various parameters are measured or calculated: diameter of the cavernosal artery, peak systolic flow velocity, end diastolic flow velocity, acceleration time, and resistive index (RI). Erectile quality should be rated each time a set of Doppler parameters is recorded. The experienced examiner will record erection hardness and correlate hardness with PDDU measurements. Recently, the Erection Hardness Scale (EHS, scale 1–4) has been correlated with validated patient reported outcomes in men with ED treated by PDE-5 Inh: IIEF, Quality of Erection Questionnaire, Sexual Experience Questionnaire, and SEAR [72]. This was a sophisticated analysis of an intuitive concept that the degree of penile axial rigidity is associated with perceived performance and satisfaction. Figure 24.3 compares the EHS model supplied by drug manufacturer Pfizer® to a commercially available Erectile Quality Monitor (EQM®, FastSize LLC.) which grades axial rigidity by a series of lights (lowest 0–500 g, highest 1.3–2 kg).

Penile sonography itself is noninvasive, ICI is not. ICI can cause penile pain and prolonged erection; prolonged erection (<4 h) must be pharmacologically reversed with a second injection to avoid priapism. Recent investigations have evaluated the efficacy of oral PDE-5 Inh with genital and/or AVSS [73–75]. Oral PDE-5 Inhs and applied stimulation does increase peak flow velocities comparable to that seen after ICI, but the timeframe of a typical injection PDDU study results in recording parameters from 1 to 20 min vs. 30 to 90 min following oral pharmaco-stimulant. Flow velocities should be measured 5–10 min after injection; a delayed response is typical in both the hypertensive and the anxious patient; a rapid response is typical in young men with psychogenic ED and neurogenic patients (following prostatectomy or colorectal/anal cancer surgery).

Doppler Waveform Analysis: Schwartz et al. [76] correlated changes in Doppler waveforms with hemodynamic changes in corporal pressure during progression to full erection. In the filling phase when sinusoidal resistance is low (within 5 min after vasoactive injection), the waveform is characterized by high forward flow during both systole and diastole. As intracavernous pressure increases, diastolic velocities decrease; with full erection, the systolic waveforms sharply peak and may be slightly less than during full tumescence; in rigid erection, diastolic flow will be zero or reversed when intracavernous pressure exceeds systemic diastolic blood pressure.

Peak Systolic Velocity (PSV) and Arterial Dilation: Penile blood flow is a function of both arterial diameter and blood flow velocity.

Fig. 24.3 Estimating penile axial rigidity. Erection hardness scale (EHS) model supplied by drug manufacturer Pfizer® is compared to a commercially available Erectile Quality Monitor (EQM®, FastSize LLC.) which grades axial rigidity by a series of lights (lowest 0–500 g, highest 1.3–2 kg)

In patients with nonarteriogenic causes of ED (i.e., neurogenic, psychogenic), Lue et al. found that the PSV of the cavernous arteries consistently exceeds 25 cm/s within 5 min of ICI [77,78]. Additional studies from varying institutions have reported the mean PSV in normal subjects as 34.8 cm/s [79], 40 cm/s [80], and 47 cm/s [81]. *In the Mayo Clinic series, PSV less than 25 cm/s had a sensitivity of 100% and a specificity of 95% in patients with abnormal internal pudendal arteriography* [82]. *Severe unilateral arterial insufficiency results in (right/left) cavernous asymmetry, with PSV differences greater than 10 cm/s.* An increase in penile arterial blood flow velocity after injection is accompanied by an increase in cavernous arterial diameter. In patients with severe vascular ED, the diameter increase is usually less than 75% and postinjection luminal diameter rarely exceeds 0.7 mm [78,83]. Evidence supports that a rigid erection (4 on scale of 4) is associated with PSV >35 cm/s and negative or near zero end diastolic velocity (see Fig. 24.4).

Duplex Ultrasound Evaluation in Veno-occlusive Dysfunction. The trapping of blood within the corpora cavernosa, limiting venous outflow, is a necessary step to achieving and maintaining rigid erection. Cavernous venous-occlusive dysfunction is defined as the inability to achieve and maintain erection despite adequate arterial inflow. *When the Doppler spectral waveform continues to exhibit high systolic flows and persistent end-diastolic flow velocity (EDV) (>5–7 cm/s), the patient is considered to have cavernous venous occlusive ED.* In 1974, Planiol and Pourcelot [84] proposed a RI to describe vascular resistance from the Doppler spectrum. The formula follows: RI = (PSV minus EDV)/ divided by PSV. As penile pressure equals or exceeds diastolic pressure, diastolic flow in the

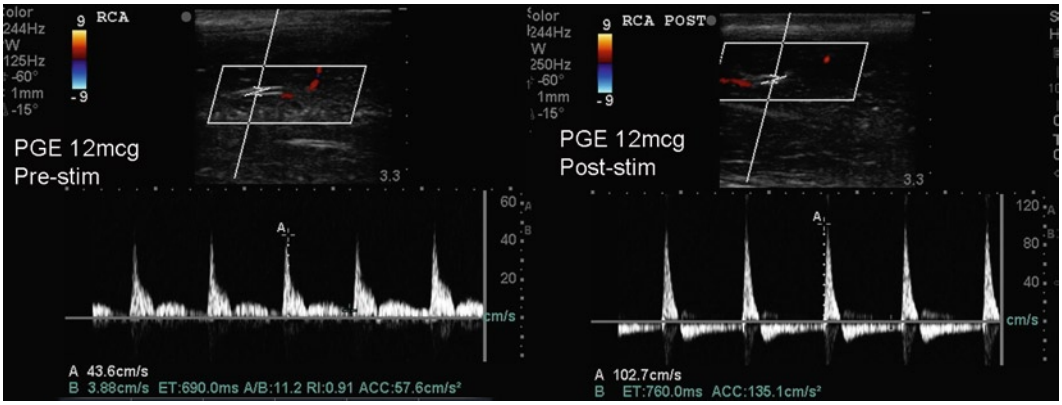

Fig. 24.4 Normal Doppler wave form progression from tumescence to rigid erection. Patient is 28 years old; pharmaco-penile duplex Doppler ultrasound (PDDU) after intracavernous Alprostadil and visual sexual stimulation. Doppler testing was instrumental in demonstrating the etiology of ED complaint was psychosexual

corpora will approach 0 and the value for RI approaches 1. During tumescence and in partial erections diastolic flow is elevated (+); the calculated value for RI remains less than 1.0. *Naroda et al. (1994) found that an RI greater than 0.9 was associated with normal results during dynamic infusion cavernosography in 90% of their series and an RI less than 0.75 was associated with venous leakage in 95%* (Fig. 24.5). Zimmern et al. [85] compared different diagnostic techniques in a group of normal men with prostate cancer, prior to therapy. They compared biothesiometry, NPT, and color pharmaco-penile duplex Doppler ultrasonography. Only color PDDU showed normal results in most patients (93%); Rigiscan NPT and biothesiometry correlated poorly with preop potency.

Recommendations of the ICSM on Penile Vascular Testing

When vascular evaluation is indicated, ICI with color duplex Doppler ultrasound is the most informative diagnostic test. This may be all that is needed to define and determine severity: arterial insufficiency, CVOD, and mixed vascular disease (Fig. 24.6). Color duplex ultrasound should be used before other tests are considered because it is the least invasive technology for evaluating vascular ED, distinguishing high-flow priapism from veno-occlusive priapism, and assessing Peyronie's plaque. Color duplex ultrasound accurately assesses venogenic ED and should be performed before cavernosometry and cavernosography.

Selective Internal Pudendal Arteriography

Arteriography is performed by ICI of a vasodilating agent (papaverine phentolamine and/or alprostadil) followed by selective cannulation of the internal pudendal artery and injection of radiographic contrast. The anatomy and radiographic appearance of the iliac, internal pudendal, and penile arteries are then evaluated according to established criteria. Prior to duplex Doppler ultrasound, pudendal arteriography was used to diagnose cavernous arterial insufficiency, primarily in men with pelvic trauma – to evaluate their candidacy for penile revascularization procedures. Currently, it is primarily used to embolize arteriosinusoidal fistula in cases of high-flow priapism. Investigational protocols for internal pudendal angioplasty also rely on arteriography.

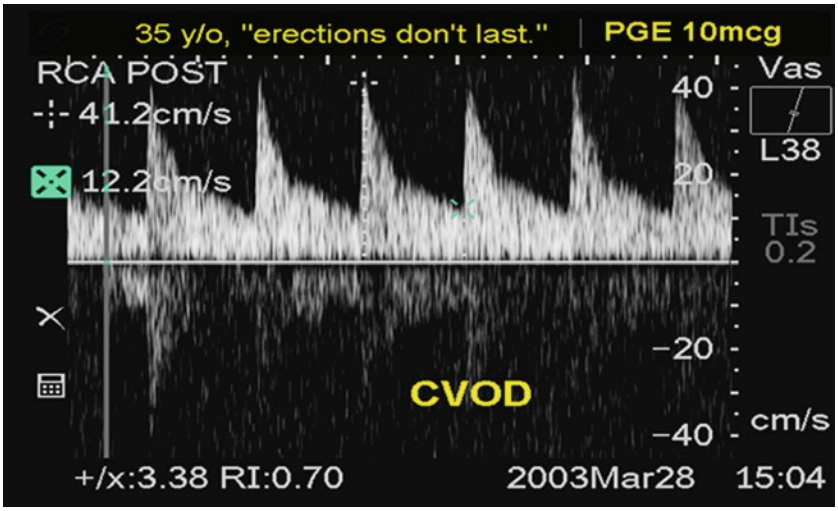

Fig. 24.5 Doppler wave form demonstrating cavernous venous occlusive disease. Patient is 35 years old; PDDU after intracavernous Alprostadil and visual sexual stimulation. Associated penile rigidity was 3 out of 4 while standing and 2 out of 4 when recumbent for measurements (Erection Hardness Scale 1–4)

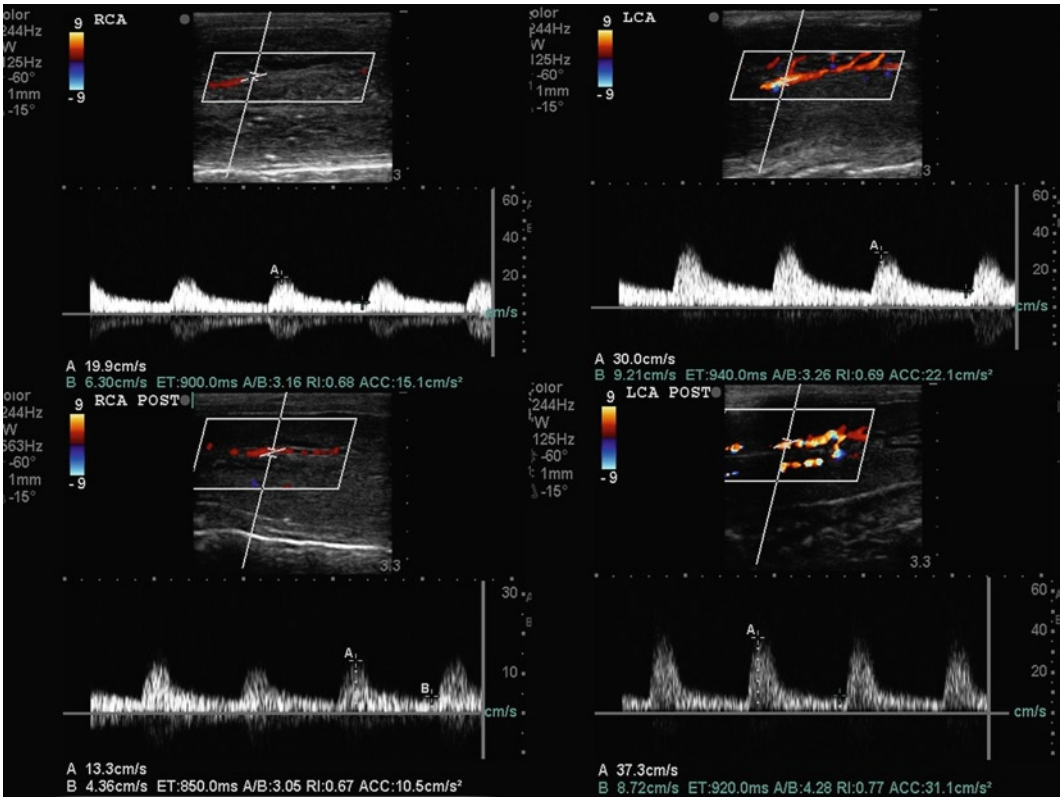

Fig. 24.6 Doppler wave forms demonstrating mixed vascular disease. Patient is 70 years old and failed trials of oral phosphodiesterase type-5 (PDE-5) inhibitors; PDDU after intracavernous injection of Alprostadil and visual sexual stimulation (pre – post). Peak systolic velocities show unilateral cavernous insufficiency 13 cm/s in right cavernous artery (RCA) and normal Peak Systolic Velocity (PSV) (37 cm/s) in left cavernous artery (LCA). Cavernous venous occlusive disease is implicated as well by elevated end diastolic velocities and low resistive indices

Nocturnal Penile Tumescence

This test was first described by Halverson [86], who documented nocturnal erections in infants. Karacan et al. [87] were the first to demonstrate that 80% of NPT occurs during rapid eye movement (REM) sleep. Total tumescence time during sleep peaks at the age of puberty, when as much as 20% of total sleep time may be spent with an erection. In the second decade of life, the average duration of a nocturnal erection is 38 min; for adults, the average duration is 27 min [88]. Initially, NPT investigations were conducted by psychologists to study sleep and dreams. Almost a decade later, NPT was applied to differentiate psychogenic from organic ED [89]. In 1985, the RigiScan was introduced and it was the first device to provide automated, portable NPT recording. The device combines the monitoring of radial rigidity, tumescence, number, and duration of erectile events with the convenience of a portable system that can be used at home [90]. The number of erections considered normal is three to six per 8-h session, lasting an average of 10–15 min each [91]. Levine and Carroll [92] also demonstrated an overall tendency in normal men for tip rigidity to decrease with age. The documented presence of a full erection indicates that the neurovascular axis is functionally intact and that the cause of the ED is most likely psychogenic. The disadvantages of NPT evaluation are that it is age dependent and alterations in or the absence of REM sleep creates false-positives. NPT is no longer recommended as a routine part of ED evaluations. Nevertheless, NPT testing remains a valuable tool in research. Heaton and Morales [93] have suggested indications for NPTR as follows: (1) suspected sleep disorder, (2) obscure cause of ED, (3) nonresponse to therapy, (4) planned surgical treatment, (5) legally sensitive case, (6) measurement of drug effects in placebo-controlled drug trials, and (7) suspected psychogenic cause (Fig. 24.7).

AVSS appears to enhance penile responses to a variety of test stimuli: vibration, ICI, topical and oral pharmacologic agents. Incrocci et al. [94] documented their experience with over 400 patients: 34% exposed to AVSS alone achieved partial or full erection, 52% who underwent AVSS and vibratory stimulation were able to initiate erection, and 82% of patients shown AVSS in combination with intracavernous papaverine achieved erection.

Hypoactive Sexual Desire

Hypoactive sexual desire as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) is "persistently or recurrently deficient (or absent) sexual fantasy and desire for sexual activity, leading to marked distress or interpersonal difficulty." HSD encompasses a variety of clinical features and these are not as succinctly identified as ED or premature ejaculation [95]. HSD is highly subjective; it is a sense of desire. Expressions of desire may be manifest as frequency of coitus, frequency of masturbation, frequency or absence of sexual fantasy, sexual thoughts, and initiation of sexual activity [96]. In the multinational survey Global Study of Sexual Attitudes and Behaviors [97], men and women 40–80 years old were questioned about sex and relationships; 13,618 men from 29 countries were included. Lack of sexual interest occasionally, periodically, or frequently was claimed by 12.5–28% of men responding. HSD may be part of another disease or co-exist with other specific sexual disorders like ED [98] (see Table 24.12). The evaluation should proceed as described in Medical and Sexual History previously. The examiner should ask about both sexual interest and level of sexual activity; although research protocols have attempted to quantify desire and sexual activity it does no service to the individual patient to judge him by those standards [99]. A patient's degree of sexual desire is subjective and best assessed in retrospect, recalling a time when he did not feel he had a problem. As with other sexual dysfunctions, the partner should also be questioned about changes in the patient's sexual well-being. Whereas hormonal assays are not mandated in the assessment of ED (e.g., normal sense of

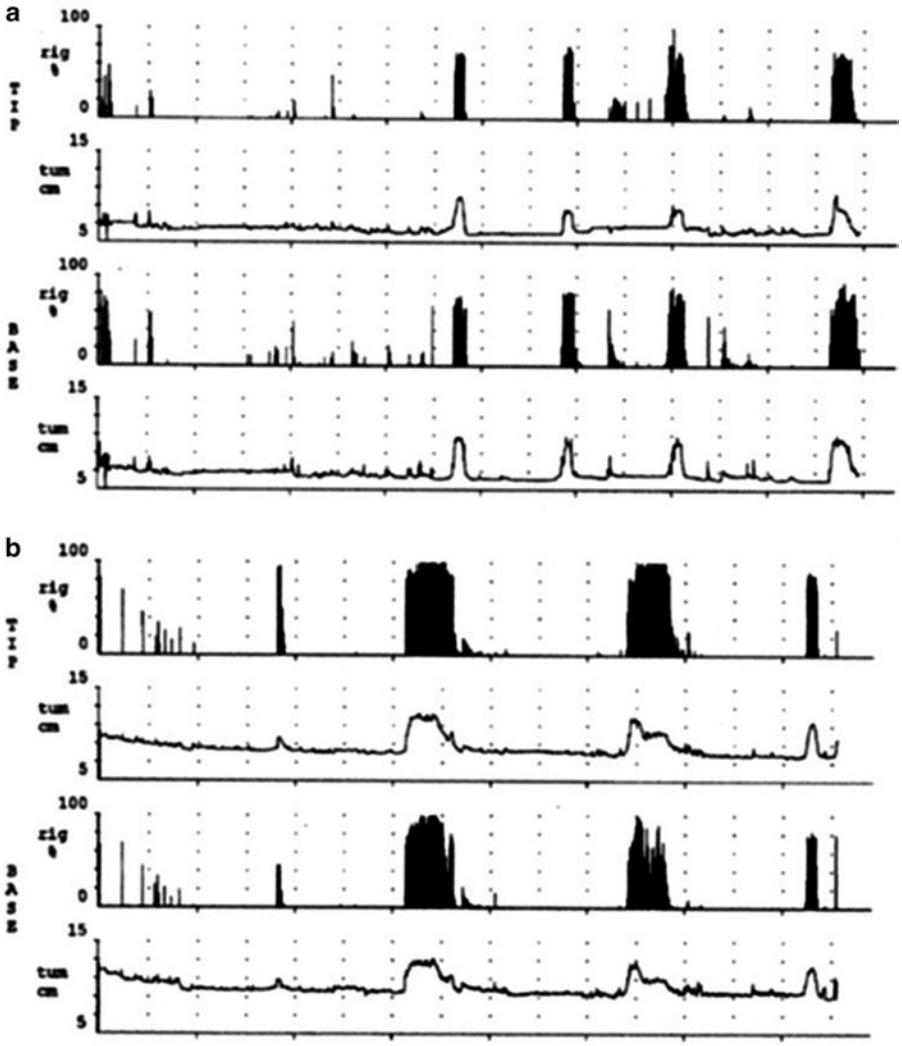

Fig. 24.7 RigiScan® (Timm Medical Technologies, Inc.) applied on two successive nights: without and then with a bedtime dosage of a PDE-5 inhibitor. Rigidity is estimated by *solid bars* and tumescence by *open bars*; penile rigidity was normal on both nights but duration of erections improved in a healthy volunteer

libido and normal testicle volumes), hormonal testing is highly recommended in the assessment of male HSD.

Ejaculatory Disorders

The third stage of the sexual response cycle is orgasm (desire, arousal, orgasm, and resolution); in the male, orgasm is accompanied by emission and subsequently expulsion of semen. Emission is the physiologic process during which semen is deposited into the posterior urethra by contraction of the vas deferens, seminal vesicles, and prostate; emission requires intact pelvic sympathetic nerves. Ejaculation is the process of forceful propulsion of semen along the urethra and out of the penis. Contractions of the bulbocavernosus muscles occurring during the rigid-erection phase are a reflex response to glans stimulation and pelvic thrusting; rhythmic

Table 24.12 Sexual disorders and conditions associated with male HSD

Androgen deficiency
Erectile dysfunction
Premature ejaculation
Relationship conflict
Depression
Antidepressant drug therapies
Posttraumatic stress syndrome
Eating disorders
Aging
Stroke
Epilepsy
Renal insufficiency
Heart failure
HIV
Cancer

Modified from Meuleman and Van Lankvled [98]

contraction of the bulbospongiosus and ischiocavernosus muscles results in ejaculation [100]. Any process (trauma, surgery, radiotherapy, or pharmacology) which interferes with the peristaltic function of the vas deferens and closure of the bladder neck may result in either failure of emission or retrograde ejaculation. Retrograde ejaculation or failure of emission should be suspected when there is absent ejaculate or volume less than 1 mL. The causes of retrograde ejaculation or failure of emission are either anatomic or neurologic. Men with retrograde ejaculation due to anatomic causes which have damaged the bladder neck or may have obstructed the ejaculatory ducts (e.g., electro-resection or laser incisions of the bladder neck vs. brachytherapy) will not respond to medical therapies. Patients with failure of emission or retrograde ejaculation due to neurologic causes may respond to medical, vibratory, or electro-ejaculation treatments (diabetes mellitus, multiple sclerosis, spinal cord injury, retroperitoneal lymphadenectomy for testis cancer, sympathectomy or colorectal/anal surgery for cancer). Multiple drugs are associated with retrograde ejaculation including phenoxybenzamine, clonidine, guanethidine, prazosin, tamsulosin, terazosin, and antipsychotic drugs. The diagnosis of retrograde ejaculation is confirmed by examination of the postejaculate urine sample. Patients seeking fertility who are at risk for failure of emission or retrograde ejaculation should be referred to a urologist with specialty interest in male sexual dysfunction or infertility. *Ejaculatory disorders range from premature to delayed/inhibited to an ejaculation, and include retrograde and painful ejaculation (dysorgasmia).* For male cancer survivors, sorting out ejaculatory dysfunctions can be quite complex, emphasizing the importance of the sexual history and correlating specific cancer interventions with the development of symptoms. A persistent and consistent complaint and onset related to therapy should be sought during the interview.

Cancer Survivors and Ejaculatory Dysfunction

Ejaculatory Dysfunction following cancer treatments is less well studied than ED. The bulk of the literature is in prostate cancer survivors, treated with open radical retropubic prostatectomy. In a prospective study of 600 survivors after RRP, Hollenbeck et al. [101] reported that for men younger than 58 years old, who had bilateral nerve sparing prostatectomy, 84% "were able to achieve orgasm" compared to 94% of controls. Factors associated with better orgasmic outcomes were younger age, nerve sparing status, time since prostatectomy, smaller prostate size, higher education level, and higher household income. Correlates to erectile function were not given. Koema et al. [102] looked at a smaller group of RRP patients ($N=20$) using structured interview and self-report measures. No patient in their series had normal erections postop; diminished desire was reported in 50%; in seven men, orgasmic sensation was "weakened"; four men reported normal pleasure and no change compared to before operation; in five men, there was involuntary loss of urine during orgasm. Barnas et al. [103] used a self-report measure in 239 RRP patients. They report 22% of men had no change in orgasm intensity, 37% had complete absence, 37% had decrease orgasm intensity, and 4% more intense orgasm. Barnas et al. [103]

also describe dysorgasmia in 14% of men, at least one-third had pain with every orgasm. Choi et al. [104] specifically evaluated climacturia; this was complained of in 20% of patients post-RRP; orgasm-associated incontinence was more likely to occur within first 12 months of surgery. Dubbelman et al. [104a] made use of self-report measure before and after RRP to assess baseline sexual function and postop dysfunctions in over 400 men during a 2-year follow-up period. Preoperatively, sexual interest, sexual activity, spontaneous erection, and orgasmic function were normal in 99, 82, 90, and 90% of men, respectively. After operation sexual function was decreased in all domains: interest to 97%, activity to 67%, spontaneous erections to 29%, and orgasmic function to 67%. Orgasmic function was independently related to nerve sparing status, age, and incontinence (more than 2 pads/day). They note that 2 years after surgery 71% of men had ED and sexual activity was absent in 33%. The neurologic and pathophysiologic etiologies of painful ejaculation are not known; for the prostatectomy survivor inflammation (prostatitis) cannot be the mechanism. In these men, the surgical absence of the prostate and seminal vesicles means that there is no emission and no ejaculate, but conceptually if there has been pelvic nerve sparing rhythmic contraction of ejaculatory muscles should occur. Barnas et al. [105] have noted the α-blocker tamsulosin may lessen dysorgasmia in post-RRP patients. Others have suggested that treatment with PDE-5 Inh seems to improve orgasmic function following RRP, but the beneficial effects on erectile function and secondary effects on the perceptions of orgasm need sorting out [106].

Specific Ejaculatory Dysfunctions

Premature ejaculation has been dealt with elsewhere. *Painful ejaculation is a poorly reported condition, most often associated with inflammations and lower urinary tract symptoms, (urethral stricture, obstructive benign prostatic hyperplasia, prostatitis, seminal vesiculitis, ejaculatory duct obstruction, obstruction of the seminal vesicles, and pelvic pain syndromes).* Unilateral obstruction of a seminal vesicle may be congenital and due to entrance of an ectopic ureter, leading to infection. Obstruction in adults may be secondary to infiltrating cancers from the bladder or prostate. Prostate cancer survivors treated with brachytherapy, external beam radiation, or cryosurgery may experience decreased ejaculates and or painful ejaculation. Prostate cancer survivors who have had radical prostatectomy will have no ejaculate and may lose urine at the time of climax; some have reported pain while others heightened sense of orgasm.

Inhibited ejaculation (IE) is far less common than PE. Patients do not usually have difficulties attaining or keeping erection, but do report lower levels of subjective sexual arousal [107]. IE is poorly characterized in the literature with little contemporary research defining or categorizing the condition. IE may be global (occurring with every partner), intermittent, or situational. There are no medical conditions with consistent association. It is regarded to be primarily psychogenic with one study noting 75% of patients reporting better erections and ability to reach orgasm through masturbation than with penetrative sex [108]. Perelman [108] has noted that these men have an "autosexual" orientation which may be a learned disorder, based on idiosyncratic and vigorous masturbation style, carried out with high frequency. Evaluation is based on sexual history and directed physical examination. The clinician must review conditions under which the patient can ejaculate, with special attention to the facilitating stimuli. The patient should be questioned about onset, coital and masturbatory patterns, arousal, fantasy, and anxieties regarding performance. Medication history and recreational drug use should be reviewed and prior treatments discussed. A focused physical examination should rule out genito-urinary pathology and should be conducted prior to referral to a mental health professional with expertise in male sexual dysfunction.

Conclusions

The evaluation and management of male sexual dysfunctions comes under the purview of many different health providers. Unfortunately, many are reluctant to ask patients about sexual health. Identification of sexual dysfunctions is hampered by traditional and difficult to overcome barriers: embarrassment, lack of expertise in sexual history taking, concerns about the safety of treatments, and lack of time. For cancer survivors, there are long-term physical and psychological factors that significantly impact sexual function. For the male patient, these include ED, ejaculatory dysfunction, loss of desire/arousal, infertility, pain, changes in body image, depression, and anxiety. In clinical practice, a good case history, preferably taken from both partners, physical examination, and proper laboratory studies form the cornerstone in the evaluation of MSD. The goal of a specialized evaluation is to define the etiology and severity of MSD, usually in cases where empiric therapy has failed. Confirmatory testing is not mandatory, but the patient should have the option of a comprehensive evaluation. Given the significant prevalence of sexual dysfunctions among cancer survivors, the severity of those dysfunctions and the lack of specific training in sexual health – the ultimate resource for cancer survivors seeking assessment and care may reside in the office of specialists and in cancer centers.

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Chapter 25
The Impact of Cancer on the Partner's Sexuality

Eusebio Rubio-Aurioles

Keywords Partner • Distress • Bother • Female sexual dysfunction • FSD

Introduction

Sexual interaction between two individuals may lead to satisfaction, joy and a sense of intimacy, or it may lead to frustration, pain and alienation. Intact sexual function is by no means a guarantee of emotional satisfaction [1] but may increase the likelihood chances of positive outcomes in most cases. On the other hand, sexual dysfunction typically leads to negative consequences for the partner. In fact, the very expression of sexual function usually implies the presence or participation of a partner, although sometimes the partner is present only in fantasy.

When a patient develops a sexual dysfunction, the consequences for the partner should always be considered [2]. The tendency to treat "the problem" instead of the patient and his/her partner context has engendered a relative disregard for partner relationship factors in the emergence of sexual medicine as a clinical field in the last two decades. Despite the appearance of very effective therapeutic tools such as the phosphodiesterase type 5 inhibitors, the need to include the partner in the assessment and treatment has been neglected and in some instances even questioned because of the time demand that including partners in the assessment and treatment processes would impose on medical practice. Notwithstanding, there have been repeated and urgent calls for inclusion of partners in the assessment and treatment processes [2, 3].

In the case of cancer patients, partner consequences of sexual dysfunction may be complicated due not only to the impact of the loss of quality in sexual function, but also to the impact that the cancer diagnosis and its treatment may have on the partner [4, 5].

This chapter provides a conceptual model that helps to organize the clinical interventions with partners of cancer patients. We provide also a review of the current clinical perspectives and approaches in this area. Recent publications on the topic are reviewed, particularly those that have addressed the impact of cancer on patients' partners, especially in reference to sexual function and quality of life. Finally, specific recommendations are made for inclusion of partners in the healthcare process of patients with cancer.

What is Sexuality? Concepts of Human Sexuality

Human sexuality is often thought of either as a broad concept that practically pertains to all human aspects or, to the contrary, to highly

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specific sets of behaviors that lead to sexual arousal and orgasm with their components of pleasure and satisfaction. This extreme views are not helpful overall to clinicians. Having an overly restrictive view on sexual function may stand in the way of understanding some relationship complexities. Perhaps the best example is the failure to restore sexual health of erection drugs for a man who has difficulty with erection since his partner relationship has deteriorated, and he is unable to perform in the face of his wife's disapproval.

According to consensus definition:

> Sexuality is a central aspect of being human throughout life and encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, ethical, legal, historical, religious and spiritual factors [6].

This definition was derived in a consensus process among over 60 international and national experts on sexuality and sexual-health-related issues. Sexual health was defined using a framework similar to the WHO definition of health as follows:

> Sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled [6].

In the case of a person who is diagnosed with cancer, specific mental and physical processes start to impact the person's general health and also his or her sexual health. In addition, the partner of this person suffers an impact on his sexual health (and his/her general health) that very often goes unnoticed by the health practitioner. The partner of a cancer patient very often has to undertake the role of care-taker, and in so doing many times he or she experiences impact on his or her own health and fails to look for help even if there are interventions designed to help them [4].

What follows is a conceptual model that is offered to explain/interpret most of the findings in the literature on the topic.

Human Sexuality from a Systems Perspective: The Four Component Sexual Model

In a previous publication, a model of human sexuality was proposed based on General System Theory principles, as proposed originally by Von Bertalanffy [7]. This theory attempted to state broad principles by which systems are organized. Following these ideas, I proposed that sexual interactions can be best accounted for if four subsystems (or sexual holons) are considered: (a) the reproductive potential that all human beings have; (b) the fact that the species has developed in a dimorphic way and which translates into the conformation of a gender identity in all of us; (c) the potential to develop strong emotional ties to specific persons both in a primary fashion (like the bond between mother and child) and most importantly in a secondary fashion when we develop romantic and other forms of emotional attachment to specific persons – a dimension denominated interpersonal bonding and; (d) the capacity to experience pleasure associated to the desire, arousal and orgasmic responses typical of copulatory behavior that in fact can occur in many other circumstances beyond the copulation – a dimension denominated eroticism [8–11]. This model of human sexuality bears a close resemblance to the current WHO working definition quoted in the previous section: while the WHO working definition has more elements than the four subsystems identified in the holon model, the other elements proposed in the WHO definition are in fact a result of the particularities of the organization of the primary four elements: sex, gender identities and roles are derivatives of the second holon that

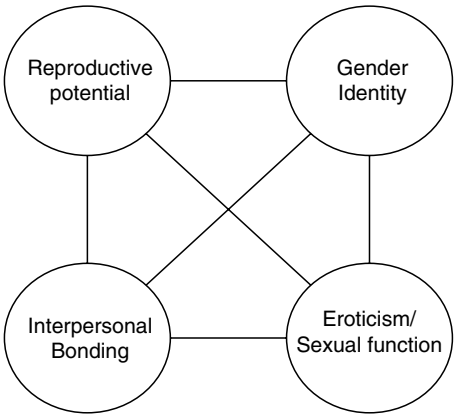

Fig. 25.1 Sexual subsystems (holons)

translates at the psychological level into gender identity, eroticism and pleasure represent expressions of the fourth holon: eroticism; intimacy relates to one of the most clear expressions of the interpersonal bonding capacity of human beings; reproduction relates to the reproductive potential and; sexual orientation is an expression of the particular organization of eroticism and interpersonal bonding sexual holons. Figure 25.1 represents these four sexual subsystems or sexual holons, each holon interacts with the other three basically through the meanings that experiences, feelings and behaviors produce with human development and social interaction [11].

The Impact of Cancer on Sexuality from a Systems Perspective

The diagnosis and treatment of cancer can have a profound impact on sexuality of the individual or couple. This chapter will present a review of the evidence that has been published on this particular topic but, as means of introduction, we will present a conceptual model of how these impacts are organized using the systems perspective just presented, immediately followed by a review of the supporting evidence that has been published.

The reported impact of cancer on sexuality of patients is presented in Fig. 25.2 organized by sexual subsystem that is impacted.

There are several cancers that impact reproductive ability in a direct way and many, as a result of treatment maneuvers. Reproductive potential is affected particularly in couples who are in the reproductive years of life: a not uncommon case is the female partner of a prostate cancer patient who was planning a pregnancy before the diagnosis or a younger woman who develops breast cancer, or a young man that develops a cancer that will shorten his life. In each of these instances, the reproductive function of sexuality can be severely impaired.

Cancers that directly impact body parts (through cancer itself or its treatment) and which are critical for body image constituents of gender identity usually can affect the patient's self-image and his/her concept of himself or herself as a man or a woman. In other instances, the disability that cancer or its treatment may lead to limit one or more aspects of what is to be socially expected in the patient's sex role as a provider or care-taker role of children in the family. The patient's sense of gender identity, especially in its sense of being able to fulfill his or her roles, can be severely impacted.

The diagnosis or treatment of cancer can impact the interpersonal bond between patient and his or her partner. The transition from a sexual-partner role to a patient-in-need-of-care role, as well as the stress that a real threat to life may pose to the individual, can impact in a significant degree the interpersonal bond of the patient and the partner. Sometimes, the pre-existing relationship dysfunction experiences a worsening because of the stresses generated by the life-threatening condition.

The impact of cancer on the sexual function of the individual patient is often significant, as it is reviewed in detail in other chapters of this book. The cancer itself or its treatment as well as associated depression or anxiety resulting from or aggravated by the cancer processes are likely to cause problems in sexual function ranging from erectile dysfunction, ejaculatory dysfunction and loss of sexual desire in the man, to

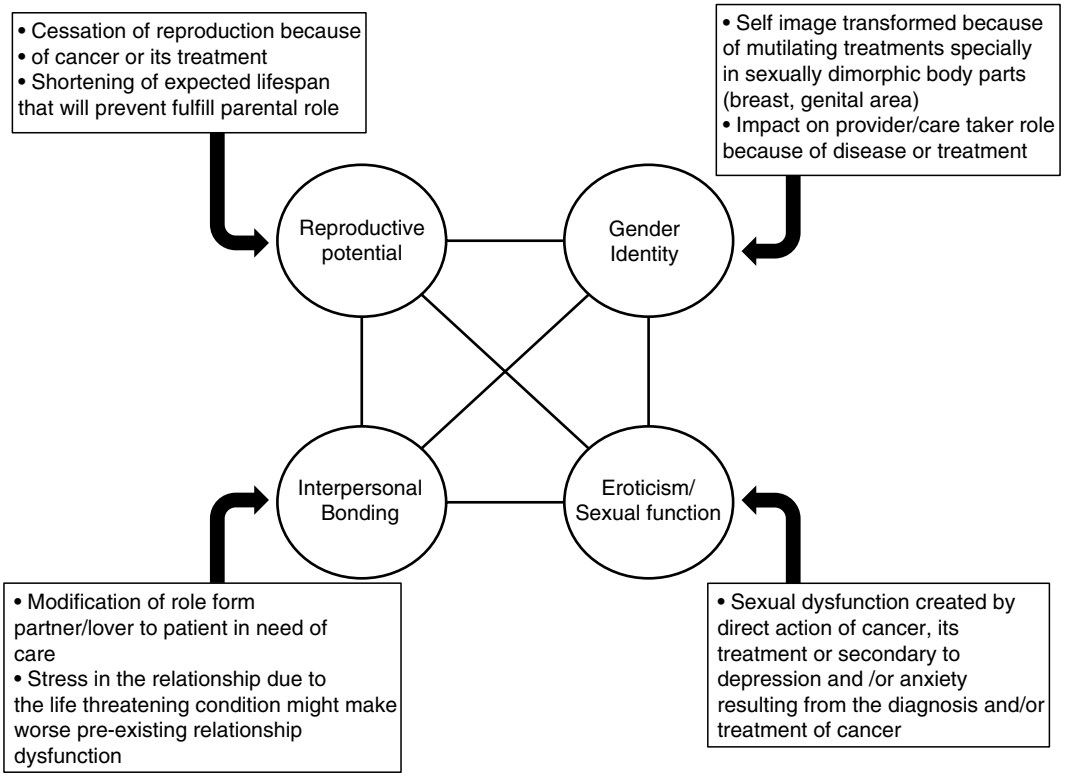

Fig. 25.2 Impact of cancer on sexual holons

pain, arousal and orgasm difficulties and desire impairments in the woman.

Impact of Cancer on the Partner's Sexuality from a Systems Perspective

The adverse effects that cancer can cause on patients' sexuality may cause, in turn, an adverse effect on the partners' sexuality. The following sections present a review of studies and published data on these effects. Here, a conceptual model is proposed to understand these changes in an orderly fashion, identifying the sexual subsystem that is most directly affected.

Figure 25.3 is a representation of the different effects that cancer might have on partner's sexuality. In Fig. 25.3a the impact on reproductive potential is represented: while this impact is seen only among patients and partners that have not fulfilled their reproductive desires, when this is the case such as in cases on prostate cancer when the female partner is still in reproductive age and with plans to procreate with the cancer patient, the impact on her reproductive potential is clear as it is the impact of gender-related expectations – some women do see themselves as complete women when they become mothers.

Figure 25.3b represents the impact on gender identity of cancers that alter the self-image due to alterations of body parts that are critical for the identification of the person as woman or man. Gender identity can be also impacted by the impairment of expected social roles as provider or care-taker in the family. The impact on the partner of these changes can inflict stresses on the interpersonal relationship or the capacity to see the partner as a sexually attractive person.

Figure 25.3c represents the potential consequences of cancer for the roles' partners may have before and after the cancer: ranging from partners in an equal level relationship to caretaker–patient relationship. If the couple had a dysfunctional relationship, the stress generated by the threat to

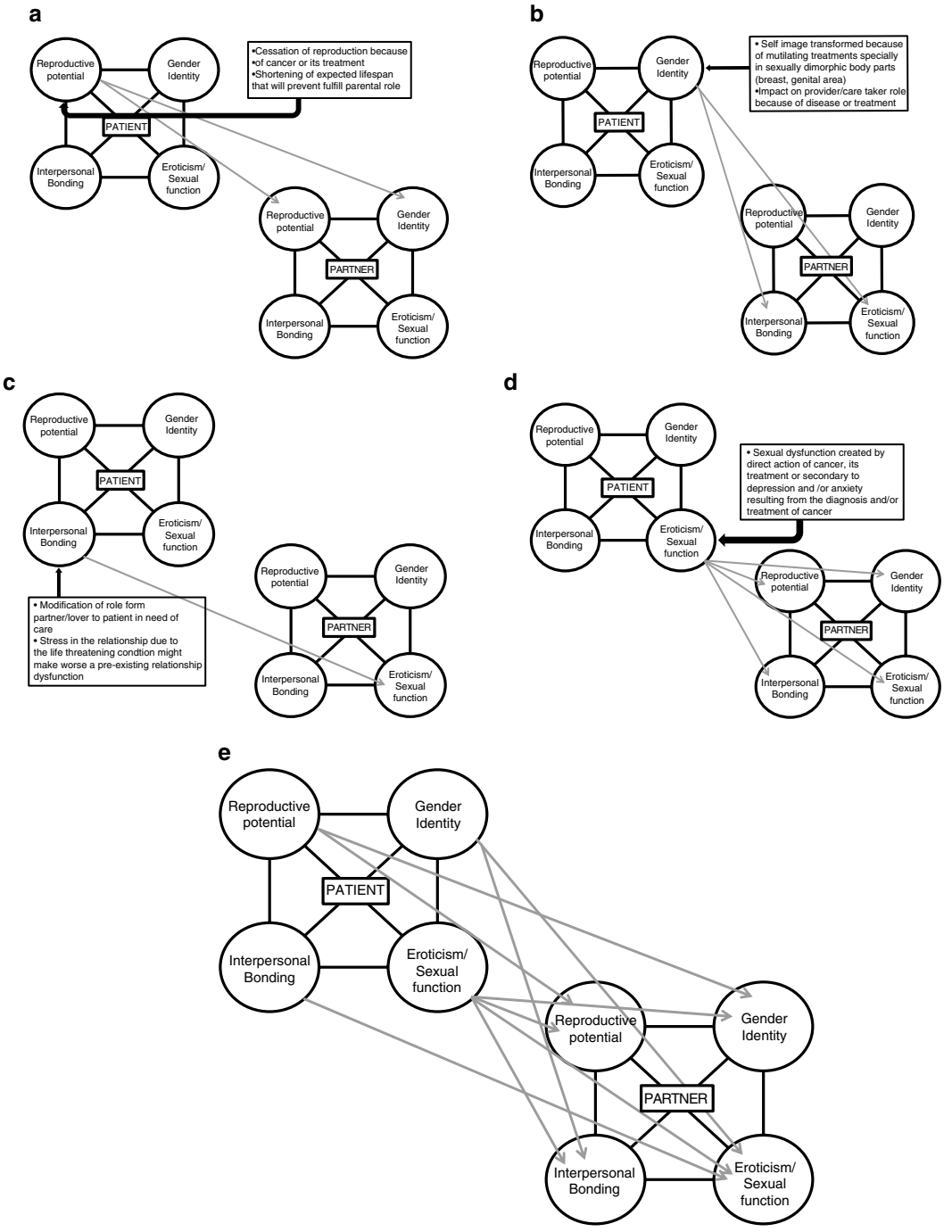

Fig. 25.3 Impact of sexual changes of cancer patients on partner sexuality from a systems perspective. See text for description of the five different diagrams (**a**–**e**)

life and quality of life can easily make the pre-existing problems in the relationship significantly worse. These changes can impact the partner's ability to experience the interaction with the patient as erotic determining the appearance of sexual difficulties or dysfunctions.

Figure 25.3d represents the potential effects of cancer on sexual function of the patient. These changes have been reviewed in detail in other chapters on this book. There is evidence that the sexual dysfunction precipitated, maintained or worsened by the cancer, the cancer diagnosis through its psychological impact, and the cancer treatment does impact the sexuality of the partner in many dimensions: when the reproductive needs of the partner have not been fulfilled the impact is clear, the gender identity of many people whose partner cancer that determines sexual dysfunction such as the disappearance of sexual desire can be impacted with feeling of rejection and isolation. The fact that the cancer patient can become sexually unavailable can impact the nature of the interpersonal bond with his or her partner, creating a nonsexual bond and finally, the presence of a sexual dysfunction will determine a deterioration of the partner sexual function that might translate into dysfunctional levels.

Figure 25.3e represents the complex interactions among these effects. What is important from a clinical-intervention point of view is to recognize that the several types of effects do not necessarily impact directly on the sexual function of the partner, but potentially indirectly though effects on other areas on the partner's sexuality.

In the following sections, recent studies and articles that have addressed these issues will be briefly reviewed. The review will touch on literature documenting the impact of sexual dysfunction on the female or male partner, and the impact that cancer may have in general, as well as specific types of cancer and their impact on the sexuality of partners.

Impact of Male Sexual Dysfunction on Partners

There is now a large body of data on the impact of erectile dysfunction on the female partner. The Female Experience of Men's Attitudes to Life Events and Sexuality (FEMALES) study [12] included the responses of 293 female partners of men with erectile dysfunction to a questionnaire that investigated their frequency of sexual activity and the nature of their sexual experience, both before and after the development of the partner's erectile dysfunction. Women participating in the FEMALES study reported lower frequencies of sexual activity, lower levels of sexual desire, arousal or orgasm and satisfaction with sexual relationship comparing the measures after and before the appearance of erectile dysfunction in the partner. In a recent reanalysis of this data set an analysis of the concordance and discordance of answers given by the male and the female partners was presented [13]. A high level of concordance was encountered for most of the items investigated: the perception of the female partner on the level of functional impairment and the frequency of male erection difficulty was strongly associated with assessment made by the male partner. This high level of concordance was also demonstrated in the development of a questionnaire that when answered by the female partner gives the same quality of information for detection of erectile dysfunction compared with the information given by the male partner [14].

A qualitative study to identify areas of impact and clues for detection of the male erectile dysfunction by the female partner was part of the development of the female erectile dysfunction detection scale (FAME) [14]. The descriptors identified are relevant for the present discussion as they portrait very well the female experience of her partner erectile problems. These categories are reproduced in Table 25.1.

The effect of erectile dysfunction on female sexual function and on the quality of sexual quality of life of the female partner can be restored if proper treatment for the male erectile dysfunction is implemented. A clinical trial using a double blind placebo controlled and randomized design evaluated the impact of the treatment with vardenafil on the female sexual function

Table 25.1 Impact of male erectile dysfunction as perceived by the female participants in two focus groups [14]

Psychological impact on the man
Anger
Anxiety over sexual performance
Denial of erectile failure
Depressive mood
Loss of confidence in obtaining erections
Psychological impact on the woman
Increase of female somatic complaints
Anger in the woman
Impact on the relationship
Preoccupation with unfaithfulness of the woman
Fear of unfaithfulness of the man
Woman feels rejection
Man becomes aggressive
Man blames woman for erectile failure
Man seeks reassurance of his male identity
Man concedes failure in his male duties
Man compensates for failure with other behaviors
Communication about erectile failure becomes difficult
Woman becomes concerned with man's health
Sexual satisfaction of the woman
Erection feels less satisfying
Sexual desire diminishes in the woman
Foreplay produces less arousal in the woman

which improved significantly when female sexual function was considered as a whole, and in the domains of desire, arousal, lubrication, orgasm and satisfaction [15]. The quality of sexual life of both the male and his female partner was also improved when couples were treated with daily doses of tadalafil as reported in another double blind placebo controlled and randomized clinical trial [16]. Finally, treatment of erection dysfunction with sildenafil was also shown to improve the rates of sexually satisfying encounters and sexual function and intercourse success rates in a placebo controlled trial [17] and in an open label trial, it improved the quality of sexual life of the women partner [18].

There is considerably less information with respect to other male sexual dysfunctions and their impact on the female partner. One report that examined the frequency of sexual dysfunction among female partners of men with premature ejaculation offers some information [19]. Female partners of men with premature ejaculation had higher frequency of sexual dysfunction (77.7%) than controls with no sexual dysfunction partners (48.2%), the most common problem was problems with arousal sensation and orgasm, when all domains were considered (desire, arousal sensation, arousal lubrication and orgasm) significantly higher rates were found among partners of men with premature ejaculation. In a review of studies that have addressed the impact of premature ejaculation on psychosocial function and partner effects, Rosen and Althof [20] concluded that women are impacted by premature ejaculation as much as their male partners and possibly more; studies included report high levels of interpersonal difficulty, avoidance of discussion of sexual problems with partner and lack of satisfaction with relationship in general.

No published reports were available for this review on the impact of male desire problems on sexual function in their female partners. However, given the clear role that sex has as a form of validation of one's attractiveness and desirability, it seems reasonable to assume that the disappearance of one's partner sexual desire has an impact on how the partner feels about herself or himself. This observation is supported by the author's clinical experience.

Likewise, there is a paucity of research addressing the impact of male sexual dysfunction on male partners for the case of *same sex couples*. There are, however, a number of reports in the literature indicating that there are specific issues in gay couples that create special clinical needs such as the impact of homophobic or heterosexist attitudes and the consequence in societal isolation; however, many other aspects of the interaction among gay couples actually share the dynamics and particularities with heterosexual couples [21, 22]. It is possible that similar effects on the male partner of the male with sexual dysfunction are observed, but this area clearly needs further research.

Impact of Female Sexual Dysfunction on Male Partners

There is surprisingly little published data on the impact of female sexual dysfunction on the male partners' perceptions and function. There is a cultural assumption that asserts that the one who suffers the effects of the diminished quality of sexual interaction is the female partner, but this assumption is based entirely on cultural stereotypes that portray males as reflexive and insensible participants in the couple dynamics. Clinical practice support the idea that a man whose female partner experiences a sexual dysfunction certainly realize the problem, and the reactions that have been documented in the male sexual dysfunction literature: feelings of rejection, lack of validation of one's identity, isolation and the like. The old idea that in sex, men are the "doers" and women the passive "recipients," seems to pervade the current literature. The untruthfulness of this assumption was critiqued effectively more than 40 years ago by Masters and Johnson [23].

The more adjusted the couple is, the less impact a woman's sexual dysfunction will have on female distress level [24]. The issues investigated by authors looking at the effects of partner compatibility on the distress associated with female sexual dysfunction included: too little foreplay before intercourse, too much foreplay before intercourse, partner more interested in sex than the female, lack of perceived partner's ability to do things right during sexual activity, lack of perceived personal ability to do things right during sexual activity, partner's sexual needs that the female is not willing to satisfy, female sexual needs that partner is not willing to satisfy, partner not attractive enough, poor communication about sex, and partner sexual dysfunction (erectile dysfunction or premature ejaculation). All of these factors were associated with higher levels of sexually related distress in the female.

Information on the impact of female sexual dysfunction on lesbian couples is also scarce and anecdotal [25, 26]. Again, in addition to topics specific to sexual orientation, the impact on partners resembles the pattern observed among heterosexual population.

Impact of Cancer Diagnosis and Treatment on the Partner's Sexuality

Psychological Impact of Cancer on Partner

In recent years there has been a growing awareness of the impact of cancer diagnosis and treatment on partner's sexuality and couples' interpersonal issues. The challenges that cancer brings to both patients and partners are worth considering. A review by Pitceathly and Maguire [4] offers a perspective on the impact of cancer on the couples' relationship that can be summarized as follows.

Psychological distress and psychiatric morbidity is common among partners of cancer patients. While most partners adjust to the diagnosis, about 20–30% develop psychiatric morbidity in the form of major depressive disorder, anxiety or adjustment disorders. Since most studies are performed only at a specific point in time, Pitceathly and Maguire [4] point out that the actual prevalence is likely much higher if one considers the progression of the cancer over time. Psychological difficulties sometimes are not recognized by partners, and it is estimated that only half of those with psychological problems will actually seek help.

The psychological impact of cancer will vary depending on vulnerability, intrapersonal and interpersonal factors. Among the vulnerability factors it seems that females are more likely than males to develop depression and affective disorders (an association that has been described for the general population but that holds true for partners of cancer patients) [4].

Personality factors (e.g., high levels of neutoticism) and a previous history of depressive disorders also increase vulnerability. The stage of the cancer and the number and degree of symptoms are also of relevance: psychological problems and morbidity increase as the illness progresses, particularly when patients are suffering from advanced and terminal disease [4].

There are intrapersonal factors that can play a protective or precipitating role in the development

of psychological problems. The partner coping style, that is the person's characteristic strategies to deal with life problems or traumas, has been described as a factor: partners and caregivers that have an avoidance coping style are more likely to develop problems, when the partner uses a more problem focused coping style the frequency of mental health problems decreases. The appraisal of the cancer in the partner has been linked to the quality of the adjustment: partners who have optimistic appraisals tend to be less depressed than those with negative appraisals [4].

A number of interpersonal factors also mediate the appearance of psychological complications. The amount and quality of informal support (family, friends) seems to exert a protective role. The quality of communication with partner also has some protective role. Of special note is the quality of the marital/sexual relationship of the couple prior to cancer, as it predicts psychological problems in the partners/carers. Couples that had a supporting and close relationship do better. However, the quality of the relationship can be difficult to evaluate in some instances because the impact of the cancer can deteriorate the relationship. Psychological problems in the partner are less common when the needs for medical information are met [4].

In summary, Pitceathly and Maguire [4] review effects on cancer patients who develop high levels of emotional distress or psychiatric morbidity and have more negative reactions to the patient's illness. The use of avoidance as a coping style is related to more psychological problems in the carer. Deterioration of the couple relationship may also affect the partner's adjustment and factors such as personality, gender, age and marital difficulties predating the cancer may play a precipitating role. Formal and informal support seems to be helpful in adjusting to the cancer.

Sexual and Intimacy Effects of Cancer on the Partner

Hawkins et al. [5] investigated with qualitative data the changes in sexuality and intimacy after cancer using open-ended questionnaire responses of 156 care-givers of persons with cancer who were also sexual partners. In depth interviews with an additional 20 participants completed the information. Most participants reported an impact of cancer in the sexual relationship: 64% of those with "nonreproductive" cancer types and 84% of partners caring for a person with cancer involving "reproductive" sites. Cessation or decreased frequency of sex and intimacy was reported by 59% of the women and 79% of the men. Renegotiating of sexuality and intimacy was reported only by 19% of the women and 14% of the men. The main reasons for the changes in sexuality given by participants were: impact of cancer treatments, exhaustion due to caring and repositioning of the person with cancer as a patient, not as a sexual partner. Additional reactions to the impact of cancer on sexuality included reports of self-blame, rejection, sadness, anger and lack of sexual fulfillment although positive impacts were also reported like acceptance of the changed sexual relationship and increases in closeness and intimacy.

As stated, most participants in the Hawkins et al. [5] study reported complete cessation of sexual activity or a marked decrease in frequency. For those experiencing a complete cessation, the "end" of the sexual relationship was reported as a sudden event: "our sex life disappeared overnight…" "A big chunk of your life is lost"… …"you are a widow with somebody that's still around" are extracts of interviews presented by authors that reveal the nature of the feeling reported by participants of this study.

Interestingly, some participants found ways of renegotiating sexual and nonsexual intimacy: men (12%) where more likely than females (1%) to report having developed alternative sexual behaviors than those practiced before the cancer, the changes included changed sexual positions, or alternative means of stimulation such as oral sex, massage, masturbation or the use of a vibrator. On the other hand, women (18%) were more likely than men (5%) to report that renegotiation included nonsexual intimacy such as hugging and cuddling.

For almost a third of the women (28%) and half the men (47%) participating in the Hawkins et al. [5] study the caring role resulted in a repositioning of the person with cancer as a patient, which subsequently influenced their sexual relationship. The following excerpt from one of the interviews is illustrative of this point: "I feel disgusted with myself that I would inflict sex upon a dying woman, having said that my wife does not object and occasionally welcomes it, saying it is a life giving and loving act and part of our sacrament… I was never a fast lover, nut now I try to get it over and done with for her [45 year old man caring for a 44 year old wife with breast cancer]."

For some care-takers the cancer and consequent changes in sexual activity in their lives have facilitated more intense feelings of closeness and intimacy, for others these changescreated feelings of sadness, rejection, anger, exclusion, self-blame and sexual frustration.

One finding reported by Hawkins et al. [5] has direct implications for clinical care. Only 20% of partners of persons with cancer participating in the study reported that they had had a discussion on sexuality with the healthcare professional. The rate varied with the type of cancer: 50% of those with a partner with prostate cancer, 33% for brain, 33% for pancreatic, 30% for breast, 29% gynecologic, 20% for cancer affecting a sexual organ, 17% for colorectal/digestive, 17% for mesothelioma, 9% for hematologic and 0% for respiratory. What is even more disturbing is the fact of the 20% of participants who had had a discussion with the health professionals, only 37% indicated that they were satisfied or very satisfied. When participants were interviewed, the accounts are openly critical of the healthcare professionals on the point of discussion of sexuality: they reported being told things as "oh, you do not need to know that and things like that," or that they were "irresponsible to be thinking about children" in response to a question on fertility, for the majority they simply indicated that sexuality was not discussed at all.

Psychosocial Impact on the Partner of Men with Prostate Cancer

The case of prostate cancer represents a special one as advances in prostate cancer treatment are leading to a growing proportion of patients living with the effects of cancer and its treatment. In a review of the literature about the psychosocial adjustment of partners of prostate cancer patients, Couper et al. [27] present the following summary: Prostate cancer can have marked psychosocial repercussions for the partner. Studies have reported that partners are frequently more distressed than patients. Although distress may diminish over time, a proportion of partners remain adversely affected years after the death of the patient. According to this review, partners of prostate cancer patients are more active in seeking information and making treatment decisions than partners of women with breast cancer. Also, there is some evidence that involving the partner of prostate cancer patients in treatment decisions and planning helps the patient to increase his well-being. A prevalent concern exhibited by patients is related to sexual function: partners tend to reassure patients who experience erectile dysfunction and do not address their own sexual needs. Urinary incontinence, on the contrary, may have a greater adverse psychological impact on the partner than on the patient himself.

Social support, coping style that employ problem solving strategies or seek social support instead of avoidance or impulsive seem to protect the partner. A number of interventions which incorporate the partner could be devised but authors point out to the need for research in this area. Logical alternatives would be interventions that increase protective factors: coping style and social support [28].

The sexual function of the female partner of the prostate cancer patient has been evaluated in a study that utilized validated measures for both the male and female sexual function. Although the reported response rate to an invitation sent to 1,134 couples was extremely low (8%, 90 couples) female sexual function was correlated

to male erectile function: the more affected the erection function, the lower the indexes of female sexual function. Perhaps more interestingly, participants indicated that their sexual function assessed subjectively had decreased significantly in 58.4% of participants, and a further 20.2% indicated that it had decreased somewhat [28].

Impact on the Partner of Women with Breast Cancer

Despite the rather abundant literature on the psychosocial impact of breast cancer on the patient, limited attention has been given in the literature to the impact on the partner. A brief comment in a report that included 558 patients that had completed primary treatment for breast cancer comments that 60% of patients were sexually active at the end of their breast cancer treatment; the limitations to sexual activity were reported by patients as follows: 1/3 reported no limitations, 24.4% reported not having a partner, or reported problems related to partner as the reason for limitation of sexual activity: 7.2% reported that partner was not interested, 8.8% reported that partner had physical problems that precluded sexual activity, and 4.7% reported that partner was too tired [29].

The impact of breast cancer will be covered at length elsewhere in this book. There is also some evidence that the influence of psychological response on survival of breast cancer does impact the survival rates on breast cancer patients [30]. Body image has been shown to be clearly related to sexual satisfaction in women [31]. Clinical experience indicates that the frequency with which it is the male partner that experiences difficulties in recognizing the patient as a sexual being is frequent and troublesome. The impact on sexuality of breast cancer patients has been shown to be related to the degree of alteration of parts of the body that impact body image and feelings of attractiveness: among 1,957 breast cancer survivors 29.8% of patients undergoing lumpectomy reported negative impact on sex life, compared to 45.4% of those who underwent mastectomy with reconstruction and 41.3% of those who had mastectomy alone [32]. How much of these effects are related to partner reactions deserves to be explored and empirically tested, although the conclusion from clinical experience is that the partner reaction, ability to cope and adjust to the changed body image of his (or her) partner and the ability to develop a more integrated form of interaction with the complete person, and not with a specific body part, are critical for the adjustment of the couple to the new situation.

Clinical Intervention of Health Care Professionals

This chapter has reviewed the evidence that documents the impact on the partner's sexuality when cancer is diagnosed and treated. While partners are usually reluctant to be treated when his or her partner is being treated for a life-threatening condition, the evidence suggests that ignoring the needs of partners can be detrimental to them and to the patients themselves: when a more positive outlook is constructed the survival rates can be improved, at least in some forms of cancer [30].

While the inclusion of the partner in the healthcare plan of the cancer patient might seem unnecessary and be viewed as a unnecessary investment on the part of the health care professional, the reality is that with a relatively brief intervention, the inclusion of the partner in the process of cancer treatment or rehabilitation can improve the outcome of the therapeutic efforts of the healthcare team.

Table 25.2 presents a series of questions that have been adapted based on the consensus approach developed by Dean et al. [3]. These questions can serve as a lead in during the consultation of the cancer patient to assess and suggest avenues for improvement or referral when a patient is being treated for a cancer condition.

Table 25.2 Questions that clinicians can use addressing the impact of cancer and its treatment on partners sexuality

Have you spoken with your partner about your sexual ability?
Is your partner supportive of you getting treatment to improve your sexual satisfaction or his/her sexual function or satisfaction?
Does your partner have any concerns about the treatment impacting your sexuality?
Does your partner want to come and talk to me or to another doctor about improving your sex life together?
Do you know if your partner has any concerns about her/his own sexual function, or about any other health issues?
Is there anything else I should know to help me understand the impact that cancer has in your sexuality?

Modified after Dean et al. [3]

Conclusion

This chapter has presented an integrated vision of the impact of sexuality of the partner of cancer patients. The evidence reviewed indicates that cancer patients and their partners experience significant effects in multiple domains. A conceptual model has been proposed for understanding these effects. While sexual health has been neglected by medical practice for many years, the fact is that sexual health remains a central aspect of health and well-being for individuals and couples. While improving quality of life of cancer patients has become a more recognized goal of clinical intervention, addressing the sexual needs of partners can change the quality of life of cancer patients, as well as improving the chances of survival as the recent research on the effects of psychological consequences on cancer survival (at least on breast cancer) has shown [30]. Overcoming the obstacles to address these needs is a responsibility of health care professionals generally; we hope the present review might provide a tool toward this end, which ultimately will benefit our patients.

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Chapter 26
Gay and Lesbian Patients with Cancer

Anne Katz

Keywords Stereotype • Discriminate • Homosexuality • Human papilloma virus • HIV/AIDS • Ovaries • Prostate • Disclosure • Heterosexism • PLISSIT model • Relationship

Introduction

There is a paucity of research on gays and lesbians with cancer and the sexual consequences of the cancer and its treatments. It may reasonably be assumed that the sexual issues facing all men and women during and after treatment for cancer apply to gays and lesbians; however, are there special circumstances or issues for this group of people? It is suggested that between 2 and 3% of the population would self-identify as gay or lesbian [1] and so most oncology care providers would expect to see some gays or lesbians in their practice each year. There is of course regional variation with larger metropolitan cities having greater numbers of gays and lesbians and so one could reasonably expect that oncology care providers in these cities would see more gay/lesbian patients. But perhaps the central issue is that many gays/lesbians do not disclose their sexual orientation to their health care providers, deeming it either not necessary to their care or they limit who they tell.

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Health Care Provider Assumptions

Health care providers generally do not place much importance on an assessment of sexual functioning as part of routine care and this may be even more apparent in the oncology setting where treatment and its consequences are seen as a life and death matter; quality of life may be seen to be less important than cure or something that is not the physician's responsibility. However, sexuality is an important aspect of quality of life for the cancer patient [2]. Barriers to providing sexual health assessment in the clinical setting include too little time, lack of knowledge, and the perception that it is someone else's responsibility [3]. In one study, 98% of health care providers in a cancer ward stated that they discussed sexuality with less than 50% of their patients and most of the time (65%) the patient initiated the conversation [4].

Most health care providers have had very little education about homosexuality and the health care needs of this population. As a result they may be liable to make assumptions about not only the health care of this population but also about their sexuality. As an example, the assumption that all gay men engage in anal intercourse may result in an overestimation of the risk for anal cancer among gay men. The assumption that lesbians do not have penetrative intercourse may result in these women never being offered a Pap test. In reality, many gay men do not have anal intercourse and some lesbians do have intercourse with men occasionally or regularly and yet identify as lesbian. In order to avoid confusion it is important that the health care provider encourage

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openness about sexual orientation but that also means that the health care provider must educate him/her self about homosexuality and avoid stereotyping or discriminating against gay and lesbian patients. Some health care providers may have strong religious beliefs that homosexuality is wrong and this may of course present some unique challenges to providing comprehensive care.

Health care providers may also make assumptions about cancer risk for this population. It is well described that lesbians attend for routine screening such as mammography less than their heterosexual counterparts and many will not ever be pregnant and so miss regular contact with health care providers [5]. Because it is often assumed that lesbians are not having penetrative intercourse, they may not be screened for the human papilloma virus (HPV) even though they may have been exposed years before [6] and may indeed be at risk for cervical cancer. Because some lesbians may never have taken oral contraceptives or have breastfed infants, they may lack the protective benefits for ovarian cancer [7]. A greater acceptance of higher body mass may also mean that lesbians are more obese and thus at greater risk for cardiovascular disease and diabetes [8] as well as ovarian cancer [9].

Because of the dominance of HIV/AIDS in the gay population over the past 20 years, little attention was paid to other health care needs and risk. There is mounting evidence for the role of HPV in the development of anal cancer in men who have receptive anal penetration; this risk is amplified for those who use recreational drugs in the rectum [10]. Gay men with HIV/AIDS are at higher risk for cancer such as lymphoma because of the immune suppression caused by the HIV infection. A gay man's risk for prostate cancer is about the same as heterosexual men; however, there are far fewer educational materials aimed at gay men [1] specifically.

Special Considerations for Lesbians

Lesbians with breast cancer appear to have greater support and acceptance from their female partner and friends than heterosexual women [11]. For many lesbians, long standing issues exist with family of origin related to acceptance of their sexual orientation [12]. They may also experience greater acceptance of their altered bodies [13]. Lesbian women who chose reconstruction after mastectomy experienced regret while those who refused reconstruction adjusted to their altered body over time in one study [14]. But their interactions with health care providers during the diagnostic phase of cancer are often fraught with tension [15]. Part of this tension relates to disclosure issues; women have reported hostility from health care providers when they have disclosed their sexual orientation [12]. Others have reported sub-standard care including being told to be stoic because "lesbians are tough and should be able to tolerate pain" [16].

Still others are dissatisfied with the assumption that they are heterosexual which forces them to disclose (or come out) repeatedly to health care providers. However, lesbians who are partnered are more likely to disclose their sexual orientation to health care providers [17] and will do this to ensure that the partner is included in care decisions [18]. Support groups for women with breast cancer often do not address the needs of lesbians. The predominant issues for heterosexual women act as a barrier to lesbians who may not wish to disclose their sexual orientation to the group or find that their support needs are different [18].

Special Considerations for Gay Men

Prostate Cancer

Gay men with prostate cancer may struggle to find information that does not have vaginal intercourse as the main topic presented. Mention of a partner in terms of treatment decision making also focuses on the female partner in language and images. The preferred sexual role of the gay man with cancer will play an important part in how he weighs the importance of side effects; if

he is the insertive partner during anal sex, then the erectile dysfunction common after both surgery and radiation may be very important to him. However, if he is the receptive partner in anal sex then erection capacity may not be that important. In that case, the potential for rectal damage may be more important [1]. For some gay men, direct stimulation of the prostate through the rectal wall is an important part of sex play and the absence of the prostate itself following surgical removal results in a significant alteration to sexual pleasure. This needs to be acknowledged by the urologist when informing the man about treatment side effects.

These nuances may never be discussed with the patient and the urologist or radiation oncologist presenting the treatment options may not know about the man's sexual orientation or may not want to discuss anal sex with him. The patient may thus not be able to make a treatment decision based on full and complete information. Much like lesbians with breast cancer, prostate cancer support groups cater to heterosexual men and gay men and their partners may not feel welcome or comfortable attending or have their support needs met [19]. Internet based support groups for gay men with prostate cancer do exist; however, the man may not know about these or may not think to search on the Internet for such groups. In larger metropolitan centers support groups specific to gay men may exist; however, the man may have to find these on his own if his health care team do not tell him about such groups.

Colorectal Cancer

Gay men with colorectal cancer may experience many of the same sexual issues as those with prostate cancer; however, if the rectum has been surgically removed, receptive anal intercourse will no longer be possible and this will present a significant challenge to the man whose sexual expression was focused on this activity. The surgical treatment of colorectal cancer often involves the creation of a permanent or temporary ostomy; this can have a negative impact on body image and integrity. The gay community is often regarded as being one where physical appearance is very important and the real or perceived impact of having to wear an ostomy bag cannot be underestimated. The gay man who is not partnered may find this to be an insurmountable barrier to finding a new partner. The weight loss often associated with cancer treatment may also prove to be an issue for gay men particularly in the light of the weight loss associated with AIDS [19].

The authors of a review of sexual functioning in lesbian women with cancer suggest that the sexual consequences of cancer are related to the site of the cancer; however, there is no evidence to suggest that on a physical level homosexual and heterosexual women are any different. What may be different is the psychosocial response of the woman and her partner or support system [13].

Attitudes of Health Care Providers to Gay/Lesbian Patients

Gays and lesbians may be reluctant to disclose their sexual orientation to health care providers for any number of reasons including having had a previous poor experience when they did disclose or not believing that disclosure is necessary or relevant to the health issue. However, there are two concepts that underlie the experience of most gays and lesbians; these are homophobia and heterosexism.

Homophobia

The term homophobia refers to an irrational fear of gays and lesbians on the part of heterosexual individuals. The fear is usually based on myths and misperceptions and many homophobic individuals will state that they have never met a homosexual, but they just don't like them or believe that they are immoral, evil, predatory or many other negative assumptions. Homophobia is often shown in making derogatory jokes, using

harmful language and discriminating against persons believed to be homosexual in different ways. Homophobia occurs along a spectrum of behaviors, from negative comments on the more benign end to gay bashing on the more extreme end.

Some gay men and women internalize these negative beliefs and attitudes over their life time, perhaps because they have not seen any positive role models in their formative years. This subconscious acceptance of homosexuality as abnormal and bad can lead to self-loathing and lack of self-acceptance and is known as internalized homophobia. This negative self-image can lead to self-destructive behaviors such as substance abuse and high risk sexual activity.

Heterosexism

Heterosexism refers to seeing the world through an exclusively heterosexual lens, not acknowledging that something other than the heterosexual model exists, and believing that to be a heterosexual is normal and anything else is abnormal. Much of our health care system is heterosexist in nature; we assume that a person's partner is of the opposite sex and ask if a patient's wife or husband is with them. We use the pronouns "him" and "her," assuming that the partner is of the opposite sex. Many of the demographic forms that patients complete as part of hospital registration are heterosexist in that they give limited choices for partner status, ignoring the fact that in many states and jurisdictions, homosexual couples cannot by law be married and do not give the option for "domestic partnership" or some other term that would validate a homosexual relationship of long standing. These heterosexist attitudes ultimately alienate homosexual individuals and couples and while they may not appear as harmful as homophobia, they still have far reaching social and emotional effects.

Health care providers frequently hold the same heterosexist and perhaps homophobic attitudes as the general population. This may be noticed by gay and lesbian patients who are then less likely to disclose or even accept care from the practitioner. However, with specialty oncology care or in smaller cities and towns, patients may not be able to access another specialist. Many health care providers regard themselves as being neutral when it comes to the sexual orientation of their patients. They believe that health care should be available to all and that no one group or population is different [20]. This belief negates the context of the individual's life and suggests that everyone is the same and will lead to health care providers not asking about sexual orientation. If a patient does disclose that they are gay or lesbian, the provider may ignore this information in an attempt to not treat anyone as different. It is more appropriate to acknowledge this information and show acceptance; this will encourage the patient to be open in future interactions [21]. Some gay/lesbian patients may react negatively if the practitioner's response is neutral only [15] and if the disclosure is met with silence as is often the case, further communication is not likely to occur [22]. Health care providers may be concerned about offending the patient after disclosure or may claim ignorance about gay/lesbian lifestyles and sexual practices [23]. This may then be used as an excuse to not engage with these patients in a meaningful way.

Disclosure of Same Sex Attraction or Relationship

One of the more difficult tasks for the gay or lesbian person may be to disclose their sexual orientation to their health care provider. Their ease or difficulty with this may in part depend on previous experiences disclosing to family and the age at which this was done. It is recognized that concealing this important aspect of the self can lead to poor health outcomes [24] and risk taking behaviors such as smoking, alcohol and other substance abuse [25]. It may be even more difficult for lesbians to disclose; some are fearful of the treatment they will receive once it is known that they are lesbian or because they believe that sexual orientation is a private matter [26]. Disclosure is more likely to occur if the person thinks that the environment is safe and that the health care provider is someone who is responsive to the needs of lesbians.

In a small study of cancer patients, Katz [19] found that most gays and lesbians had disclosed their sexual orientation to oncology care providers and were insistent that their partners be recognized as an important part of the patient's life. In this study, overt homophobia was not encountered in the oncology setting. It has been suggested that being open with health care providers early on in the care trajectory and bringing the same sex partner to all medical appointments and introducing the person as "my partner" are important strategies for disclosure [15].

How Oncology Care Providers Can Help

The first step in being more sensitive to the needs of lesbians and gay patients is to recognize our own assumptions, prejudices and beliefs regarding homosexuality. This is likely to be heavily influenced by the attitudes of our own families of origin. However, many of us have challenged narrow heterosexist beliefs and have consciously adopted a more inclusive attitude and set of behaviors in this regard. Ask your patients if they are in a relationship and if the answer is "yes," enquire if it is with a man or a woman. Most gay or lesbian patients will happily answer this question as will heterosexual patients. Ask the patient what term they prefer to use when describing them self [27]. Being open and inclusive when talking to patients will encourage disclosure and form the basis for a therapeutic relationship without fear for the patient [28]. Some health care providers claim that they have never encountered a gay or lesbian patient in their practice; this is highly unlikely and rather suggests that patients did not feel ready or safe to disclose rather than an absence. Exposure to self-identified gay and lesbian patients during training influences physicians' practice with this population in a positive manner [29].

The attitudes of office staff often set the tone for the first encounter that gay and lesbians patients have within the clinical setting and it is important that they receive sensitivity training to ensure that the patient and their partner is welcomed and accepted. The forms that patients are required to complete may present few options; consider including words such as "relationship status" instead of "marital status." Consider too the educational material that is supplied to patients as an adjunct to information from the oncology care provider. Most of the patient education material is heterosexist in both words and images with an absence of inclusive language or images of same sex couples.

PLISSIT Model

Talking about sexuality with gay or lesbian patients should not be any different from talking to heterosexual patients. One framework that is useful for the initiation of this discussion is the PLISSIT model [30]. This model has four stages and it is suggested that after giving permission (stage 1) most patients require further limited information (stage 2) or specific suggestions (stage 3) to resolve their issue or need for information. Some patients may require intensive therapy; however, these tend to be the minority. Examples of phraseology for the four stages are provided below.

Permission: All oncology care providers should be able to function at this level.

A general statement normalizing the topic of sexuality in the context of cancer care and treatment is appropriate with all patients. "I ask all my patients about their sexual relationships. Do you have sex with men, women or both?"

Limited Information: Most oncology care providers should be able to give this kind of information. In the case of a male couple where radiation therapy for prostate cancer is to occur, the oncology care provider should be able to give general information about resuming intercourse. "If anal intercourse is part of your sexual repertoire, and you are the receptive partner, there are some general precautions to be aware of."

Specific Suggestion: This level of the model requires a deeper level of expertise.

Information at this level includes anticipatory guidance related to possible sexual consequences

of treatment. "You should avoid intercourse during the weeks of treatment and for some weeks after as the rectum may be much more sensitive. After completion of the course of radiation you have no pain, irritation or bleeding, it is safe to resume anal intercourse as soon as you feel like it. There is a risk of irritation to the rectum and this may persist for a while. Be sure to use plenty of lubrication and go very gently."

Intensive Therapy: This level of the model usually requires a referral to a sex therapist or specially trained counselor. Oncology care providers should know where to refer patients. "It sounds to me that sex play with your partner tends to get a little rough; it also sounds like this is something that you do not enjoy but are not able to deal with. Would you like to see one of our counselors? He has experience dealing with relationships where these issues occur."

Conclusion

The experiences of gays and lesbians with cancer are unique because of societal attitudes. For many, homosexuality remains a taboo, even in the 21st Century, and when this is coupled with the conflicting attitudes of society to sexuality, a perfect storm may be created. Ultimately however, there is a little research to base interventions for this population on. The most significant factors in the care of gays and lesbians with cancer may in fact be the pervasive presence of heterosexism and homophobia.

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Part IV
Cancer and Sex

Chapter 27
The Impact of a Cancer Diagnosis on Sexual Health

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Keywords Depression • Distress • Bother • SSRI

Introduction

Receiving a diagnosed of cancer is difficult in many ways. Patients have to cope with a myriad of issues which may include seeking multiple opinions, exploring treatment options, and anticipating the potential side effects of treatment while simultaneously being brought face-to-face with their own mortality. One aspect that is often overlooked by both the patient and the physician is the impact the cancer diagnosis can have on a patient's sexuality. Many of the previous chapters in this text have dealt with physical impact that cancer and side effects of treatment can have on sexuality. This chapter will take a slightly different focus and examine the psychosocial and psychosexual implications of a cancer diagnosis and how these implications can impact a patient's sexuality.

The published literature of the psychosocial impact of a cancer diagnosis on sexual functioning is relatively limited compared to other aspects of cancer and sexuality. As such, we have attempted to synthesize both the empirical and clinical literature. When possible we will review and present the empirical findings and evidence, however we will also rely on the writings and observations from experienced clinicians who work with cancer and sexuality. First, we will discuss the potential psychological impact that a cancer diagnosis can have on a patient and how this then may lead to difficulties in sexual functioning. Second, we will review the literature that examines the consequences of a cancer diagnosis on partners and spouses, and how this may affect the sexual lives of couples. Lastly, we will discuss the challenges of physician and patient communication around sexual issues and how this can positively or negatively influence sexual functioning.

When discussing sexual functioning, we are referring broadly to all aspects of the Human Sexual Response Cycle (HSRC) (Table 27.1). The HSRC consists of four phases: sexual desire, excitement, orgasm, and resolution. The sexual desire phase is the beginning of the cycle and is when sexual arousal takes place in men and women. Excitement is indicated by a physical sexual response which is generally considered an erection in men and vaginal lubrication in women. Orgasm occurs at the peak of excitement and is the apex of the cycle. The resolution phase is the refractory period that takes place after orgasm. One or all of these phases may be affected by a cancer diagnosis, and in a clinical setting, it is helpful to assess each of these phases. Patients with cancer may see a change in any part of this cycle. Though sexuality is usually considered a less important concern than survival after diagnosis, it is nonetheless important. Sexuality does not just reflect one's ability to participate in the act of sex; it also affects a person's self-image, personality, and social persona [1].

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Table 27.1 Human sexual response cycle

Phase	Definition
Sexual desire	The beginning of the cycle characterized by an increase in sexual arousal, often times considered heightened "libido"
Sexual excitement	The second phase of the cycle which is characterized by the physiological response of sexual excitement. For men, this is indicated by tumescence in the penis which produces an erection. For women, hardening of the nipples and vaginal lubrication on often considered the most visible indications of the sexual excitement phase
Orgasm	This phase is the peak of sexual excitement, and consists of quick muscle contractions in the lower pelvic area of men and women. It is considered the apex of the sexual response cycle
Resolution	This is the final phase of the cycle and generally considered a period "recuperation." In this phase the muscles relax, the blood pressure drops, and the body slows down from sexual excitement

The Psychological Response to a Cancer Diagnosis and Its Impact on Sexual Functioning

Mood, whether positive or negative, can have dramatic affects on sexuality [2]. Major depression in patients who have been recently diagnosed with cancer may be one cause of sexual dysfunction. Depression can impact up to 38% of newly diagnosed cancer patients [3], and unfortunately, depression often goes undiagnosed in cancer patients and the depressive symptoms often persist untreated [3, 4]. Both men and women who are depressed often report a significant drop in libido; in fact, a decrease in sexual interest is one of the diagnostic criteria for depression. When focusing specifically on men, it is also well established that depression and erectile dysfunction (ED) are related. In a study of 1,700 men, Araujo et al. reported a significant relationship between depression and ED [5] after controlling for age, health status, and lifestyle factors. Similar findings were obtained by Nicolosi et al. in a study of 1,800 men from Brazil, Italy, Japan, and Malaysia [6]. These men were all between the ages of 40 and 70, and again there was a strong relationship between the presence of depressive symptoms and ED. An important question in this research is which condition (depression or ED) triggers the other. Does depression lead to ED, or does ED lead to depression? The answer appears to be that both are true. Shiri et al. studied over 1,600 men and found a bidirectional relationship among depression and ED, finding a significant relationship between depression and ED, as well as a significant relationship between ED and depression [7]. The important implication for men with a new cancer diagnosis is that if a cancer diagnosis triggers depressive symptoms, this could also potentially impact both sexual desire and ability to obtain an erection. In addition to depression, several men have noted that a cancer diagnosis can lead to changes in their sexual self-image and some report fears of infection (either themselves or their partner) related to sexual activity after a cancer diagnosis. These have also been reported as reasons for a decrease in libido or having difficulty with erections in men diagnosed with cancer [8].

Although ED is thought of as an "individual" problem, it is important to note that ED can negatively impact intimate relationships and the female partner's sexual health. Men with ED often express that they feel ashamed, frustrated, and "less like a man." This may trigger men to withdraw not just from sexual activity but also from physical intimacy of any kind as physical intimacy reminds them of their ED, reinforcing their anger and frustration [9]. Thus, there may be an underlying fear to engage in any intimate behavior [8]. The combined loss of sexual and intimate activity can prompt relationship strain and resentment. This starts a cycle that may lead to feelings of helplessness related to sexuality and intimacy which only reinforces the depression and relationship conflict [10]. This cycle can be especially damaging in men recently diagnoses with cancer as the spouse often helps decipher treatment options, assists in the treatment decisions, and is usually responsible for care-taking duties

for a period of time after treatment. Increased conflict in the relationship may take away from the support provided by a spouse and complicates the spouse's emotional burden of dealing with the cancer diagnosis. In addition, there is evidence that the man's ED can lead to sexual dysfunction in their female partners [11, 12].

When focusing on women, psychological issues can clearly alter sexual functioning [13]. A diagnosis of cancer can trigger a number of emotional reactions in women which include frustration, stigma, embarrassment, anxiety, anger, irritability, and loneliness. All of these emotions may potentially impact women's sexuality in all phases of the HSRC [2, 14]. Hughes also notes that fear of death and the fear of rejection as a result of cancer are prominent emotions that can impact a women's sexuality [2, 15]. A cancer diagnosis can perpetuate any one or combination of these factors, and thus can lead to complicated and multifaceted sexual dysfunction.

Not surprisingly younger women seem to be at higher risk for various age-associated adjustments that may reflect on their sexuality. Research suggests that younger women have more difficulty adjusting and their quality of life suffers more than their older counterparts following a diagnosis of breast cancer [14, 16]. One study of 864 women diagnosed with breast cancer demonstrated that even though older women had poorer physical functioning at the time of diagnosis, they report better emotional well-being and adjustment following the diagnosis [14]. In a study of 204 women previously diagnosed with cancer, Avis et al. reported associations among sexual functioning, age of the women at diagnosis, and the amount of elapsed time since diagnosis [16]. Of most importance to women under the age of 50 were concerns over early menopause and fertility. Age at the time of diagnosis was positively correlated with the level of sexual dysfunction, and conversely, the age of diagnosis showed a negative relationship with regards to concerns about pregnancy as one might expect. Interestingly, the more time that elapsed since diagnoses, the fewer problems were reported regarding sexual dysfunction and pregnancy concerns. In addition, women who missed 90 days or more of work demonstrated a greater amount of impaired sexuality including decreased sexual interest, which implies the severity of the treatment or impact on mood from the cancer experience (two primary reasons for missing work) can have significant implication for sexual functioning. However, this relationship is apparently not related to the severity of the disease [16].

Schover outlined a number of important factors that may impact sexual functioning for women at diagnosis [13]. These factors included: having a committed partner; the quality of relationship with a committed partner; the presence of and number of children; age at time of diagnosis; and the presence of any previous sexual dysfunction or any sexual trauma in the past (i.e., rape or sexual abuse). If a women appears "at risk" on any of these factors (e.g., single, poor quality of relationship, younger age) the clinician should consider a more in-depth interview related to sexual concerns. It is also helpful for the woman to discuss the ramifications of cancer treatment on aspects of sexuality, such as body image and pregnancy concerns as the diagnosis of cancer can bring with it issues such as grief, fear, and anger that need to be addressed. Age should not be a limiting factor in these discussions, as older women are often sexual active. Schover points out that a counseling session after the diagnosis can go a long way in helping to mitigate the onset and severity of sexual dysfunction that may result after a diagnosis [13].

Partners Perception of Diagnosis and Affects on Sexuality (Table 27.2)

An often overlooked factor when considering a patient's sexuality is a partner's attitude toward the diagnosis of cancer. How the patient's support network reacts when faced with the diagnosis can alter the way the patient perceives her/himself sexually [1]. After a cancer diagnosis, the relationship dynamic is often altered in ways that can have a significant impact on both partners. This may result in a shifting of roles between one partner and the other. The partner may be

Table 27.2 Changing roles and perceptions of partners which may impact sexuality

Factors
Financial concerns or the partner may be forced to become the primary wage-earner
The partner may need to become the primary care-giver for children or parents
The partner may need to take on multiple other roles such as household chores, cooking, and coordination of family activities, increasing distress and fatigue
The perception that sexual intercourse with the partner with cancer is inappropriate, and viewing them in an asexual, sickly manner
Men may feel they are "inflicting" sex or may cause harm to their partner with cancer
The partner may view their significant other in a "child" role in need of being cared for, and feel inappropriate to act in a sexual manner

forced to become the primary wage-earner, putting immense stress on him/her and therefore decreasing the partner's desire for sexual interaction. Similarly, increased financial concerns that can result from a cancer diagnosis may also factor into this role shift between the couple. Another role that can change is that of the primary care-giver for children or the patient. A new stressor for the relationship can have negative downstream effects on a couple's level of intimacy. A patient's fear of abandonment and fear of rejection, and how the partner responds to these fears can potentially create problems in a couple's sexual dynamic [17].

In a study of 122 partners of patients diagnosed with cancer (43 men and 79 women), Hawkins et al. reported that 78% had a dramatic decrease in levels of intimacy in their relationships [18]. In this study, though there were many reasons for the cancers negative impact on the couple, specific themes emerged. Some partners stated that the thought of engaging in sexual intercourse with someone with cancer was inappropriate. This was mentioned predominately by men and focused on the idea of "inflicting" sex on a person with cancer [18]. These partners seemed to view their significant others in an asexual, sickly manner making sexual feelings almost impossible. Some partners expressed their concerns related to their significant other's mortality. The thoughts of the spouse or partner dying seemed to persist and decreased the desire for sexual activity. These feelings were joined by the underlying notion that sex could potentially harm or cause discomfort to the partner with cancer. In some instances it was the partner who felt unattractive because of the lack of desire that was demonstrated by the mate who had the diagnosis. For all these reasons, the subjects reported that the cancer diagnosis made it very difficult for those involved in a relationship to return to their customary prediagnosis sexual behaviors [18]. Another theme related to changes in roles that the partner experiences. The partner with cancer was thought of as "sick" and thus needed to be cared for. These roles inhibited the partner from seeing their mate in a sexual role. In some cases, the partner saw their significant other as a "child" thus making it feel inappropriate to act in a sexual manner. This role reorientation is especially stressful on the relationship early after the cancer diagnosis as both the patient and the partner are adjusting to the new dynamic and reevaluating their ideas of "normal" and what the "future" means [18].

[27] reported similar trends in a study of 50 Israeli husbands of women diagnosed with cancer. These men expressed difficulty adjusting to work, finances, and household tasks in the face of the cancer diagnosis of their wives. When asked specifically about their sexual relationships, 75% of the men said that the cancer had a negative impact. Interestingly, other research has noted that men seem to cope better with their partner's cancer diagnosis and demonstrate lower levels of anxiety than women whose husbands were diagnosed with cancer [19]. Men may adjust more quickly to a partner's cancer diagnosis, however they are still affected and sexuality appears to be an area of major concern.

It seems clear that a cancer diagnosis affects both partners' sexuality, and may impact the partners considerably more than most medical

professions may consider. For this reason, the partner's feelings and beliefs need to be accounted for when evaluating for possible impairments, and discussing sexuality with patients.

The Lack of Discussion of Sexuality at Diagnosis (Table 27.3)

Traditionally, amidst the whirlwind of information that patients have to cope with at the time of diagnosis, often both the oncology team and patients do not consider information about sexual health or how a cancer diagnosis may impact the patient's sexuality. Although the cancer diagnosis and treatment should naturally take center stage in initial discussions after diagnosis, the treatment team should not ignore important quality of life issues. In the initial phase of a cancer diagnosis, the general attitudes of the physician and the patient toward sexuality have a vital impact on the way sexual health will be dealt with as treatment progresses. Considerations include the value the patient places on sexuality, the level of comfort the physician has with the topic, or even the amount of information the physician feels is appropriate to disseminate.

Patients recently diagnosed with cancer may feel that getting as much information about their disease is paramount, and ignore any information deemed superfluous. Vital information often includes prognosis, treatment options, or the impact the cancer will have on their immediate future. Sexual ramifications can feel less important at the time. Even if sexuality is a concern, some patients repress the thoughts [20]. These attitudes increase the responsibility of the treatment team to inquire about sexuality and discuss with the patient the impact a diagnosis or treatment may bring.

It has been noted that many patients would like to discuss the topic of sexuality, but do not. One retrospective study of women diagnosed with cancer showed that 80% received no information or counseling concerning sexual health from their healthcare professionals. Of these women, over 60% wanted to talk with someone about their concerns with sexuality. Unfortunately, the patients did not act upon these initial instincts because of the patients' feelings about how they would be perceived. They felt there would be a sense of rejection associated with broaching the topic of sexuality in the face of cancer [17]. Patients also report that there is a lack of written information concerning the impact of caner and its treatment on sexuality, and one viable option may be providing pamphlets on how sexuality may be impacted to newly diagnosed patients and their partners [21].

Hordern and Street interviewed 50 patients about discussing sexuality with their physician in the face of a cancer diagnosis [22]. Some patients did not want to burden their healthcare professionals with questions about sexuality when they were already responsible for so much in terms of

Table 27.3 Reasons why sexuality may not be discussed in a medical visit

Reasons patients may not discuss sexuality	Reasons physicians may not discuss sexuality
Information about the disease is paramount, and may ignore superfluous issues	View sexuality as "taboo" in the face of cancer
Concerned how physician would perceive them if they discussed sexuality, afraid they may be viewed as not taking their cancer seriously	Lack of time
Do not want to burden their physician	A sense of embarrassment
Disregard feels of sexuality since cancer is most important topic	Own personal beliefs that sexuality is not important
Accept changes in sexuality as part of the cancer experienced, and do not know they can be addressed	Lack of training and confidence to discuss sexuality with the patient
Assume all important information will be discussed by the physician	Assume that the patients will bring up the topic if they feel it is important

the medical aspects of their disease. Coping with sexual problems were often thought to be better than being dead, so they disregarded any feelings they had toward sexual health. Others just accepted any changes to their sexuality as part of the cancer experience and chose not to dwell on those problems. Patients often assumed that anything important would warrant a discussion by the physician. If the physician did not acknowledge the topic of sexuality, then patients did not feel it warranted their concern either. This type of logic places the responsibility and comfort of discussing sexuality squarely on the shoulders of the physicians. Some patients revealed that they would only discuss topics like sexuality with certain healthcare professionals. This search for the right type of physician might leave the patient without vital support and information. These patients often did not feel that their primary doctors were adequate to speak with about their sexual health [22].

The attitude of the medical professional delivering the diagnosis may have an immense affect on the way the patient perceives their own sexuality. Difficulties arise when some physicians do not focus on the topic because of the taboo nature of a patient's sexuality in the context of cancer and palliative care [23, 24]. Doctors and nurses need to be aware of, and acknowledge, their own personal attitudes toward sexuality in order to provide the best care possible. They also should try to minimize any influence that their own personal beliefs may have on the patient or the partner regarding sexuality as this can be detrimental.

Sundquist and Yee discussed why physicians did not see the importance of discussing sexual health with patients in light of a cancer diagnosis [25]. These included: a lack of time to fully discuss sexual health, the physician's embarrassment in discussing sexual behavior, a lack of experience in discussing sexuality with patients, or the belief that by virtue of having cancer, the patient was too ill to participate in sexual activity. It seems clear that these attitudes have an impact on patients. Many patients report a sense of unmet needs regarding support with their sexuality after their cancer diagnosis. Hordern and Street reported that patients felt that they were not given adequate advice, emotional support, or information about sexual health [22]. Unmet needs were sometimes attributed to the physician's divergent view of the importance of sexual health when compared to that of the patient. The physician prioritized what was important in their view and sexuality fell toward the bottom of the list. Many physicians assumed that patients shared their views that beating the cancer should be the sole focus. The physician's idea of how patients valued sexual health seemed to be determined by various independent factors. These included the patient's culture, diagnosis, age, gender, or presence of a partner. The physicians determined from this how much, if at all, they would focus on sexual health and the ramifications of a cancer diagnosis [24].

An obvious important factor is the physicians' own attitudes about sexuality. For instance, when a doctor diagnoses someone with cancer who is around the same age as the doctor's parents, s/he may confuse thoughts about the patient with those of his/her parents. A doctor may not feel that his/her parents are active sexually so assumes the patient is not active either. Sometimes the doctor is not comfortable with the thought of someone their parent's age being sexually active so they avoid the topic entirely [24]. Some physicians simply feel that sexuality and intimacy issues are not a medical concern in light of a cancer diagnosis. The physicians may feel that in a discussion of treatment options, sexuality is expendable [26]. Another aspect of this dynamic is the legal ramifications. Healthcare professionals may not be completely comfortable with the topic of sexuality and thus avoid it for fear of legal consequences. The age of medical litigation has created an atmosphere in which doctors may be afraid to delve too deeply into topics that are perceived to be nonmedical in nature or beyond their expertise [24]. Alternatively, they may need to also consider the implications of not addressing issues that may strongly impact quality of life.

Other healthcare professionals may not broach the topic because of the clinical environment. These include clinical settings where stray comments can be heard by people in the surrounding area,

or the topic of sexuality was not deemed appropriate due to the people present with the patient. The doctors did not want to discuss sexuality in the presence of family or friends for fear it would put the patient in an uncomfortable situation [24].

Doctors who avoid the topic of sexuality with the patient may do so in various ways. Sometimes the physicians simply distanced themselves from the topic. To do this, they became purposefully vague and nebulous with their answers or just hoped questions about sexual health were not asked [23]. Other times the physicians resorted to jargon to avoid the topic. Doctors may "medicalize" the sexual and intimacy issues of patients making it difficult for the patient to verbalize any nonphysical sexual dysfunction. This is not necessarily done consciously by the doctors, but perhaps, as a defense mechanism when confronted with an uncomfortable topic. Sometimes the physician felt the topic would be discussed by another person down the line who was more qualified or capable. This frequent omission of information because of the assumption that others would handle it eventually meant the patient did not get the information, even after seeing multiple doctors [24].

Conclusion

Oncologists and medical staff need to be cognizant of the importance of sexual matters when they deal with a newly diagnosed patient and can model the acceptance of addressing sexual health needs throughout cancer treatment and survivorship. They should be aware that the range of psychological reactions to a cancer diagnosis may impact sexuality, and that the dramatic changes to patients' lives that result from dealing with cancer can have significant implications on how a couple relate to each other sexually. Medical professionals can encourage patients and their partners to deal with issues as they provide a supportive environment to help encourage optimal sexuality and intimacy recovery after a cancer diagnosis.

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Chapter 28
Breast Cancer

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keywords Sexuality • Sexual function • Sexual problems • Sexuality activity • Aromatase Inhibitors • Mastectomy • Survivorship • Breast Cancer

Breast Cancer Epidemiology and Population Data on Sexuality

In the United States, breast cancer is the most common cancer diagnosed in women and is second to lung cancer as the leading cause of cancer death [1]. It is estimated that there will be 194,280 cases of breast cancer diagnosed and 40,610 deaths from breast cancer in 2009 [1]. Of the new diagnoses, 192,370 will be in women and 1,910 will be in men [1]. Breast cancer in men is significantly more likely to be estrogen-receptor positive [2] and is associated with risk factors including testicular and benign breast conditions, age, family history, Klinefelter syndrome, and Jewish ancestry.

Figure 28.1 shows the distribution of U.S. breast cancer cases by female age and life course in relation to the prevalence of partnership and sexual activity by age. Between 2003–07, the median age for breast cancer diagnosis in the US was 61 years; 12.4% of new breast cancer cases occurred in reproductive age women (age 44 and younger), 22.6% of new cases occurred in perimenopausal women (ages 45–54), and the remainder occurred in menopausal women [3]. The vast majority of women with breast cancer are both partnered and sexually active. As a first example of the many ways in which sexuality is relevant to breast cancer, some women report that their intimate partner had a role in detecting or confirming a breast-related change that led to medical evaluation and diagnosis of their breast cancer; sometimes this occurs during sexual activity and can have emotional implications for future sexual encounters in women diagnosed with breast cancer.

Cancers that directly affect the sexual organs are the most common types among cancer survivors. Among the more than 11.4 million cancer survivors in the United States, female breast cancer is the most prevalent cancer type (23%), followed by prostate (20%), and colorectal cancer (10%) [3]. Fourteen percent of survivors have had a gynecologic cancer (uterine, ovarian, cervical, vaginal, vulvar, or fallopian tube). About 1% of breast cancers occur in men (1.2 incident cases per 100,000 men in 2006), as compared to 187,427 cases (123.4 incident cases per 100,000) in women [3]. Although breast cancer survivors are, on average, younger and more prevalent than prostate cancer survivors, development and translation of surgical and medical strategies to preserve sexual function in prostate cancer are very far ahead of interventions available for people with breast cancer.

Average incidence rates of breast cancer rose markedly between 1975 and 2006 (from 105 to

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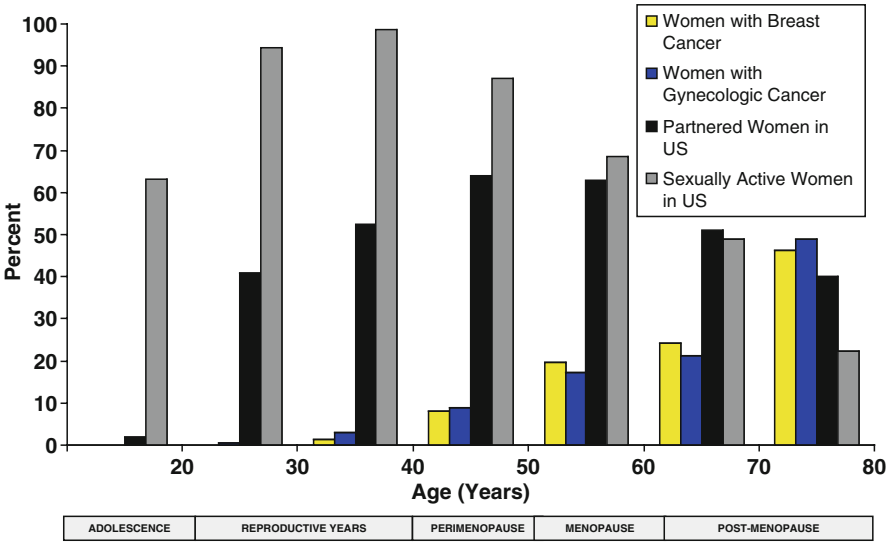
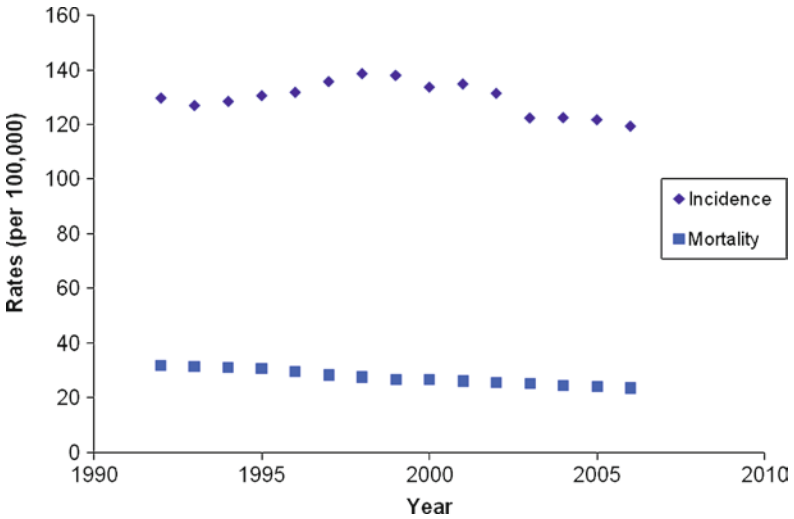


*Data estimated from the *CDC National Survey of Family Growth* (2002), *Surveillance, Epidemiology, and End Results Data* (2006), *U.S. Census Bureau* (2006), Lindau, S. T., L. P. Schumm, et al. (2007). "A study of sexuality and health among older adults in the United States." New England Journal of Medicine **357**(8): 762-774.

Fig. 28.1 Distribution (%) of incident female breast cancer cases 2009, partnership, and sexual activity by age and life stage in the United States



Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups -Census P25-1130).
Incidence source: SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.

Fig. 28.2 Average incidence and death rates of breast cancer in the United States

123 cases/100,000 for women and 0.85–1.2 cases/100,000 for men), while average death rates due to breast cancer over that period have declined from 31 to 23 deaths/100,000 women and 0.37–0.29 deaths/100,000 for men (Fig. 28.2). Decline in deaths due to breast cancer over the last 35 years has been attributed to a combination of factors, including improvements in early diagnostic technologies, public health breast cancer prevention programs, health care policies,

improvements in medical and surgical therapies, reduction in risk factors, and interventions to prevent breast cancer in carriers of BRCA 1 and 2 mutations [4, 5]. Relative survival rates have also increased notably since 1975. Among those diagnosed with breast cancer in 2000, more than 90% were alive after 5 years, as compared to fewer than 75% of those diagnosed in 1975 [3].

Population data affirm that most people who become diagnosed with breast cancer have a partner and are sexually active, although older women are significantly less likely than younger women or older men to have a partner. Many individuals with and without a partner, including older adults, value sexuality as an important part of life, have sexual thoughts, and engage in masturbation [6]. People with cancer identify sexuality, marital integrity, and body image along with death among their top worries [7]. Cancer care providers should approach the topic of sexuality across the continuum of care with all breast cancer patients, even those who are older or without a current sexual partner.

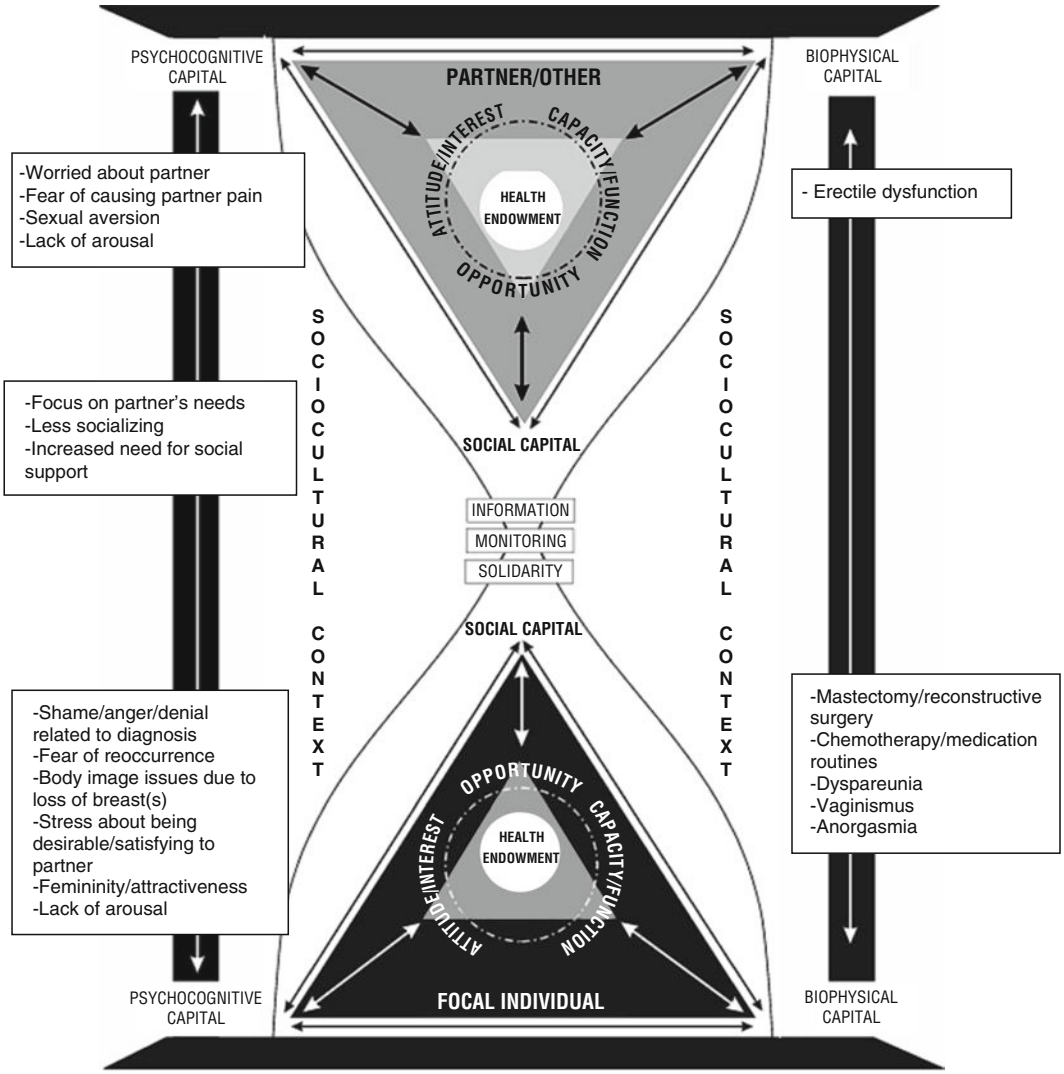
Because the overwhelming majority of breast cancers occur in women, this chapter focuses primarily on sexuality of women and their partners. Both clinical experience and research are exceedingly limited to specifically inform specialized care of sexuality issues in men with breast cancer.

The Interactive Biopsychosocial Model Applied to Sexuality and Breast Cancer

The general medical model approach to understanding female sexuality focuses primarily on prevention of sexually transmitted disease and HIV/AIDS, female contraception, unwanted pregnancy, sexual and domestic violence, and sexual behavior as a health risk factor. Since the introduction of highly successful drugs to treat male erectile dysfunction in the late 1990s, more attention has been paid to identifying female sexual dysfunction. Activities include major new investment in development of interventions to treat it (aside from the use of estrogen to treat dyspareunia, no pharmaceutical has yet received U.S. Food and Drug Administration approval for treatment of female sexual dysfunction). While clinically valid, this medical view of sexuality defies its multidimensional nature and limits understanding of the meaning of sexuality for health more broadly.

The Interactive Biopsychosocial Model (IBM) provides a conceptual framework for understanding the bidirectional relationship between sexuality and breast cancer throughout the life course (Fig. 28.3). As discussed in more detail below, breast cancer, other physical and mental health problems, fatigue, worry, surgeries, and medications can all contribute to or cause sexual problems and dysfunction. Just as in other women, sexual behavior of women with breast cancer can result in other health problems such as sexually transmitted infection or unwanted pregnancy. The IBM represents this reciprocal relationship between sexuality and health but also incorporates the possibilities that sexuality may be health promoting and that cancer or aging may confer advantages for sexual life. For example, one study of 204 breast cancer survivors (diagnosed at age 50 or younger) found increased closeness and intimacy with their partners following breast cancer diagnosis [8]. In a qualitative study of couples affected by lung cancer, several said that since the cancer diagnosis, they physically touched more often and appreciated each other more [9].

In addition to emphasis on the bidirectional relationship between sexuality and health, health is defined as jointly produced by a woman in conjunction with her spouse or intimate partner. Joint production of health means that both partners of the couple contribute assets (or liabilities) and these assets and liabilities impact the health of the other. For example, if the male spouse of a woman with breast cancer has erectile dysfunction, she may be distressed about her sexual desire or satisfaction or may report her own inability to experience orgasm. A breast cancer survivor with dyspareunia and vaginismus due to aromatase inhibitor (AI) therapy may have a partner who experiences sexual aversion



Adapted from Lindau, S. T., E. O. Laumann, et al. (2003). "Synthesis of scientific disciplines in pursuit of health - the Interactive Biopsychosocial Model." Perspectives in Biology and Medicine **46**(3): S74-S86.

Fig. 28.3 The Interactive Biopsychosocial Model of sexuality and breast cancer

due to fear of causing her pain. Body image and sensory changes caused by mastectomy and/or breast reconstruction can interfere with both partners' ability to feel sexually aroused. The hourglass shape of the model symbolizes the dynamic nature of both health and intimate relationships over time. Clinically, this model is used as a mnemonic for the broad domains of inquiry pertinent to assessing a patient's sexual history (physical, psychological, social, contextual) and reminds the clinician of the importance of ascertaining whether the patient has a partner, the quality of the relationship, the partner's health and sexual function, and how these factors have changed over time. Furthermore, the model serves as a visual reminder to the breast cancer patient that treatments to address sexual problems often require a partnered and life-course approach. Initial improvements with therapy may wane if the partner or the partner's health changes or if new health issues or cancer recurrence arise for the patient.

Interestingly, we have observed that if female sexuality is addressed in the context of breast cancer care, the focus tends to be more around sexual function and less on preventive or health maintenance issues related to sexuality. For example, few breast cancer survivors are offered counseling and testing for sexually transmitted infections or HIV. Screening for partner violence or serious relationship difficulties, which can escalate during or following cancer treatment [10], is often overlooked. Comprehensive care for sexuality issues in women with breast cancer requires attention to both functional and preventive issues.

Sexuality and the Breast Cancer Care Continuum

Breast Cancer Risk Factors and Sexuality

Sexual behavior and activity are known risk factors for some cancers. For example, sexual transmission of human papillomavirus (HPV) can cause cervical or anal cancers via skin and mucosa contact during penetrative intercourse [11]. Oral sex can also transmit HPV to the anogenital or oropharyngeal tracts [12, 13]. Other sexually transmitted infections, including Hepatitis B, C, and human immunodeficiency virus (HIV), can also cause or complicate cancer (hepatocellular carcinoma and Kaposi's sarcoma, respectively) [14]. There are no known sexually transmitted causes of breast cancer. However, behavioral risk factors for breast cancer, such as high alcohol use, obesity, lack of physical activity, and possibly high-fat diet, may be exacerbated by a partner who shares these behaviors [15]. Environmental exposures may result from partnership with a smoker (secondhand, but not primary, tobacco smoke has been associated with breast cancer in some studies [16]) or with someone who works or lives in a high toxin environment [17]. Whether women could be exposed to breast carcinogens via semen or saliva from a partner is unknown, but some carcinogens (including nicotine and its metabolites) are known to concentrate in seminal fluid [18] and saliva. Genetic risk factors for breast cancer are influenced by partner selection (for example, an Ashkenazi Jewish woman without a BRCA mutation selects an Ashkenazi Jewish mate who is a BRCA carrier), thereby determining breast cancer risk in offspring. (Note that the BRCA 1 and 2 mutations are autosomal dominant, so an individual with one affected parent can inherit the trait and an individual with two affected parents has twice the risk of inheriting the trait).

A woman who is comfortable with and aware of her body may be more likely to detect and act on early changes such as a breast lump or breast skin changes due to cancer. Likewise, it is also plausible that a sexually active woman with a partner who regularly sees or touches her breasts may be more likely to identify a cancerous breast change. A spouse or partner may also be instrumental in providing a woman information that could enlighten her to breast cancer risk reduction, alert her to concerning breast changes, or in encouraging a woman to seek care if such changes occur. The IBM, applying social capital theory [19, 20], typifies dimensions of social support that can influence health between spouses or partners, including solidarity or love, education or information, monitoring of health, and instrumental support such as assistance in going to a doctor's appointment or paying for care.

In assessing the sexual history in women with breast cancer, the circumstances leading to diagnosis and feelings about risk factors are important to explore. For example, a woman may have been concerned about her breast and begun avoiding sexual contact before her diagnosis. Or, partner involvement in identifying a breast lump or a patient's delay in seeking care despite her partner's urging may affect sexual feelings or relationship dynamics following cancer diagnosis. A woman's concern about whether she might have transmitted cancer risk to her children or whether she should not reproduce to prevent this could also strain her relationship or inhibit her sexual desire and arousal [21].

Breast Cancer Screening and Sexuality

Sexuality encompasses sexual and gender identity, orientation, physical capacity and social opportunity for sex, and psychological, emotional, attitudinal, and cognitive dimensions [22]. Sexual agency refers to an individual's ability to control her own sexuality, including when and with whom to engage sexually. Women with low sexual agency, shameful feelings about sex, poor body image, low self-esteem, and women with a history of sexual or emotional abuse may be less likely to access breast cancer screening. Breast cancer screening allows for early detection of breast cancer, which saves lives and allows for less aggressive surgery and adjuvant therapy [23]. The American Cancer Society has developed cancer screening guidelines, which were last updated in 2003 for average risk women and in 2007 for high-risk women [24]. The United States Preventive Services Task Force published its most recent guidelines in 2009, including a controversial recommendation against routine screening mammography in women ages 40–49 years [25–27]. In addition to taking a sexual history including screening for sexual risk factors and dysfunction, health care providers practicing in the field of female sexual medicine should be competent in advising patients about screening guidelines and addressing sexual attitudes that might interfere with breast cancer screening (Table 28.1).

Average-Risk Women Screening Guidelines

In women with average risk for breast cancer, screening should begin at age 20 with clinical breast exams performed every 3 years [28]. During their twenties and thirties, in addition to clinical breast examinations, women should also receive counseling on the importance of bringing any new breast symptoms to the immediate attention of a physician. Starting at age 40 (latest ACS guidelines) [29] or age 50 (latest USPSTF recommendations) [25], average-risk women should receive clinical breast examinations and begin routine screening mammography every 1–2 years. Evidence regarding the proven benefits of mammography for early detection of breast cancer prior to symptom development should be discussed with every woman, and an individualized plan should be created. There is no upper age when mammograms should be routinely discontinued, although the benefits from screening past age 75 are unclear because of insufficient evidence. Screening should continue in women who are in good health and would be candidates for breast cancer treatment.

The value of monthly breast self-examination in reducing breast cancer mortality is controversial [25, 29]. The American Cancer Society no longer recommends monthly self-breast examinations. However, all women should learn about the potential benefits, limitations, and harms (false positive results) of breast self-examinations. Women should receive instructions regarding proper technique for breast self-exams and then individually may choose to perform them monthly, occasionally, or never. Even a brief sexual history can help alert the provider to a woman who is uncomfortable with her body or who has concerns about her breasts and presents an opportunity to remind a patient about the value of early detection should symptoms occur. Primary care providers, breast oncologists and surgeons, and female sexual medicine specialists should be competent in advising women about breast self-examination.

Very High-Risk Women Screening Guidelines

Very high-risk women are women with either a known inherited risk (BRCA mutation or other rarer genetic syndromes), suspected risk (untested, but has a first degree relative with a known mutation), prior chest/mantle (neck, mid-chest and axilla, which includes the main lymph nodes and areas in the upper half of the body) radiation at a young age, or an approximately 20–25% or greater lifetime risk of breast cancer based on breast cancer risk assessment tools [30]. Therefore, it is essential for physicians to take a

Table 28.1 Breast cancer screening guidelines by age and breast cancer risk

	20s	30s	40s	50s	60s	70s	80s+
Family history	Physicians should have good family history of each patient, so that candidates can be indentified for more intensive cancer screenings at a younger age						
Counseling on symptoms	Should receive counseling on the importance of bringing any new symptoms to the immediate attention of a physician						
Clinical Breast Exam (ACS)	Every 3 years		Annually for women in good health				
Clinical Breast Exam (USPSTF)	Current evidence insufficient to assess additional benefits and harms of CBE						
Regular Screening Mammography(ACS)	Annually for high risk		Annually for women in good health				
Regular Screening Mammography (USPSTF)	High risk only		Individual's decision to begin biennial screening	Biennial			No recommendation. Current evidence insufficient to assess additional benefits and harms in women 75 years or older
Screening MRI(ACS)	Annually for high risk (ACS)						
Screening MRI (USPSTF)	Current evidence insufficient to assess the additional benefits/harms of MRI instead of film mammography as screening modality for breast cancer						
Breast Self Exam(ACS)	Screening option for women starting in their twenties						
Breast Self Exam (USPSTF)	Recommends against teaching breast self-examination						
Risk-reducing mastectomy	High risk may consider preventive mastectomy as a way of decreasing their risk						
Risk-reducing oophorectomy	High risk may consider preventive oophorectomy as a way of decreasing their risk						

Data compiled from the American Cancer Society (ACS) & U.S. Preventive Services Task Force (USPSTF), 2010

Table 28.2 BRCA 1 and 2 mutation-related cancers: hormones and Her-2/Neu characteristics

Cancer type	BRCA1	BRCA2
Breast	+++++	+++++
Ovarian	++++	++++
Colon	+	
Cervical	++	
Uterine	+	
Pancreatic	+	++
Liver	+++	
Stomach		+
Gallbladder		+++
Bile Duct		+++
Melanoma		+
*Lymphoma		+
Receptor Characteristics		
Estrogen Receptor Positive	10%	66%
Progesterone Receptor Positive	21%	55%
Her-2/Neu Expression	3%	3%

*Kadouri L, Hubert A, Rotenberg Y, et al. Cancer risks in carriers of the BRCA1/2 Ashkenazi founder mutations. *Journal of Medical Genetics* 2007; 44(7):467–471.

Thompson D, Easton DF, the Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. *Journal of the National Cancer Institute* 2002; 94(18):1358–1365.

The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. *Journal of the National Cancer Institute* 1999; 91(15):1310–1316.

Lakhani, S. R., M. J. van de Vijver, et al. (2002). "The pathology of familial breast cancer: Predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2." Journal of Clinical Oncology 20(9): 2310-2318.

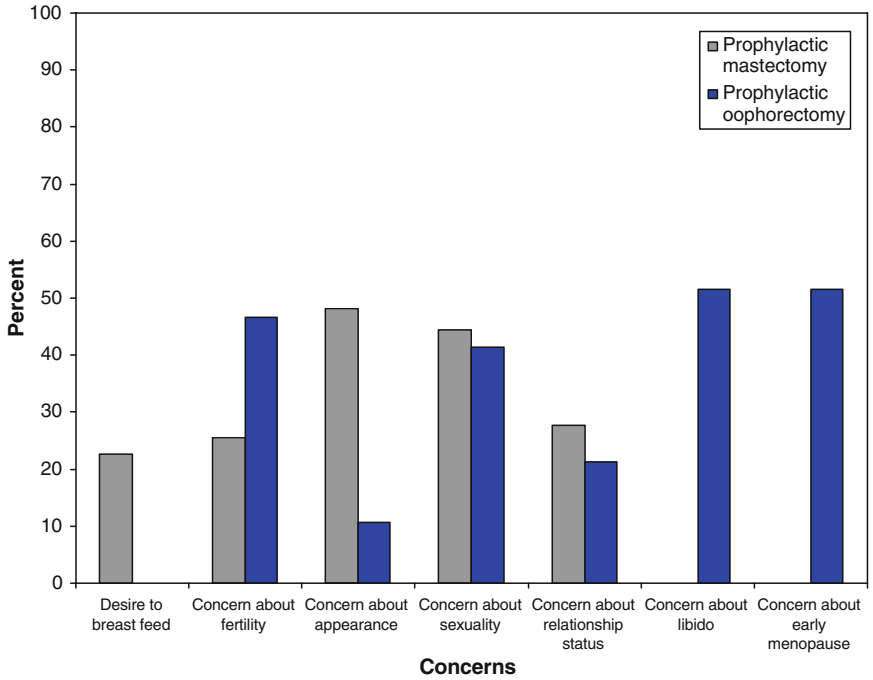
good family history from each patient because certain women will be identified as candidates for more intensive cancer screening at younger ages [31]. In very high-risk women, annual MRIs and mammograms are recommended starting at age 30, or 20 years before the age their youngest relative was diagnosed with breast cancer [32].

Women with BRCA 1 and BRCA 2 mutations (Table 28.2) or those at high risk of ovarian cancer may consider risk reducing bilateral salpingo-oophorectomies or bilateral mastectomies [33]. Prophylactic mastectomy decreases the risk of breast cancer by 95% [34]. Bilateral oophorectomy in BRCA 1 carriers and genetically uncharacterized high-risk women reduces the risk of breast cancer by approximately 50% [33, 35]. Such treatment also significantly reduces the risk of subsequent ovarian cancer with a hazard ratio of 0.04 (95% CI: 0.01–0.16) [33]. Oral contraceptives also decrease the risk of ovarian cancer. Premenopausal women who undergo a bilateral oophorectomy have an immediate reduction in estrogen levels to the postmenopausal range and often develop abrupt and dramatic postmenopausal symptoms.

Very high-risk women with known inherited breast cancer risk have several options for cancer prevention, which include intensive screening, prophylactic surgery, and chemoprevention. A total of 50% of women with BRCA 1 and BRCA 2 mutations opt for screening only even though chemoprevention with tamoxifen decreases the risk of breast cancer in half [36]. Patients elect against chemoprevention because they are concerned about the side effects of tamoxifen, psychosocial implications, or have limited access to medications. Tamoxifen is often recommended in the United States, Canada, and Poland, but not in western Europe, Israel, Austria, or Norway, which explains large differences in chemoprevention use based on country of residence. In general, tamoxifen is used for chemoprevention in less than 20% of eligible women.

Sexual and relationship concerns arise for women both in contemplating whether to undergo genetic testing and in coping with a diagnosis of elevated genetic risk for breast cancer. Diagnosis with a breast cancer risk gene can have major impact on key aspects of intimate life, including marriage, childbearing, and disclosure of cancer risk information to a potential life partner. In one study, concerns about appearance (48%), sexuality (45%), and relationships (28%) were highly prevalent among BRCA carriers who chose not to have risk-reducing mastectomy. These same concerns, in addition to worries about loss of libido (52%), were found among BRCA carriers who had opted not to have prophylactic salpingo-oophorectomy [21] (Fig. 28.4).

Risk-reducing surgery in BRCA carriers directly affects critical female sexual organs (the breasts and ovaries) along with a woman's psyche, yet few women report that their preoperative counseling involved assessment of baseline sexual function or guidance about sexual outcomes following surgery [21]. In general, women tend not to initiate discussion with their physician



Adapted from Staton, A. D., A. W. Kurian, et al. (2008). "Cancer risk reduction and reproductive concerns in female BRCA1/2 mutation carriers." Familial Cancer 7(2):

Fig. 28.4 Sexual and relationship concerns among female BRCA carriers who opted out of risk-reducing surgeries

about sexual issues, even though repeated studies show that women of all ages regard sexuality as an appropriate topic for a physician to address [37]. Despite prevalent fears that removal of the breasts or ovaries will render them unattractive, masculine, asexual, or feeling "castrated," some BRCA carriers express feeling guilty or embarrassed to ask about sexual effects of treatments that may be life saving [38].

In one retrospective study of 213 sexually active premenopausal BRCA carriers ages 25–40 in the United States, 70% of those who had risk-reducing mastectomy or bilateral salpingo-oophorectomy reported negative sexual changes following the procedure as compared to none in the group who opted out [21]. In a Swedish prospective longitudinal study of 90 BRCA carriers ages 20–69 undergoing bilateral prophylactic mastectomy between 1997 and 2005, 65 women were followed for 12 months after surgery. Nearly half reported feeling self-conscious (48%), less sexually attractive (48%), and dissatisfied with their scars (44%) 1 year following their operation. The women rated their sexual pleasure lower 1 year following the procedure compared with baseline. No differences were found over time in sexual behaviors, discomfort, or activity [39]. An evidence base to inform the optimal timing of and interventions to prevent negative sexual sequelae in BRCA carriers is needed.

Based on the interdisciplinary experience of these authors, some key ingredients for positive outcomes include baseline assessment of sexual function and anatomy prior to cancer or risk reduction interventions; partner status and relationship quality; physician-initiated discussion of sexuality implications as treatment options are being considered; inclusion of even a single question about sexual concerns in the basic review of systems throughout the treatment period (under genitourinary review of systems: "Do you have any concerns about or problems with sexual function?"); validation that sexual changes do occur and can be related to the treatments; and a willingness to link the patient to specialty services if needed.

Diagnosis

Women may present with a palpable mass or an abnormality that appears suspicious on radiographic imaging with either a mammogram, ultrasound, or breast MRI. These lesions are subsequently biopsied in order to confirm the initial diagnosis. Tissue diagnosis is the gold standard for the diagnosis of breast cancer. Unlike women, the majority of men diagnosed with breast cancer present with a palpable mass.

Breast cancer is a heterogeneous disease that is characterized by tumor size, lymph node involvement, hormone receptor status, histologic grade, and lymphovascular invasion. Early detection is an important factor for favorable outcomes. Mammogram is the criterion standard for screening, but 5–10% of breast cancers may be mammographically occult, especially in young women with dense breasts. Breast cancer can be noninvasive in situ carcinoma or invasive carcinoma. Noninvasive carcinoma in situ includes lobular carcinoma in situ (LCIS), which is not a true cancer but a marker of risk, and ductal carcinoma in situ (DCIS), which is stage 0 breast cancer. Invasive breast cancer is diagnosed when malignant cancer cells invade through either the ductal or lobular basement membrane into the surrounding stroma [40]. Breast cancer may be multifocal, multicentric, diffusely infiltrative, or localized in one quadrant of the breast. Many cancers have more than one histology. Invasive carcinomas include lobular carcinoma (10%), ductal carcinoma (80%), tubular carcinoma (5%), medullary carcinoma (5%), mucinous carcinoma (6%), and rarer inflammatory carcinomas and Paget's disease. Pure mucinous, tubular and medullary carcinomas have a favorable prognosis.

All breast cancers should be evaluated by immunohistochemistry (IHC) staining for estrogen and progesterone receptor status and human epidermal growth factor receptor type 2 (HER-2) overexpression. The presence of the estrogen (ER) and/or the progesterone receptor (PR) imparts a more favorable prognosis. In addition, these receptors are predictive of response to hormonal therapy. A HER-2 IHC score of 0 to 1+ is considered negative, 2+ is equivocal, and 3+ is positive. Equivocal HER-2-positive tumors undergo fluorescence in situ hybridization (FISH) analysis for evaluation of HER-2 gene amplification. HER-2 amplification of 2.0 or greater is considered positive. HER-2 is also referred to as HER-2/neu or ErbB-2. It is a 185-kDa transmembrane tyrosine kinase that regulates cell growth, survival, migration, differentiation, and adhesion. Overexpression of HER-2 leads to dimerization of the receptors, which causes activation of the tyrosine kinase. HER-2 overexpression is seen in approximately 20–30% of all breast cancers and was traditionally considered a more aggressive and a less favorable disease with reduced disease-free and overall survival. However, the development of biologic agents such as trastuzumab (Herceptin, Genentech) has revolutionized the treatment of this type of breast cancer.

The single most important predictor of disease-free and overall survival is axillary lymph node status. Lymph node negative breast cancers have a better prognosis than lymph node positive cancers. Other important prognostic factors in breast cancer include tumor size, histologic grade, and lymphovascular invasion. Well-differentiated breast cancers have a better prognosis than moderately or poorly differentiated cancers. Likewise smaller tumors are more favorable than larger ones and the absence of lymphovascular invasion is better than its presence.

All stage 0–III breast cancers are recommended for surgical resection. The surgical margins should be free of both DCIS and invasive cancer. However, 30–40% of women will have residual microscopic disease after surgery that if left untreated will lead to either a local, regional, or distant recurrence [41]. Therefore, surgery alone is often not sufficient to effectively treat breast cancer.

In the diagnosis phase, which in the United States typically occurs over days to weeks, anxiety, stress, and time spent in medical care can strain interpersonal relationships and interfere with a woman's desire for sex. At the University of Chicago Program in Integrative Sexual Medicine for Women and Girls with Cancer, we have had several patients describe the strength, devotion, and commitment of their spouse during

the diagnosis and acute treatment phase of their cancer care, even in cases where the relationship was seriously suffering prior to the diagnosis. For example, one woman described that her husband had disclosed an extramarital relationship to her just prior to her diagnosis. The diagnosis refocused his attention on their relationship, which she needed and appreciated, but put the issue of infidelity on hold until her recovery. This issue was prominent in her posttreatment sexual concerns. We know of few studies that provide detailed data on sexuality during the breast cancer diagnosis phase, or how support for relationship and sexuality issues during diagnosis might affect sexual outcomes among breast cancer survivors.

Treatment

The IBM (Fig. 28.3) provides a practical framework for summarizing the broad mechanisms through which breast cancer treatment can affect sexuality. Ganz and Meyerowitz also offer very useful frameworks, specific to breast cancer, for understanding sexual health in women after breast cancer diagnosis [42, 43]. Of course, treatment has biological functional, psychological, and social implications for patients and their partners and can interfere with physical capacity for sex, desire, interest, feelings of attractiveness, femininity, and opportunities for sexual partnership and activity. A woman's sexual history, the quality of her relationship at the time of her breast cancer diagnosis, and other factors such as spirituality; attitudes about sex, marriage, and masturbation; and social support can all contribute to clinical variation in the impact of breast cancer treatment on her sexuality. Several studies document a high prevalence of sexual problems among women treated for breast cancer, although the populations and methods used vary substantially and few include same-age population controls [44] (see Table 2, p. 225 in Trinkaus et al. for a recent review). In a 2005 study, 55 women ages 41–69 with breast cancer who had completed initial therapy (surgery, radiation, or chemotherapy) or were still undergoing adjuvant hormonal therapy were recruited during well-patient follow-up visits. Psychosocial issues, including relationship distress, depression, and traditional role preferences, were more strongly associated with sexual function and dyspareunia than were cancer treatment type or hormonal levels [45].

Treatment of breast cancer requires a multimodality approach, as do prevention and treatment of sexual problems in the course of cancer care. Invasive breast cancer treatment usually starts with surgical resection of the primary tumor and axillary lymph node assessment, followed by adjuvant chemotherapy and/or hormonal therapy and/or biologic therapy with or without adjuvant radiation therapy.

Table 28.3 summarizes key epidemiologic and therapeutic terms used throughout the following section.

Surgery

Women with breast cancer can be offered either breast conservation surgery (typically lumpectomy with a lymph node evaluation, followed by breast radiation) or mastectomy. Overall survival is equivalent when comparing mastectomy to breast conservation surgery followed by radiation therapy [41, 46, 47]. However, in certain situations, mastectomy is preferred to a lumpectomy. For example, mastectomy is recommended for women with multicentric disease, in the first or second trimester of pregnancy to avoid the long delay for breast radiation following delivery, women who had prior breast radiation, those with active collagen vascular disease that prevents administration of radiation therapy, and inflammatory breast cancers. Some women, based on personal preferences influenced by the recurrence risk, familial experiences with breast cancer, or genetic risk status, opt for mastectomy despite equivalent survival with conservation surgery. Increasingly, women who undergo mastectomy are electing breast reconstruction surgery, but this is still the minority [48–50]; women of racial and ethnic minority groups are less likely to

Table 28.3 Key epidemiological and therapeutic terms in discussion of cancer therapy and clinical trials

Term	Description
Disease-free survival (also called disease-specific survival)	The length of time after treatment for a specific disease during which a patient survives with no sign of the disease. Disease-free survival may be used in a clinical study or trial to help measure how well a new treatment works. Also called DFS and disease-free survival time
Progression-free survival (PFS)	The length of time during and after treatment in which a patient is living with a disease that does not worsen
	PFS can be used in clinical trials to test new treatments
Hazard of recurrence[1]	The risk for which a cancer can return, either in the same place it originated or elsewhere following treatment
	Rate at which recurrence or death occurs over a period of time among "at risk" individuals
	It is widely recognized that in early breast cancer, the hazard rate is highest shortly after initial diagnosis and treatment, with a peak at 2 years, and that there is a gradual decline in hazard rate thereafter
Adjuvant therapy	Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back.
	Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy
Neoadjuvant therapy	Initial treatment given to increase the likelihood of a successful follow-up treatment, usually surgery
	This therapy works to shrink a large breast cancer tumor, so that it can be removed with less difficulty
	Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy
Palliative therapy	Treatment given to relieve the symptoms and reduce the suffering caused by cancer and other life-threatening diseases as a means to improve the patient's quality of life
	Palliative cancer therapies are given together with other cancer treatments, from the time of diagnosis, through treatment, survivorship, recurrent or advanced disease, and at the end of life
Chemotherapy	Chemotherapy drugs are medications that kill cancer cells. Chemotherapy drugs can be administered orally, through infusion or through an injection into a vein, muscle, or the skin
	Chemotherapy is often used with in conjunction with surgery or radiation to treat cancer
Radiation Therapy	The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors
	Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy)
	Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body
	Also called irradiation and radiotherapy
Hormone Therapy	Treatment that adds, blocks, or removes hormones
	To slow or stop the growth of certain cancers (such as breast cancer), synthetic hormones or other drugs may be given to block the body's natural hormones
	Sometimes surgery is needed to remove the gland that makes a certain hormone
	Also called endocrine therapy, hormonal therapy, and hormone treatment
Targeted therapy	A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells
	Targeted therapy may have fewer side effects than other types of cancer treatments
Biological Therapy	Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases
	Also used to lessen certain side effects that may be caused by some cancer treatments
	Agents used in biological therapy include monoclonal antibodies, growth factors, and vaccines. These agents may also have a direct antitumor effect
	Also called biological response modifier therapy, biotherapy, BRM therapy, and immunotherapy

(continued)

Table 28.3 (continued)

Term	Description
Breast cancer stages	
Stage 0	Used to describe noninvasive breast cancers such as DCIS and LCIS
	No evidence of cancer cells or noncancerous abnormal cells breaking out of the part of the breast in which they started, or of getting through to or invading neighboring normal tissue
Stage I	Used to describe invasive breast cancers where cancer cells are breaking through to or invading neighboring normal tissues
	The tumor measures 2 centimeters at most
	No lymph nodes are involved
Stage II	*Stage II is divided into subcategories known as IIA and IIB*
	Stage IIA
	Invasive breast cancer in which no tumor can be found in the breast, but cancer cells are found in the axillary lymph nodes or the tumor measures 2 centimeters or less and has spread to the axillary lymph nodes, or the tumor is larger than 2 centimeters but no larger than 5 centimeters and has not spread to the axillary lymph nodes
	Stage IIB
	Invasive breast cancer in which the tumor is larger than 2 centimeters but no larger then 5 centimeters and has spread to the axillary lymph nodes, or the tumor is larger than 5 centimeters but has not spread to the axillary lymph nodes
Stage III	*Stage III is divided into stages IIIA, IIIB, IIIC*
	Stage IIIA
	The cancer is either smaller than 5 centimeters and has spread to axillary lymph nodes, which have grown into each other or into neighboring structures, or is larger than 5 centimeters and has spread to the axillary lymph nodes beneath the arm
	Stage IIIB
	Invasive breast cancer in which the tumor may be any size and has spread to the chest well and/or skin of the breast, and may have spread to axillary lymph nodes that are clumped together or sticking to other structures or cancer may have spread to lymph nodes near the breastbone
	Inflammatory breast cancer is considered at least stage IIIB
	Stage III C
	Invasive breast cancer in which: there may be no sign of cancer in the breast or, if there is a tumor, it may be any size and may have spread to the chest wall and/or skin of the breast, the cancer has spread to lymph nodes above or below the collarbone, and the cancer may have spread to axillary lymph nodes or to lymph nodes near the breastbone
Stage IV	*Stage IV is associated with widespread tumor metastasis*
	The cancer has spread to other bodily organs, typically the bones, liver, brain, or lungs; or the cancer has spread locally to the skin and lymph nodes inside t he neck near the collarbone

All definitions were gathered from the following websites unless otherwise noted: Breast Cancer.org, Dictionary http://www.breastcancer.org/dictionary/; National Cancer Institute, Dictionary of Cancer Terms http://www.cancer.gov/dictionary/.
[1] Dignam, J.J., Dukie, V., Anderson, S.J. et al. "Hazard of Recurrence and Adjuvant Treatment Effects Over Time in Lymph Node-Negative Breast Cancer." *Breast Cancer Res Treat* (2009). 116: 595–602.

undergo reconstruction [48]. While sexuality considerations are common in these women, evidence about differences in sexual outcomes is very limited. Several studies examine quality of life outcomes comparing women with mastectomy who undergo breast reconstruction to those who do not, but virtually no data are available to inform women about the impact of breast reconstruction on breast function (e.g., erotic sensation). In a very recent study, Markopoulos and colleagues show that women with mastectomy and delayed breast reconstruction report significantly higher sex life satisfaction than those who had breast conservation surgery or radical mastectomy without reconstruction [51]. As some sexual health care providers may be unfamiliar with these surgical procedures, Fig. 28.5 provides photographs of various outcomes.

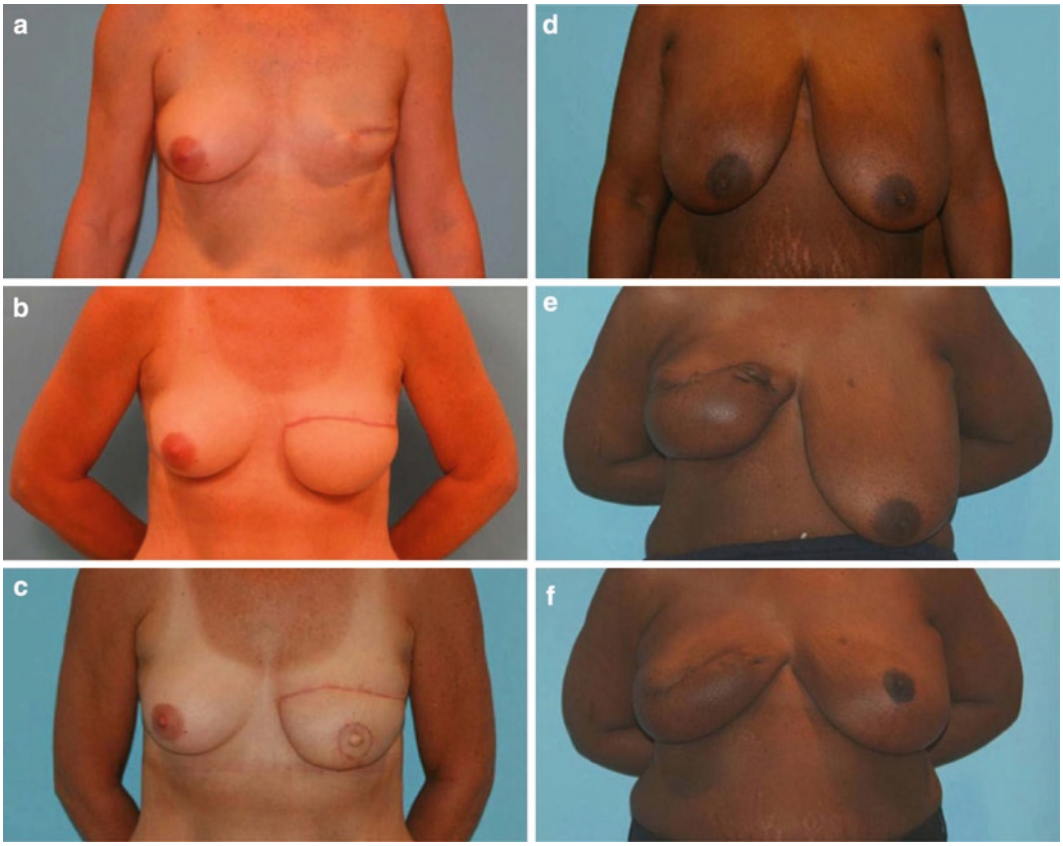


Fig. 28.5 Breast appearance following radiation and surgical reconstruction in well-healed patients. (**a**) 50 year old woman who had a left mastectomy 5 years prior for invasive ductal carcinoma. (**b**) She underwent a delayed left breast reconstruction with DIEP. (**c**) She then had a revision of the left reconstructed breast and nipple reconstruction (bottom left). She does not yet have an areolar tattoo. (**d**) 67 year old woman who presented with intraductal carcinoma in the right breast. (**e**) She had a right mastectomy with immediate reconstruction with a tissue expander, seen here at final fill volume. (**f**) She then had the tissue expander removed and a permanent silicone gel implant placed, as well as a contralateral left breast reduction for symmetry. She does not yet have nipple areolar reconstruction

Chemotherapy

Adjuvant therapy is treatment administered after surgery when there is no evidence of any remaining gross disease, but there is a risk of relapse from occult micrometastatic disease. The goal of adjuvant therapy is to improve overall survival. Since adjuvant chemotherapy is administered for a risk of recurrent disease rather than for provable disease, a proportion of patients who were already cured by their primary surgery may unnecessarily receive therapy. Neoadjuvant chemotherapy is administered prior to surgery and has the same impact on disease-free and overall survival as adjuvant chemotherapy [52]. Neoadjuvant therapy is often administered to reduce the size of the breast cancer in order to perform more effective surgery and for inflammatory breast cancers.

Many of the commonly used chemotherapies have been around for decades, but new drug development has led to improved supportive

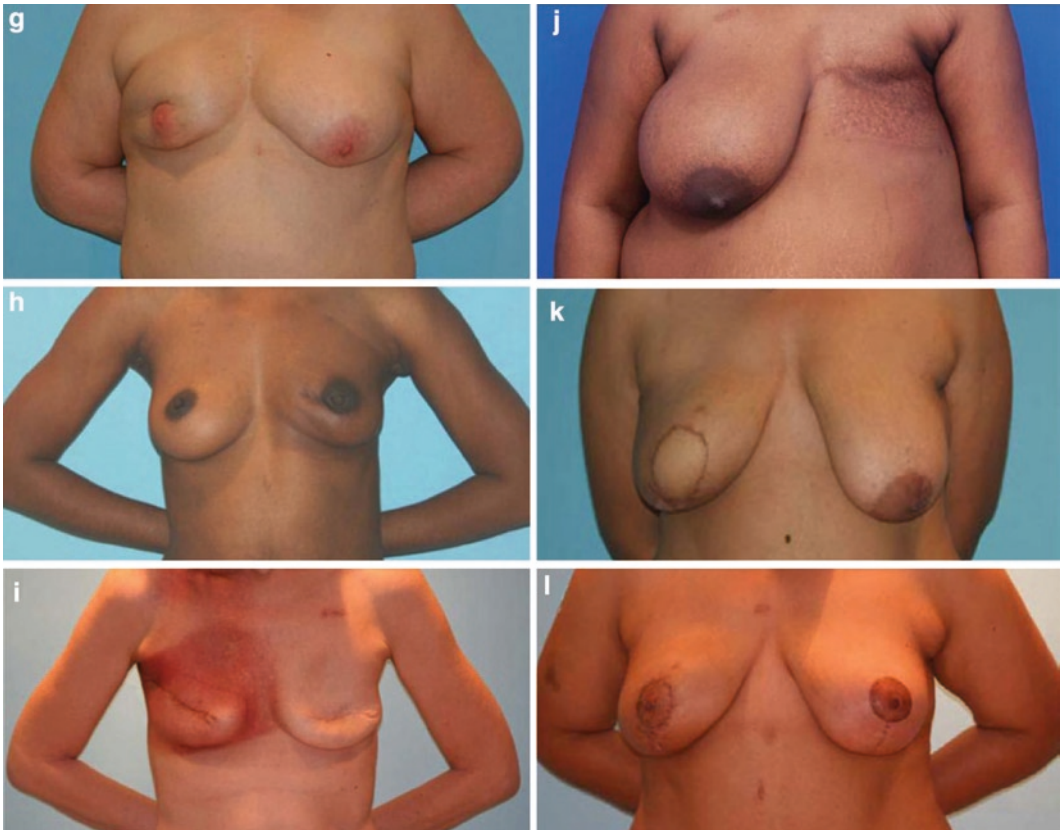


Fig. 28.5 (**g and h**) Various effects of radiation on breast tissue and skin after lumpectomy. (**i and j**) and after mastectomy. (**k**) 34 year old woman with Right ductal carcinoma in situ who underwent a right mastectomy and immediate reconstruction with a rotational TRAM. (**l**) She then had a second stage revision of right reconstructed breast, nipple reconstruction, and nipple tattoo as well as contralateral left mastopexy for symmetry

medications (e.g., antinausea medications) that make chemotherapy more tolerable with fewer side effects and lower overall toxicity. As a result, women undergoing chemotherapy for breast cancer may feel better, appear less ill, and have a better quality of life than they or their partners might expect. Some women do desire and engage in sexual activity during chemotherapy, but stress, fatigue, disrupted sleep, changes in appearance and body image, menopausal symptoms, and partner fear or anxiety are commonly cited factors by women who cease sexual activity during the active treatment phase [53].

Women with breast cancer expect their health care providers to be familiar with these therapies and their side effects. Comprehensive and informed care for and research about sexuality issues in women with breast cancer requires familiarity with these drugs and, particularly given the rapid pace of new discovery in the field, should be facilitated by ongoing collaboration with the patient's oncologist. Even by offering general information about the possible effects of chemotherapy on sexual function, oncologists can signal to patients that this is an acceptable topic for discussion should problems occur and can help prevent feelings of shame or isolation. Table 28.4 summarizes characteristics of breast cancer chemotherapies, their mechanism of action, common toxicities, side effects, and effects on sexual function. Because sexual outcomes are rarely reported in pharmaceutical clinical trials, evidence is limited about effects of chemotherapies on sexual function in women

with breast cancer. The information presented is informed primarily by clinical experience and biological plausibility based on mechanisms of action and known toxicities.

Adjuvant Chemotherapy

Adjuvant chemotherapy, administered in the postoperative setting, has been shown to improve overall survival in breast cancer patients with resectable disease. This practice is based on a meta-analysis that is updated every 5 years by the Early Breast Cancer Trialists' Collaborative Group, which shows a survival advantage to adjuvant polychemotherapy compared to no chemotherapy [54]. In women younger than 50 years old, there was a 12.3% 15-year gain in disease-free survival and a 10% 15-year gain in breast cancer specific mortality. In women between the age of 50 and 69, there was a 4.1% 15-year gain in disease-free survival and a 3.0% 15-year gain in breast cancer specific mortality. The meta-analysis also demonstrated a significant survival advantage with anthracycline- (doxorubicin, epirubicin) containing adjuvant therapy compared to nonanthracycline- [cyclophosphamide, methotrexate, and fluorouracil (CMF)] based regimens [54, 55]. In terms of overall survival and disease-free survival, escalated dose epirubicin and anthracycline–taxane regimens were determined to be the most effective. The greatest proportional decreases in 5-year death rates were seen with the following regimens: TAC – docetaxel (T), doxorubicin (A), and cyclophosphamide (C); CEF – cyclophosphamide (C), epirubicin (E), and fluorouracil (F); and FEC100 – fluorourcil (F), 100 mg/m^2 epirubicin (E), and cyclophosphamide (C). However, the anthracycline-based regimens are associated with increased toxicity.

Anthracyclines (doxorubicin, epirubicin) work by inhibiting an enzyme, topoisomerase II, essential for DNA replication. The drug interrupts tumor growth by preventing replication of the cancerous cells, but it also affects other high turnover cells throughout the body. In the 2005 meta-analysis mentioned previously, the anthracycline regimens were associated with higher rates of cardiotoxicity (1–2%), secondary leukemia (1.3 vs. 0.4% for CMF), more severe nausea, vomiting, and alopecia, including pubic hair loss [55]. CMF was associated with a higher likelihood of bleeding during the first month following chemotherapy, but women treated with this regimen were also more likely to have amenorrhea 1 year following chemotherapy and to have a higher rate of infertility [56]. Infertility is an important adverse effect of breast cancer treatments, including surgery and chemotherapy, and can negatively affect quality of life in premenopausal women undergoing treatment and survivors of the disease. A survey was performed evaluating fertility attitudes among young, premenopausal women with breast cancer [57]. Fifty-seven percent of 657 women reported substantial concern regarding the impact of therapy on fertility and 29% reported that fertility issues influenced their treatment decisions. It is important to educate premenopausal women at diagnosis regarding the effect of their treatment on fertility and to perform additional studies to better characterize the effects of breast cancer treatments on ovarian reserve and future fertility. Oncologists and female sexual medicine practitioners should recognize that a woman's feelings about and capacity for fertility may be closely intertwined with her sexuality. Cessation of menses and potential loss of fertility can have major implications for current and future relationships and both biological and psychological dimensions of a woman's sexual drive. These issues can also directly affect her partner's sexuality.

Taxanes

Taxanes (paclitaxel, docetaxel, and nanoparticle albumin bound (nab)-paclitaxel) are a type of chemotherapy that act as microtubule stabilizers, which promote formation and inhibit disassembly of stable microtubules, inhibiting mitosis. A study was performed evaluating the effect of paclitaxel and escalating doxorubicin doses as adjuvant therapy for lymph node positive primary breast cancer [58]. There was no benefit from

escalated doses of doxorubicin. However, there was an improvement in both disease-free and overall survival when four cycles of paclitaxel were administered after four cycles of doxorubicin and cyclophosphamide. The paclitaxel arms had a decrease in the hazard of recurrence by 17% (hazard ratio = 0.83, adjusted Wald $x^2P = 0.0023$) and the hazard of death by 18% (hazard ratio = 0.82, adjusted $P = 0.0064$) when compared to the nonpaclitaxel arms.

The efficacy of weekly vs. every 3-week administration of paclitaxel and docetaxel was evaluated for the adjuvant treatment of breast cancer [59]. A total of 4,950 women with either high risk or lymph node positive disease were randomized to receive either four cycles of docetaxel or paclitaxel administered every 3 weeks or either taxane weekly for 12 weeks after completing four cycles of doxorubicin and cyclophosphamide given every 3 weeks. The standard arm for comparison was paclitaxel administered every 3 weeks. The odds ratio for disease-free survival with every 3-week docetaxel was 1.23 ($p = 0.02$) and 1.09 ($p = 0.29$) for weekly docetaxel. Weekly paclitaxel significantly improved both overall survival (odds ratio, 1.32; $P = 0.01$) and disease-free survival (odds ratio, 1.27; $P = 0.006$). However, weekly paclitaxel was associated with increased grade 2, 3, and 4 neuropathy compared to every 3-week paclitaxel (27 vs. 20%). Sensory neuropathy often occurs as numbness, pain, or paresthesia that starts on the plantar surface of the toes and then develops in the fingertips. Motor neuropathy is usually mild and may cause diminished fine motor skills such as buttoning a shirt or muscle weakness such as foot drop. Neuropathy often develops within 24 hours of a paclitaxel infusion and resolves after cessation of therapy. The National Cancer Institute common toxicity criteria is a frequently used scale for grading neuropathy. Based on version 3 of this scale, grade 1 motor neuropathy is asymptomatic; weakness on examination/testing only and sensory neuropathy is asymptomatic; and loss of DTRs or paresthesia but not interfering with function. Grade 2 motor neuropathy is symptomatic weakness interfering with function, but not interfering with activities of daily living (ADLs) and grade 2 sensory neuropathy is sensory alteration or paresthesia interfering with function, but not interfering with ADLs. Grade 3 motor neuropathy is weakness interfering with ADLs requiring assistance to walk (e.g., cane or walker), and grade 3 sensory neuropathy is sensory alteration or paresthesia interfering with ADLs. Grade 4 motor and sensory neuropathy are disabling. Clinical experience suggests a possible correlation between degree of peripheral neuropathy and clitoral and vulvar sensation, arousal, and masturbation and some improvement in these factors with improvements in neuropathy over time, although these relationships have not been empirically studied.

The Cancer and Leukemia Group B Trial 9741 explored the concepts of sequential chemotherapy (one agent after another vs. combinations of drugs) and dose density (reducing the time between cycles of chemotherapy to inhibit rapid regrowth of cancer cells) of adjuvant chemotherapy based on the Norton modeling in an attempt to improve effectiveness and overall survival [60]. A total of 2,005 women were randomized to four different treatment regimens: (1) sequential doxorubicin (A)×4→paclitaxel (T)×4→cyclophosphamide (C)×4 every 3 weeks, (2) sequential A×4→T×4→C×4 every 2 weeks with granulocyte colony stimulating factor (GCSF) support, (3) concurrent AC×4→T×4 every 3 weeks, and (4) concurrent AC×4→T×4 every 2 weeks with GCSF support. At a median follow-up of 36 months, the concurrent and sequential treatment schedules were equivalent in terms of disease-free and overall survival. However, dose dense treatment significantly improved both overall survival [risk ratio (RR) = 0.69; $P = 0.013$] and disease-free survival (RR = 0.74; $P = 0.010$). The disease-free survival at 4 years for the dose dense regimens was 82% and it was 75% for the other regimens. Severe neutropenia was less frequent in patients who received the dose dense treatments with GCSF support. Therefore, the trial demonstrated that administering chemotherapy sequentially is as effective as concurrent administration, but outcomes are improved with dose-dense regimens (administered every 2 weeks).

Table 28.4 Uses and Primary Sexual and Other Side Effects of Common Therapies Used for Breast Cancer Treatment*

	Hormonal therapies				Chemotherapies							Biological Therapies		
Class	**Selective estrogen receptor modulators**	**Nonsteroidal aromatase inhibitors**	**Steroidal aromatase inhibitors**	**Estrogen receptor modulators**	**Antimetabolites (Pyrimidine analog agents)**	**Taxanes**	**Topoisomerase inhibitors**	**Nucleoside analog**	**Alkaloids**	**Alkylating agents**	**Epothilones**	**Biologics**		
Example Drugs	**Tamoxifen**	**Anastrozole/ Letrozole**	**Exemestane**	**Fulvestrant**	**Capecitabine/ 5-FU**	**Paclitaxel Nab-paclitaxel Docetaxel**	**Liposomal-Doxorubicin Doxorubicin**	**Gemcitabine**	**Vinorelbine**	**CMF**	**Ixabepilone**	**Trasutzumab (Herceptin©**	**Lapatinib**	**Bevacizumab**
Use														
Hormone Receptor Positive	+	+	+	+								Her-2(+) Disease	Her-2(+) Disease	
Early stage	+	+	+		+	+	+			+		+		
Metastatic breast cancer	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Premenopausal	+				+	+	+	+	+	+	+			
Perimenopausal	+				+	+	+	+	+	+	+			
Postmenopausal	+	+	+	+	+	+	+	+	+	+	+			
Sexual side effects														
Vaginal dryness	++	+++	+++	+		+	+			+				
Vaginal discharge	+++	++	++	+										
Vaginal bleeding	+++	++	++	+										
Endometrial bleeding	+++													
Vaginitis	+	++	++	+										
Dyspareunia	++	+++	+++	+		+	+			+				
Vulvar changes	+	++	++	+								x (skin changes)	x (skin changes)	
Urogenital atrophy	+	++	++	+										
Hot flashes	+++	+++	+++	+										
Decreased libido	++	+++	+++	+										
Other side effects														
Gynecologic														
Loss of ovarian function						+	+			+				

Endometrial cancer	+													
Gastrointestinal														
Nausea/vomiting				+	+		+	+	+	+	+	+	+	+
Diarrhea		+	+	+	++			+		+	+	+	+	+
Constipation									+		+			
Cramps/bloating				+										
Loss of appetite					+			+			+	+	+	+
Abdominal Pain					+							+	+	
Dermatologic														
Hair loss/thinning		+	+			++	++			+	+			
Hand foot syndrome					+	+	+			+				
Skin rash								+					+	
Eyes/ears/nose/throat														
Cataracts	+													
Mouth sores					+	+	+			+	+			
Nasal stuffiness					+					+				
Watering eyes					+	+				+				
Cardiovascular														
Cardiac toxicity				+	+		+					+		+
Blood clots	+											+	+	+
Increased cholesterol		+	+											
High blood pressure														+
Proteinuria														+
Neurologic														
Headaches				+							+	+	+	
Neuropathy						+			+		+			
Constitutional														

(continued)

Table 28.4 (continued)

	Hormonal therapies			Chemotherapies								Biological Therapies	
Class	**Selective estrogen receptor modulators**	**Nonsteroidal aromatase inhibitors**	**Steroidal aromatase inhibitors**	**Estrogen receptor modulators**	**Antimetabolites (Pyrimidine analog agents)**	**Taxanes**	**Topoisomerase inhibitors**	**Nucleoside analog**	**Alkaloids**	**Alkylating agents**	**Epothilones**	**Biologics**	
Fatigue		+	+	+	+	+		+		+	+		+
Body aches/joint stiffness		++	++	+		+					+		
Muscle weakness									+				
Bone density	Increase	Decrease	Decrease										
Myelosuppression					+	+	+	+	+	+			
Weight change													
Edema	+							+					

*(+) Side effect is associated with the treatment, but severity not documented in the literature. For Tamoxifen, Nonsteroidal and Steroidal Aromatase Inhibitors: (++) & (+++) indicate level of severity based on current medical literature^ Ovarian failure causes menopausal symptoms including vaginal dryness, hot flashes, cessation of menses, and problems like dyspareunia and low desire.

Side effects resulting from primary effects of the drug are not indicated (e.g., sexual side effects resulting from drugs causing ovarian failure), but should be considered.

* Cella D, Fallowfield L. Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. Breast Cancer Research and Treatment 2008; 107 (2): 167–180.

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Trastuzumab/Herceptin

Trastuzumab is a humanized monoclonal antibody that selectively binds to the extracellular domain of human epidermal growth factor type 2 (HER-2) receptor. In women with surgically resected breast cancer that overexpresses HER-2, trastuzumab combined with chemotherapy improves disease-free and overall survival [61]. Trastuzumab treatment decreases the risk of death by one-third ($p = 0.015$) in HER-2 positive breast cancer. Cardiac toxicity is a potential side effect of trastuzumab therapy and is more prevalent in patients previously treated with doxorubicin. Trastuzumab should not be administered concurrently with doxorubicin because of an increased risk of cardiac toxicity. New York Heart Association Class III or IV congestive heart failure or death from cardiac causes at 3 years was seen in 4.1% of patients treated with doxorubicin and trastuzumab in the B-31 trial and 2.9% of patients in the N9831 trial.

Radiation

Radiation therapy of the ipsilateral breast is recommended for all patients who have breast conservation surgery, four or more positive lymph nodes regardless of type of surgery (breast conservation surgery or mastectomy) and/or a primary tumor measuring 5 cm or greater [8, 16]. One possible exception is women 70 years of age or older with hormone receptor-positive breast cancer who underwent breast conservation therapy and who will be subsequently receiving adjuvant endocrine therapy [62]. In patients with one to three lymph nodes that were removed at the time of mastectomy and found to be positive, postmastectomy radiation therapy is controversial but should be considered, especially in younger patients. Radiation therapy typically occurs over 5–6 weeks with a typical dose of approximately 5,040 cGy. In many regions of the United States, radiation therapy has become very efficient so as to minimize disruption to daily life. Common side effects of radiation therapy include fatigue and local skin toxicity (rashes, erythema, blistering). Radiation therapy in the indicated patients improves both local recurrence and overall survival [41, 63]. However, radiation therapy may negatively impact reconstruction options and cosmetic outcome, both of which can affect a woman's sexuality, including sexual functioning, and should be discussed with the patient.

Hormonal Therapy: Pre- and Perimenopausal Women

In premenopausal women, the ovaries are the primary site of both estrogen and testosterone synthesis. Normal breast tissue has both estrogen and progesterone receptors and responds to these hormones throughout a woman's menstrual cycle and during pregnancy and lactation. Both hormones are also important in central and peripheral aspects of female sexuality, sexual function, and integrity of the urogenital tract (see part I, especially Chapter 2). Absence of estrogen and/or progesterone receptors in breast tumors is an indicator that the cells are more poorly differentiated and correlates with poorer prognosis. Estrogen modulation and deprivation are key strategies for treating hormone receptor-positive breast cancer and can be accomplished pharmacologically or surgically (oophorectomy) [64]. Although evidence is very limited, female sexual medicine providers caring for women with breast cancer commonly incorporate factors, such as hormone receptor status of the breast cancer tumor, use (and duration of use) of sex hormone modulators or suppressors for cancer treatment, menopausal status, and BRCA status, into educating patients about the effects of treatment on sexual function and in formulating a treatment plan with the patient and her oncologist(s). Documentation of these factors in relation to sexual concerns and outcomes as part of a registry or clinical database in female sexual medicine programs is critical for advancing the evidence base for the field.

Less than one quarter of all newly diagnosed early stage breast cancers occur in pre- or

perimenopausal women [65]. Tamoxifen is a selective estrogen receptor modulator (SERM), with both partial estrogen agonist and antagonist effects, that works by interrupting cell growth. Tamoxifen can be used for prevention of breast cancer, adjuvant therapy, or treatment of metastatic disease. Currently, it is the only hormonal agent available for adjuvant therapy in early stage estrogen or progesterone receptor positive breast cancer in premenopausal women. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that 5 years of adjuvant tamoxifen treatment is significantly more effective than 1–2 years of therapy with tamoxifen following surgery [54]. Five years of therapy with tamoxifen in both pre- and postmenopausal women significantly decreased breast cancer mortality by a third [ratio 0.66 (SE 0.04)] and the risk of recurrence by almost half [ratio 0.59 (SE 0.03)]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study compared 5 years of tamoxifen to extended treatment with tamoxifen [66]. After completing 5 years of therapy with tamoxifen, 1,172 women were disease free and re-randomized to receive either prolonged therapy with tamoxifen ($n=593$) or placebo ($n=579$). Seven-year follow-up after re-randomization showed no benefit to prolonged therapy with tamoxifen independent of age or other characteristics. Both disease-free survival 82 vs. 78% ($p=0.03$) and overall survival 94 vs. 91% ($p=0.07$) favored the placebo arm. When tamoxifen treatment was continued beyond 5 years in the NSABP B-14 trial, a significantly higher event rate such as thrombosis and death was seen in the tamoxifen arm compared to no further treatment. As a result, the trial was terminated early.

In patients with metastatic (stage 4) hormone receptor-positive breast cancer, treatment aims to achieve total estrogen deprivation. The predominant sites of estrogen synthesis in premenopausal women are the ovaries. In order to create a state of estrogen deprivation, a patient's ovaries must be ablated or suppressed [64]. Ovarian ablation was one of the first systemic treatments for breast cancer and can be performed via oophorectomy or medical suppression. Surgical castration via bilateral oophorectomy immediately reduces estrogen levels to the postmenopausal range in all women while medical suppression may take several weeks to take full effect. Medical suppression can be performed using luteinizing hormone releasing hormone (LHRH) analogs, which are administered as either monthly or every 3-month intramuscular injections [67]. LHRH analogs include goserelin, buserelin, triptorelin, and leuprolide. LHRH analogs act on the hypothalamic–pituitary–ovarian axis and suppress circulating estrogen levels. However, after the initial administration of an LHRH analog, there is a surge in both gonadotropin and estrogen levels, which may cause an initial "tumor flare" phenomenon in patients with metastatic disease. Approximately 2–3 weeks after the administration of LHRH analogs, estrogen levels decline, creating a postmenopausal state. However, the postmenopausal state is reversible after therapy is discontinued in women who were ovulatory at initiation of treatment.

A meta-analysis of four small randomized trials comparing ovarian suppression with an LHRH analog alone vs. an LHRH analog in combination with tamoxifen was performed in 506 pre- and perimenopausal women with metastatic breast cancer [68]. With a median follow-up of 6.8 years, 79% of patients received goserelin as the LHRH agonist and the other 21% received buserelin. In women with metastatic breast cancer, the combination of tamoxifen and an LHRH analog was superior to an LHRH analog alone in terms of overall survival, response rate, and disease-free survival. Given these study results, the combination of ovarian suppression plus tamoxifen is frequently used as treatment of pre- or perimenopausal women with hormone receptor-positive metastatic breast cancer. Ovarian suppression is also considered in the adjuvant setting, although trials evaluating ovarian suppression as standard of care are still ongoing (discussed below). Fifteen-year follow-up of the Early Breast Cancer Trialists' Collaborative Group study demonstrated that in the adjuvant setting, ovarian suppression in combination with tamoxifen was found to be at least as effective as

adjuvant chemotherapy with CMF not followed by tamoxifen [69].

Aromatase Inhibitors

Aromatase inhibitors, approved by the U.S. Food and Drug Administration for metastatic breast cancer treatment in 2000 and adjuvant treatment in 2005, decrease estrogen production by reversibly inhibiting the aromatase enzyme needed for peripheral conversion of testosterone to estradiol and androstenedione to estrone. Results from large randomized studies strongly support the use of AIs for adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer; three ongoing trials are addressing the benefit of use in pre- and perimenopausal women with ovarian suppression. A concern about AI use in nonmenopausal women is that it may stimulate gonadotropin secretion and therefore increase ovarian estrogen production [44]. The Suppression of Ovarian Function Trial (SOFT) randomizes premenopausal women with hormone receptor-positive breast cancer to receive either 5 years of tamoxifen, ovarian suppression with tamoxifen, or ovarian suppression with exemestane. Exemestane is a steroidal AI that irreversibly inhibits the aromatase enzyme. The Tamoxifen and Exemestane Trial (TEXT) randomizes premenopausal women with hormone receptor-positive breast cancer to receive either 5 years of triptorelin with tamoxifen or 5 years of triptorelin with exemestane. Triptorelin, as described previously, is an LHRH analog used for ovarian suppression. The Austrian Breast and Colorectal Cancer Study Group 12 (ABCSG-12) randomized 1,803 premenopausal women with hormone receptor-positive breast cancer to receive ovarian suppression in combination with either tamoxifen or anastrozole. At a median follow-up of 47.8 months, there was no significant difference in either disease-free or overall survival. To the best of our knowledge, neither these trials nor those conducted with postmenopausal women provide data on sexual function or vulvovaginal anatomical outcomes. As detailed further below, both severe disruption of sexual function and marked alteration of the vulvar anatomy have been seen clinically in postmenopausal women treated with AIs; lack of knowledge is a major barrier to designing interventions and counseling patients about expectations.

Zoledronic Acid

Zoledronic acid (marketed in the United States as Zometa) is an intravenously administered bisphosphonate that reduces skeletal-related events including pain and risk of fracture in women with metastatic breast cancer to bone. In addition, zoledronic acid treats hypercalcemia of malignancy. Side effects, more common and dramatic at the time of the first infusion, can include fatigue, muscle aches, fever, and/or swelling in the feet or legs [70]. Rarely, zoledronic acid has been associated with osteonecrosis of the jaw. Zoledronic acid is not known to interfere with female or male sexual function. Of course, pain and reduced mobility due to bone metastases, vertebral and/or hip fractures, and fear of fracture in a woman with metastatic breast cancer can seriously limit an individual's physical capacity for sexual intercourse.

The role of estrogen in pre- and postmenopausal bone metabolism in women is an active area of research. Estrogen suppression or deprivation secondary to therapy in women with breast cancer can cause osteopenia and osteoporosis and has been associated with an increased risk of fractures in this population. Studies are investigating the value of bone mineral density testing and medical treatments to prevent bone loss and skeletal fractures in premenopausal women. Although there is promising data to suggest that zoledronic acid may reduce the risk of recurrence from breast cancer in the adjuvant setting, several trials are still ongoing that will help to address this issue. At the present time, both oral (e.g., alendronate, risedronate, ibandronate) and IV (zoledronic acid)

bisphosphonates are offered to breast cancer patients to reduce bone loss and risk of fracture after treatment for breast cancer, and maintenance of bone health has become an important role for the breast cancer medical oncologist. In one study, 1,803 premenopausal women with hormone receptor-positive breast cancer were randomized to goserelin (an LHRH agonist) with either tamoxifen or anastrozole (nonsteroidal AI) with or without zoledronic acid [71]. At a follow-up of 47.8 months there was no significant difference in disease-free survival between the tamoxifen and anastrozole treated arms, supporting the use of either regimen in these patients. However, the addition of zoledronic acid to endocrine therapy prevented menopause-induced bone loss compared with no bisphosphonate therapy, and resulted in a statistically significant improvement in disease-free survival. However, there was no significant improvement in overall survival with the addition of zoledronic acid. Confirmatory studies are awaited.

Adjuvant Hormonal Therapy: Postmenopausal Women

Results from large randomized studies strongly support the use of AIs for adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer. AIs appear to be beneficial when given after surgery instead of tamoxifen (ATAC, BIG 1-98 trials) [72–74], after 2–3 years of tamoxifen (IES, ABCSG-8, ARNO-95, ITA, BIG 1-98 trials) [75–78], or after 5 years of tamoxifen (MA.17 trial) [79]. AIs consistently improve disease-free survival, risk of distant recurrence, and development of a contralateral breast cancer when compared to tamoxifen and have replaced tamoxifen as first line therapy for postmenopausal women with hormone receptor-positive breast cancer. However, there is no clear survival benefit seen with AIs. There is also a trade-off in side effects with AI treatment as compared to tamoxifen therapy. The use of AIs results in less vaginal discharge, irregular bleeding, fewer endometrial polyps and endometrial cancers, and thromboembolic problems than seen with tamoxifen, but more musculoskeletal events including bone fractures and/or osteoporosis. It should be acknowledged that there is still a role for tamoxifen in postmenopausal women with breast cancer. Tamoxifen is still an option for postmenopausal women who are intolerant of AIs, since there is no improvement in overall survival with AI treatment after surgery compared to tamoxifen therapy. Postmenopausal women also benefit from tamoxifen followed by an AI. Longer follow-up of the adjuvant studies will allow us to better understand the long-term risks and benefits of AIs. At this time, optimal adjuvant endocrine therapy for a hormone receptor-positive postmenopausal woman includes an AI at some point in her treatment.

The optimal duration of adjuvant endocrine therapy is unclear. There is currently no direct evidence to support remaining on either tamoxifen or an AI for more than 5 years. The forthcoming results of the MA.17R trial (trial fully accrued, awaiting results), which randomized patients treated with 5 years of an AI (any AI) to either placebo vs. an additional 5 years of letrozole (a total of 10 years of letrozole) will help guide duration of AI therapy. There is evidence that AIs are most beneficial while a patient is receiving this therapy [80]. Again, to the best of our knowledge, sexual and vulvovaginal anatomical outcomes are not being studied in this trial but could be very important in counseling women about treatment options. Key questions are to determine whether such changes might be reversible following cessation of AI therapy, and whether reversibility relates to AI type (steroidal vs. nonsteroidal).

Targeted Palliative Therapies

Palliative therapies are used in women with unresectable locally advanced or metastatic

breast cancer, a setting in which breast cancer can be treated but is generally incurable at this stage.

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody which targets vascular endothelial growth factor (VEGF). ECOG 2100, a large, randomized, open-label phase III trial performed by the Eastern Cooperative Oncology Group (ECOG) evaluated the efficacy and safety of paclitaxel alone vs. paclitaxel in combination with bevacizumab as first line therapy for women with locally recurrent or metastatic breast cancer [81]. The primary endpoint of the study was progression free survival and one of the secondary endpoints was overall survival. Patients were eligible for the study if they had untreated metastatic breast cancer, but prior adjuvant chemotherapy or hormonal therapy was permitted [81].

The paclitaxel/bevacizumab arm showed a significantly prolonged progression-free survival with a median of 11.8 vs. 5.9 months in the paclitaxel only arm ($p<0.001$) [81]. The addition of bevacizumab to paclitaxel also significantly improved the objective response rate from 21.2 to 36.9% ($p=0.001$). Although there was no difference in median overall survival, the overall survival at 1 year was better in the bevacizumab treated arm [81.2 vs. 73.4% ($p=0.01$)]. Paclitaxel in combination with bevacizumab was well tolerated and bevacizumab did not appear to worsen paclitaxel-related toxicities [81]. The bevacizumab/paclitaxel treatment arm had greater grade 3/4 hypertension (14.8 vs. 0%, $p<0.001$), grade 3/4 proteinuria (3.6 vs. 0%, $p<0.001$), cerebrovascular ischemia (1.9 vs. 0%, $p=0.02$), headache (2.2 vs. 0%, $p=0.008$), neuropathy (23.5 vs. 17.7%, $p<0.05$), and infection (9.3 vs. 2.9%, $p<0.001$) than the paclitaxel monotherapy arm. The results of this trial led to FDA approval of bevacizumab for first line treatment of metastatic breast cancer, and subsequent studies have confirmed these results. Bevacizumab is currently being studied in the adjuvant and neoadjuvant settings.

Lapatinib

Lapatanib is a potent and specific reversible oral small molecule dual tyrosine kinase inhibitor of both human epidermal growth factor receptor type 2 (HER-2) and epidermal growth factor receptor (EGFR). Lapatinib in combination with capecitabine (a 5-FU prodrug, see Table 28.4) was superior to capecitabine alone in women with HER-2 positive advanced breast cancer that progressed after treatment with trastuzumab (an antibody that targets the HER-2 receptor), an anthracycline and a taxane [82]. The median time to progression was 8.4 months in the lapatinib and capecitabine arm vs. 4.4 months in the capecitabine monotherapy arm. Patients treated with lapatinib in combination with capecitabine had a statistically significant higher rate of side effects such as diarrhea, dyspepsia, and rash.

Complications from Cancer Therapy

There are a myriad of potential long-term complications from multimodality breast cancer treatment, such as decrease in bone density, fractures, congestive heart failure, hypercholesterolemia, infertility, depression, and anxiety. The vast majority of breast cancer tumors (75%) express estrogen and/or progesterone receptors. Endocrine manipulation is a key component of breast cancer therapy that, depending on the treatment type and duration, results in menopausal symptoms including vasomotor and vulvovaginal symptoms and bone loss [44]. Sexual problems commonly occur as a consequence of estrogen deprivation and can be exacerbated by many of the other long-term complications of breast cancer therapy. In fewer than 1% of women treated, breast cancer therapy can also lead to secondary malignancies such as myelodysplastic syndrome and/or leukemia.

As discussed previously, sexual problems or dysfunction may result from the psychological and relationship impact of a breast cancer diagnosis and treatment and physical effects of the tumor or tumor metastases. Commonly, sexual problems and dysfunction in women with breast cancer can be attributed, at least in part, to iatrogenic causes.

Treatment of Sexual Problems in Breast Cancer Survivors

Genital tract anatomy, sex hormone physiology, communication about and diagnosis of sexual problems in women are described in detail in several prior chapters. Familiarity with these topics, excellent history-taking skills, knowledge of menopausal physiology and management (e.g., see Trinkaus et al.) [44], and differential diagnosis and treatment of common gynecologic conditions (or collaboration with a clinician with this expertise) are needed to appropriately apply the treatment information provided here. This section focuses on treatment of common symptoms in the breast cancer patient that interfere with sexual function and/or fulfillment.

Sexual problems are prevalent and substantially affect quality of life in women with breast cancer undergoing treatment and survivors of the disease. The most common sexual symptoms documented in several studies of female breast cancer survivors include (and very often co-occur): vaginal dryness, pain with intercourse, lack of interest in sex, inability to have penetrative vaginal intercourse – commonly stated as "it feels like my partner is hitting a wall when we try to have sex" – decreased or no desire for sex, and difficulty experiencing orgasm with partnered sex. We find these prevalences, significantly higher among breast cancer survivors seeking care for sexual concerns (in the range of 60–100% for all symptoms except orgasm difficulties, which we find in about 40%) as compared to the general breast cancer population. In one center, during November 2008 through May 2009, 509 women with breast cancer of any stage undergoing treatment were each queried once [83]. The mean age was 51 (range 26–91). Eighty-seven percent reported current or past hormonal treatment and 82% reported current or past chemotherapy (76% adjuvant; 24% for metastatic disease). Sexual dysfunction attributed to breast cancer or its treatment, defined as a score <26 on the widely used Female Sexual Function Index, was reported by 76% of respondents. Among these women, 79% considered their sexual symptoms to be bothersome, with 51% noting moderate or severe levels of bother (score ≥5/10). Patients attributed their sexual dysfunction to chemotherapy in 85% of cases, to hormonal therapy in 74% of cases, and to surgery in 66% of cases. Other reported contributors to sexual dysfunction include a new diagnosis of breast cancer (81%), anxiety (82%), and change in relationship with a partner (55%).

Concerns about the relationship with one's partner and body image often overlap with these physical symptoms. Less common sexual symptoms include physical or psychological aversion to sex, clitoral pain or discomfort due to elevated sensitivity with sexual stimulation, and inability to experience orgasm with masturbation. Hot flushes, sleep disruption, and weight gain can all occur with estrogen depletion and are often cited by women as interfering with sexual function [84, 85].

Vaginal Dryness

Vaginal dryness in breast cancer survivors with sexual concerns can occur due to natural menopause, but is commonly iatrogenic. Iatrogenic causes of vaginal dryness include menopause due to bilateral oophorectomy, which physically removes a woman's primary source of endogenous estrogen, tamoxifen (an estrogen receptor modulator), and AI therapy, which blocks the enzyme needed to produce estrogen resulting in subphysiologic levels even in menopausal women. Increasingly, women with breast cancer receive more than one of these estrogen-reducing therapies, such as 5 years of tamoxifen followed by 5 years of AI therapy. Menopausal symptoms

and comprised sexual function have been documented in women taking tamoxifen and AIs [86]. The literature is limited by heterogeneity of the study populations, lack of validated and comparable measures of sexual outcomes across studies, and short follow-up.

Although systemic estrogen is very effective in treating vaginal dryness and associated menopausal symptoms, virtually no providers recommend systemic estrogen therapy to female breast cancer survivors due to the concern about breast cancer recurrence. A thorough 2009 review summarizes three randomized trials evaluating menopausal hormone therapy in women with early stage, resectable breast cancer, including the Hormonal Replacement after Breast Cancer – Is It Safe (HABITS) Trial, the Stockholm Trial and the LIBERATE Trial, all of which were terminated early due to increased risk of breast cancer recurrence in women treated with systemic hormone therapy as compared to similar women who were not treated [87]. In fact, since publication of the primary findings of the U.S. Women's Health Initiative Study, systemic estrogen use has declined significantly among women in general due to concern about elevated breast cancer incidence [88]. Local estrogen preparations include conjugated equine estrogen (CEE) cream and estradiol in the form of a sustained release ring, a vaginal tablet, and a cream. Although oncologists and other clinicians caring for breast cancer survivors tend to favor these over systemic preparations for treatment of severe vulvovaginal symptoms, no randomized trials have evaluated these for safety in this population. In one study of the estradiol vaginal ring, systemic absorption was low but associated with changes in lipid parameters raising concern about the possibility of breast tissue effects. One observational study of seven women on AIs showed some systemic absorption of estradiol in six women using vaginal estradiol tablet (Vagifem®) and one woman using CEE cream (Premarin®), but the clinical implications of this are unknown [87]. Other prospective studies are underway; prospective randomized trials are needed to establish safety and outcomes of local estrogen treatment (vaginal or vulvar) in women with breast cancer. No FDA-approved alternatives to estrogen are available for treatment of vaginal dryness.

Nonhormonal treatment options for hot flashes include (1) antidepressants: selective serotonin reuptake inhibitors (SSRIs) paroxetine, fluoxetine, sertraline, and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine; (2) neurologic agents: gabapentin and pregabalin; and (3) centrally acting adrenergic agonists: clonidine, methyldopa [89]. Randomized controlled trials evaluating supplements such as isoflavone extracts and herbs have been negative. The section on psychiatric medications addresses important considerations in the use of SSRIs and SNRIs in women on tamoxifen.

For women with breast cancer and chronic dryness (e.g., feels dry, itchy, and/or irritated even with walking or sitting), over-the-counter vaginal moisturizers are commonly recommended for every 2- to 3-day intravaginal application. The main ingredient in the most common moisturizer used in the United States and Canada (Replens®, WellSpring Pharmaceutical Corporation) is a polycarbophil compound that works by adhering to epithelial cells lining the walls of the vagina, delivering water and electrolytes into underlying cells. The polymer detaches when the lining of the vagina sheds naturally every 2–3 days [90]. This product has been shown in one small study to be comparable to estrogen in improving vaginal symptoms, and has been shown to normalize vaginal pH [91]. This product has also been evaluated in breast cancer patients as one component of a multifaceted intervention to alleviate menopausal symptoms [92], although the independent effect of Replens® was not analyzed. Many patients report some immediate relief, but maximum effect is often not realized until several weeks of consistent use. Common reasons for discontinuation include discharge of the cream into undergarments/messiness and burning or worsening of irritation. Anticipatory guidance is important: patients are instructed to start with a quarter or half an applicator full of moisturizer and increase as desired, to use at night to reduce discharge, and to discontinue should symptoms expand or worsen. Patients are advised against adding a panty liner or sanitary pad to their regimen (some do this to

address vaginal discharge); perfumed products can cause irritation or dermatitis and the wicking effect of the pad can further exacerbate dryness. Particularly in women who are not comfortable with tampon use or vaginal insertion and in women with severe vaginal atrophy, demonstration and practice of proper applicator insertion during the clinical exam is important so as not to cause pain or injury. Vaginismus may need to be addressed first (see below).

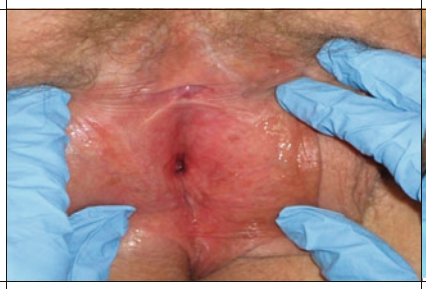
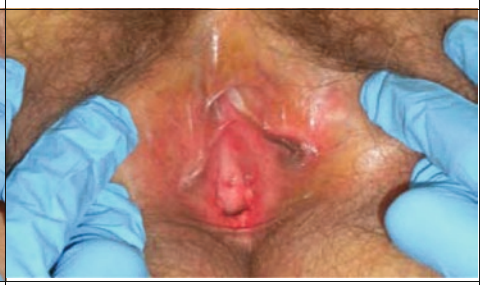
Vaginal dryness is commonly exacerbated by antihistamines used for treatment of seasonal allergies or rhinitis. When asked, patients experiencing vaginal dryness due to antihistamines may also report dry eyes, mouth, and thirst. Patients and their primary physicians are often willing to reduce the number, dose, or frequency of antihistamines to ameliorate chronic vaginal dryness and related symptoms. It is important to note that vaginal dryness may also be due to or exacerbated by lack of adequate sexual arousal (see Chapter 5). Counseling about the value and techniques of foreplay and partner communication is an important adjunct and, for some couples, the primary therapeutic intervention required.

Pain with Intercourse

Pain with intercourse commonly occurs in combination with and due primarily to vaginal dryness, particularly in women without a prior (pretreatment) history of dyspareunia. With appropriate time to heal after surgery, oophorectomy and hysterectomy are not common causes of painful intercourse, although granulation tissue at the surgical vaginal apex can cause sensitivity and postcoital spotting or brownish discharge following hysterectomy. A vaginal exam with a speculum is needed to diagnose this problem which can typically be treated by a gynecologist in the outpatient setting. Patients with painful intercourse due to estrogen depletion commonly describe tightness and painful stretching around the opening of the vagina (introital pain), a "sandpapery," "tearing," or "searing" feeling along the vaginal walls, and/or a sharp midline anterior pain (urethral) as their partner (or a sexual device) moves in and out. Women with clitoral phimosis may complain of pain with arousal or masturbation or loss of clitoral sensation (see section on orgasm difficulties). Within months to about a year of estrogen suppression or depletion for women who were premenopausal at the time of diagnosis, the vulvovaginal exam may not necessarily reveal gross signs of atrophy (loss of vaginal rugae, pallor of vaginal tissue, erythema of the vulvar vestibule, shrinkage of the labia, thinning of the fat pad at the mons pubis, loss of pubic hair, clitoral changes), but a maturation index obtained from a cytological smear of the vagina [90, 93] will typically show microscopic evidence of atrophy (few superficial epithelial cells) and a pH test will show higher vaginal alkalinity ($pH > 5$) due to loss of the vaginal Lactobacillus population [44].

Women treated on long-term regimens of tamoxifen and/or AIs exhibit menopausal signs and symptoms and commonly have gross evidence of vaginal and vulvar atrophy (Fig. 28.6). In some cases, among women seeking care for sexual problems, this appears quite severe with loss of normal vulvar architecture, clitoral atrophy or phimosis, and severe narrowing of the vaginal introitus. We have observed too few cases to have a full understanding of the link between these therapies and structural vulvovaginal changes. Whether such changes are reversible following cessation of treatment is unknown. Because systemic estrogen can compromise AI effect and monitoring, Kwan and Chlebowski suggest that women on AIs with severe vulvovaginal symptoms may be optimally treated by switching to tamoxifen and adding local estrogen therapy. While exogenous estrogen does not impede tamoxifen effect, progesterone may. The International Breast Cancer Intervention Study I shows that endometrial cancer is not increased in women with an intact uterus who are simultaneously treated with tamoxifen and local estrogen [87] (but not progesterone).

Provoked vulvodynia or pain with contact to the vulvar vestibule can be found in breast cancer survivors with estrogen depletion. The main physical findings are focal pain on a Q-tip test [94], and vestibular erythema, sometimes with a purplish hue. Provoked vestibulodynia may be

Patient	50-year-old woman w/ loss of labial architecture	45-year-old woman with vulvar atrophy
		
Duration of AI Therapy	5 years Letrozole	2 years Anastrozole
Main Treatment*	5 year Tamoxifen Doxorubicin, Cyclophosphamide and Paclitaxel	Doxorubicin, Cyclophosphamide and Paclitaxel Trastuzumab
Sexual Side Effects	Vaginal dryness Dyspareunia	Severe Vaginal Dryness Dyspareunia

Photos courtesy of the Program in Integrative Sexual Medicine for Women and Girls with Cancer. The University of Chicago, Chicago, Illinois. ©2010
**This is an abbreviated list of medications, focusing on breast cancer therapies.*

Fig. 28.6 Vulvar changes and sexual dysfunction seen in women on tamoxifen and/or aromatase inhibitor therapy for breast cancer

caused by contact or hypersensitivity dermatitis that in this patient population commonly arises from self-remedies such as wipes, soaps, creams, and oils used for vaginal dryness or as sexual lubricants. It may also be due to trauma from intercourse or attempts at penetration, in which case vaginal or vulvar ecchymoses may be present. Patients with dermatitis tend to have more generalized erythema including the vulva and sometimes extending in a key hole fashion around the anus and may have fissures or paper-cut-like lacerations. Counseling on irritants, hygiene, and toileting can be routinely incorporated into patient education, but is a particular focus for these patients. If fissures are present, especially with crusting or weeping, culture and treatment for secondary bacterial infection may be needed before anti-inflammatory therapies. As discussed in Chapter 12, topical estrogen appears to be an effective treatment for provoked vestibulodynia in some patients. Nonhormonal therapies are also available, including topical anesthetics and centrally acting agents. With all of these options, the risks and benefits are carefully considered with the patient and her oncologist or primary physician. In the case of topical vulvar estrogen for vestibular pain, some degree of absorption likely does occur. As mentioned earlier, research is needed to determine the impact and safety of vulvar estrogen for breast cancer patients. If estradiol cream is used, systematic observation of pre- and posttreatment serum estradiol levels in relation to patient outcomes could be monitored, although no thresholds of safety have been established.

Small observational studies of intravaginal estrogen (ring and tablet) for treatment of vaginal dryness and dyspareunia in women with breast cancer demonstrate that systemic absorption does occur [95–97]. Oncologists' practices and attitudes vary with respect to use of intravaginal estrogen in breast cancer survivors, although the general trend is extreme caution. In some cases, with the patient's needs, quality of life, prognosis, duration of survival, and tumor type weighing heavily in the decision, oncologists will support use of intravaginal estrogen. A word of caution: sexual health care providers should avoid making inferences about the safety of estrogen therapy by the patient's BRCA or tumor receptor status. For example, although the majority of BRCA1 carriers with breast cancer have "triple negative" tumors, as many as 10% show estrogen receptor positivity. Furthermore, survivors of an estrogen receptor negative cancer may develop recurrence or a new primary estrogen-sensitive tumor in the future. Decisions about use of intravaginal or vulvar estrogen in breast cancer patients should be made with disclosure and the patient's full understanding

about the lack of available evidence, the likely risks and benefits, and the collaboration of the treating oncologist. Again, for the purpose of systematic observation and tracking outcomes in this patient population, use of estradiol products is advantageous because serum estradiol levels can be monitored in most clinical laboratories. Sensitive assays are needed and can vary substantially across laboratories [44].

A vast variety of lubricating products (hundreds on the world market) are available to reduce friction and pain with insertional intercourse and/or genital contact. These products are used for vaginal and anal intercourse, masturbation (alone or with a partner, with or without sexual devices), and some are marketed for oral sex. Table 28.5 summarizes classes of commonly used vaginal lubricants and highlights clinical circumstances that might affect selection of one class over another. Silicone dilators, vibrators, or other sexual devices are miscible in combination with silicone lubricants. These products give a lusher feel, are longer lasting, and seem to work particularly well for couples opting for anal intercourse (some couples are receptive to exploring anal intercourse for the first time as an alternative to vaginal intercourse, but many report that they have not ever tried before). Water-based products are widely available and regarded as relatively safe because they are commonly used for clinical gynecologic and urological procedures. However, these products quickly become tacky and "crunchy," like dried mucus. This can exacerbate both the sensation of dryness and friction and is typically only favored by women using condoms. Of note, condom use can also be very difficult in women with severe vaginal and vulvar atrophy and requires appropriate lubrication. Oil-based lubricants are contraindicated with condom use. Atrophy and dryness increase a woman's susceptibility to infection and trauma; patients must be counseled about the importance of condom use for preventing sexually transmitted infection and HIV. In our program, we have seen new diagnoses of both HPV and genital herpes in sexually active cancer survivors. Patients are routinely assessed for sexual risk behavior and are offered (or recommended, if appropriate) HIV and sexually transmitted infection testing. Condom (male or female) and dental dam use should be discussed to reduce risk of sexually transmitted infection, including appropriate use of lubricants with these products.

Education about the differences between moisturizers and lubricants is essential for proper use and may need to be repeated over time. A summary pamphlet or handout can be useful to guide patients and their partners in trying various options (Table 28.5 may be copied and distributed for clinical purposes, with acknowledgment). Patients commonly present having used moisturizing products inappropriately as a sexual lubricant, rather than as regular use. As with moisturizers, the evidence base for safety and effectiveness of lubricants for treating vaginal dryness in women with breast cancer is very slim [96]. These products are considered by the FDA as "cosmetic" and are not subject to pharmaceutical-level scrutiny [98]. Commonly used lubricants typically contain several distinct chemical ingredients, including glycerine, parabens, and odorants. Breast cancer patients at low risk for sexually transmitted infection often opt for vegetable or olive oil as a low-cost, natural lubricant with good effect, in our experience (taking care to avoid staining of bed linens or garments). Based on clinical observation, these products do appear to reduce dryness symptoms, improve comfort and pleasure with sexual intercourse, and sometimes improve the appearance of the vulvovaginal tissue. However, patients should be counseled about the limited evidence base for their use. None of these products have been studied for safety in women with breast cancer.

Vaginal Stenosis

Although vaginal stenosis is much more common in patients with genital tract or colorectal cancers treated with pelvic radiation, breast cancer survivors, particularly those treated with tamoxifen and/or AIs, can experience narrowing of the vaginal introitus and loss of vaginal length due to

Table 28.5 Summary and Comparison of Lubricants and Moisturizers

Lubricants	Pros	Cons
Water-based	• Inexpensive • Compatible with condoms and silicone • Some do not decrease sperm-motility (Pre-Seed)	• Dries out easily • Feels tacky • May contain glycerin and/or paraben
Silicone-based	• Never dries out • Can be used in water • Feels lush	• Expensive • Difficult to wash off • Incompatible with silicone/rubber • Impairs sperm motility • Causes staining of sheets • Most do not contain glycerin and/or paraben
Oil-based	• Stays slicker longer • Good for masturbation • Natural • Low cost	• Degrades condoms • Impairs sperm motility • Causes staining of sheets
Moisturizers	• Helps moisturize vaginal canal • Makes vaginal and surrounding tissue more pliable and less dry • Maintenance use every 2–3 days • Compatible with condoms	• May contain glycerin and/or paraben

loss of collagen, glycogen, and other proteins in the hypoestrogenemic urogenital epithelium [44]. The extent of vaginal stenosis in this population is difficult to quantify because baseline measures of vaginal anatomy are almost never available. Patients with vaginal stenosis will report feeling "like a virgin again," or will say that the vagina feels very "taut" or "stretched" during attempts at intercourse or other penetration. In fact, in these patients, loss of the vaginal rugae literally does leave the vaginal canal a smooth, inflexible tube rather than the accordion-like structure found in well-estrogenized women. A pelvic exam using bimanual technique (one finger for the vaginal exam may be necessary to minimize pain), a speculum exam using a metal, warm, lubricated speculum for inspection of the vagina and cervix, along with a comprehensive assessment of pelvic floor musculature and strength are necessary for diagnosis of vaginal stenosis. In women who have not been sexually active for prolonged periods (years) and in those who have had prior hysterectomy or vaginal or rectal surgery, asymmetry of the vaginal canal and/or adhesions of the vaginal walls may be encountered. Although stenosis frequently co-occurs with vaginismus in women who have been experiencing painful attempts at penetrative intercourse, vaginismus is more common and can present with similar symptoms. The vaginal exam is critical for differentiating between the two conditions.

Vaginismus

Vaginismus is a sexual pain disorder involving recurrent or persistent involuntary contraction or spasm of the muscles surrounding the distal third of the vagina (perineal and levator muscles) that interferes with vaginal penetration [99]. In women with breast cancer, vaginismus may occur due to psychological factors, such as fear of penetration that develops as a psychological response to body image concerns or the trauma of cancer, or as a conditioned response to pain from prior attempts at penetrative intercourse. As mentioned earlier, patients will commonly describe this as the feeling that their partner is "hitting against a wall" when penetration is attempted. Some women will only experience this with partnered intercourse and will be confused

as to why they can insert a dilator or vibrator themselves without any difficulty. It is not uncommon for women with vaginismus to be able to allow penetration in controlled situations like a gynecologic exam or with self-insertion, demonstrating the mind-body nature of this condition.

Although it is beyond the scope of this chapter to provide full detail on treatment for vaginal stenosis and vaginismus, both can be addressed with a combination of patient education, vaginal dilator therapy, and pelvic physical therapy in addition to vaginal moisturization and lubrication. Psychotherapy, including sex therapy, is discussed in more detail below. The University of Chicago Program in Integrative Sexual Medicine for Women and Girls with Cancer, vaginal dilators are used routinely at the initial exam to establish the patient's self-perception of her vaginal capacity, her perception of her partner's penis size (for women with male partners), and to objectively measure the vaginal diameter and length. Frequently, patients underestimate their own vaginal capacity and gain benefit from the biofeedback provided by the objective measurement with the dilator. In our experience, a woman's realization that her vaginal capacity is adequate to accommodate her partner can help alleviate vaginismus. The partner's size, or the size of a preferred sexual device such as a vibrator or dildo, allows the patient to establish a target for vaginal dilation therapy.

Vaginal dilator packages typically come in sets of three or four graduated devices and are manufactured by several different suppliers. Our clinic stocks two sterilizable sets each of small, medium, and large varieties of dilators from three manufacturers in order to provide patients with a range of options best suited to their anatomy and comfort. Vaginal dilator sets vary in cost from about US $40 to US $150. They also vary in color, material (e.g., plastic, silicone), rigidity, and shape. Some products require a physician prescription, whereas others can be obtained directly by the patient via a specialty pharmacy or online. We know of no randomized trials of dilator therapy use to address vaginal stenosis or vaginismus specifically in breast cancer patients. For patients with a hysterectomy, it is important to advise caution with deep insertion of the dilator so as not to weaken the surgical scar at the apex of the vagina (also called the vaginal cuff). Collaboration with pelvic physical therapy can optimize and accelerate treatment of both vaginal stenosis and vaginismus in this patient population. The American Physical Therapy Association (http://www.womenshealthapta.org/plp/index.cfm#reg) and the International Organization of Physical Therapists in Women's Health (http://www.ioptwh.org/members/map.html) provide specialized training, research, and standards in women's health physical therapy; sexual health providers should identify individuals with experience in transvaginal and transrectal techniques for addressing female pelvic floor and sexual dysfunction and work closely with these specialized physical therapists to optimize care for breast cancer patients with these conditions.

Low or Absent Sexual Desire and Difficulty with Arousal and Orgasm

Details on the etiology of and general treatment approaches for these conditions can be found in Chapter 9–11. In breast cancer survivors, symptoms of low desire, difficulty with physiological and psychological arousal, and orgasm very commonly copresent with vaginal dryness and painful intercourse. Both estrogen and testosterone have been found to play an important role in these aspects of female sexual physiology. In women without breast cancer, particularly those who have had their ovaries removed, both estrogen and testosterone therapy have been studied for effectiveness in addressing desire, arousal, and orgasm problems. A randomized trial of transdermal testosterone vs. placebo in 150 postmenopausal cancer survivors with decreased libido resulted in elevated serum testosterone levels in the treatment group, but found no difference in libido between the two groups [100]. As with concerns about exogenous estrogen therapy in women with breast cancer, exogenous testosterone may contribute to breast cancer risk through physiologic conversion to estrogen or directly through effects on androgen receptors in

breast tissue [101]. Although no FDA-approved testosterone products are available for treatment of sexual problems in women, more than 20% of prescriptions written for testosterone in 2003 were prescribed to women [102]. Prescribing practices in breast cancer survivors are not known, but anecdotally appear to be quite low.

Nonhormonal treatments to assist with arousal and orgasm include individual, relationship and sex therapy, erotic media, sexual devices (e.g., vibrators), and an FDA-approved clitoral pump device which can be used to facilitate clitoral tumescence and orgasm. Vibrators or other sexual accessories can be used in the genital and/or breast area or other erogenous zones to promote arousal. Patients may need explicit suggestions about this and will want reassurance regarding safety, hygiene, and partner involvement in incorporating these products into their sexual encounters. Pelvic physical therapy may be beneficial in addressing physiologic arousal and orgasm, particularly in women with pelvic floor dysfunction [103, 104]. Hypnotism and medical acupuncture (http://www.medicalacupuncture.org/) may also have a role in treating desire/arousal/orgasm and other sexual disorders in women with breast cancer, but the evidence base for these approaches is extremely limited [105]. Patients seeking these therapies should be advised to consult their state/national licensing requirements and credentialing for these practitioners.

Role of Psychotherapy, Sex Therapy, Couples and Marital Therapy, Psychiatric Medications

Ideally, sexual health care providers work in an interdisciplinary team setting, even if at a distance, that involves mental health and sex therapy expertise in addition to gynecology, medical and surgical oncology, nursing, physical therapy, and breast reconstruction. Table 28.6 illustrates the complementary roles of key interdisciplinary team members. Close interaction with cancer wellness or support centers is also very valuable for the sexual health providers and patients. Mental health needs, including specialized support for coping with breast and body image issues, are high and under-recognized among breast cancer survivors. It is not uncommon that patients have experienced sexual problems for years and with terrible strain before they find the courage to raise the issue with the oncologist. Guilt about inability to please a partner and worry about the sustainability of marriage or other intimate relationships given breast cancer and sexual problems are common concerns that can exacerbate precancer relationship strain. In addition, many women with breast cancer and sexual concerns present on treatment with antidepressant (for depression or treatment of hot flushes), antianxiety, and sleep medications but are not under the care of a mental health professional. All of these conditions can originate with or be exacerbated by abrupt onset of iatrogenic menopause. These medications, and the conditions they are prescribed to treat, can further impair female sexual functioning in the menopausal breast cancer patient.

It is important to note a new body of evidence showing that some SSRIs may interfere with tamoxifen effect by reducing enzymatic conversion of tamoxifen to its active metabolite, endoxifen. Highlighting the future potential of genomics and personalized medicine in breast cancer care, a 2005 prospective observational study found that women with a heterozygous ($n=29$) or homozygous variant ($n=3$) genotype for the cytochrome P450 (CYP) 2D6 allele who were taking antidepressants that inhibit the CYP2D6 enzyme had significantly lower mean plasma endoxifen concentrations than women with a homozygous wild type variant ($n=48$) [106]. Some SSRIs are more potent inhibitors of CYP2D6 (e.g., paroxetine) than others (e.g., venlafaxine). Despite limitations in the study design, including the small sample size and that most women in the study had the homozygous wild type variant of the key allele, this research has translated into a practice among oncologists of favoring venlafaxine (marketed in the United States as Effexor®) for treatment of both depression and hot flushes in breast cancer survivors. In the sexual health field, bupropion has been favored as an antidepressant with fewer

Table 28.6 Interdisciplinary approach to sexuality and cancer

Services provided	Registered nurse	Physician/APN	Physical therapist	Psychologist
Assessment/education				
Initial sexuality assessment/screening*	X	X	X	X
Detailed sexual history		X		X
Ongoing assessment	X	X		
Coordination of care	X	X		
Referral to support group	X	X		
Early education	X	X		
Education of partner	X	X	X	X
Ongoing education		X		
Advanced pelvic floor assessment			X	
Musculoskeletal and neurological exam			X	
Focused gynecological assessment (pelvic floor strength, clitoral sensation, detailed vulvar exam)		X	X	
Biophysical interventions				
Dilator therapy		X	X	
Medication management		X		
Basic pelvic floor exercises	X	X	X	
Pelvic floor massage/retraining exercises			X	
Psychosocial and behavioral				
Psychotherapy (individual or couples)				X
Sex therapy (individual or couples)				X
Individual therapy				

*Also performed by oncologist

negative sexual side effects [107], but it too is a potent inhibitor of CYP2D6 [108]. Findings vary across studies with respect to sexual side effects of antidepressants in women, but recent reviews indicate physicians consistently underestimate the prevalence of antidepressant associated sexual dysfunction [109, 110]. This should be considered in a woman without depression who is using venlafaxine or SSRIs to treat hot flushes. For women with mild to moderate depression, psychotherapy may serve as an effective alternative or adjunct to pharmacotherapy. Some patients will be willing to tolerate hot flushes or pursue other management options for depression in exchange for improved sexual function.

The sexual health care provider obtains a detailed medication history including circumstances and timing of diagnosis of physical and mental comorbidities and treatments. In some cases, interventions to improve wellness such as weight loss, exercise, smoking and alcohol cessation, sleep hygiene, and nutrition can have salubrious effects on other physical and mental health conditions, as well as sexual function, and enhance the patient's sense of control. While we find very few patients with breast cancer and sexuality concerns who would not benefit from psychotherapy and/or sex or couples therapy, cost can be prohibitive for some. In talking with patients about referral for psychotherapy (individual, sex, couples), the sexual health provider needs to convey the well-established benefits [111] while taking care not to suggest to the patient that her sexual symptoms are solely "in your head." Phone consultation with the mental health professional can help the patient make a fully informed decision about costs and benefits before deciding whether to proceed. It can be appropriate in some cases to recommend abstention from sexual activity until the patient's symptoms are fully diagnosed and medical, physical, and psychological support can be implemented. This recommendation, in the form of a written prescription, can be particularly helpful for a patient feeling pressured by her partner to have sex. Women with breast cancer, as with other women, are at risk for intimate partner violence, abuse, and partner infidelity whether they have a

male or a female partner. The sexual health care provider of any disciplinary background should be adept and thorough in assessing and addressing these conditions. In our experience, the vast majority of patients benefit from a holistic, biopsychosocial approach to treatment of sexual problems and are receptive to psychological support and interventions. This is true for women with and without breast cancer.

Cancer Survivorship and Health Maintenance

The majority of women with early stage breast cancer are alive and free of disease at 5 (87.8%) and 10 years (80.7%) [3]. Therefore, quality of life and symptom control, both in the short term during treatment and in the long term throughout survivorship, are of increasing importance [112]. Some complications of breast cancer treatment that can profoundly affect women and their quality of life are sexual dysfunction, infertility, and decrease in bone density [113].

Evolution of the U.S. health care system in response to federal policy changes will likely have important implications for cancer survivorship care. More than 1 in 30 Americans is a cancer survivor. As the population of cancer survivors grows, models of survivorship care are also evolving. Following acute care for breast cancer, most breast cancer survivors receive ongoing health care indefinitely with their oncologists with or without "shared care" in a primary care practice setting (internal medicine, family medicine, or ob/gyn) [114]. In a growing number of academic medical centers, survivorship clinics provide specialized, interdisciplinary care attuned to the needs and concerns of cancer survivors and serve as an alternative to returning to a general primary care setting or following exclusively with an oncologist. This means that, at some point in the cancer care continuum (commonly 2–5 years following completion of therapy if no recurrence), patients are phased out of routine oncologic care. Some oncology-trained pediatricians, internists, and other specialists focus their practices on survivorship care and research, but the majority of survivorship programs are run by physicians, nurses, or mental health professionals without formal oncology subspecialty training. Likewise, most programs do not offer specialized care for female sexual problems and have limited ability to identify and address vulvovaginal abnormalities beyond empiric treatment for vaginal dryness or psychosocial support for relationship issues.

Female sexual medicine programs tailored to women and girls with cancer are scarce at this time; the few in existence are led by gynecologists or internists, typically working in collaboration with nursing, psychology, psychiatry, physical therapy, and oncology. Whether providing care for sexuality issues in the context of a specialized clinic or a primary care practice, health maintenance issues are an important component of survivorship care [115]. Attention to health maintenance and secondary prevention issues in female breast cancer survivors, including mammography, cardiovascular risk assessment, colon and cervical cancer screening, weight and sleep management, exercise, and bone density screening is important for the patient's overall health and can inform a health maintenance and treatment plan in alignment with the patient's priorities. For example, some patients may choose to prioritize time and resources for a screening colonoscopy before investing in physical therapy for dyspareunia or psychotherapy for relationship distress (or vice versa). Research is needed to determine the best, most cost-effective models for optimizing cancer survivor care [115, 116].

Bone Health

The AI use is associated with a loss of bone density and increased risk of fractures [72, 73, 76, 117]. The risk of fractures is the greatest during active AI therapy [80]. According to the ASCO guidelines for bone health, medical oncologists should play an expanded role [118]. Patients should be referred for osteoporosis screening, receive prevention information and treatment, if necessary. High-risk patients should be monitored closely with DEXA scans.

High-risk patients are considered all women over age 65, all women between the ages of 60 and 64 with a body weight <70 kg, family history of osteoporosis, a prior nontraumatic fracture, postmenopausal women receiving AIs, and premenopausal women with therapy associated premature menopause. All postmenopausal women at risk of bone loss should be encouraged to take calcium and vitamin D supplements, to perform weight bearing exercise and to stop smoking. Patients with osteoporosis should be treated with bisphosphonates. However, it is not currently recommended to use bisphosphonates for adjuvant therapy to reduce bone metastases, but we are awaiting data from ongoing trials.

Cardiovascular Health

Prior to receiving adjuvant therapy with an anthracycline-based regimen or trastuzumab, patients should have a baseline cardiac evaluation. The evaluation should include an EKG and either an echo or MUGA scan for evaluation of wall motion and left ventricular ejection fraction. Congestive heart failure is a potential complication of breast cancer treatment. Women between the ages of 66 and 70 years old who received adjuvant anthracyclines had significantly higher rates of CHF than women who received either no chemotherapy or nonanthracycline chemotherapy [HR = 1.26 (95% CI: 1.12–1.42)] [119]. During the 10-year follow-up period, the rates of heart failure continued to increase. The following baseline characteristics were found to be predictors for congestive heart failure: age (HR = 1.79 per 10 years; 95% CI: 1.66–1.93), black race (HR = 1.40; 95% CI: 1.30–1.50), trastuzumab treatment (HR = 1.46; 95% CI: 1.21–1.77), hypertension (HR = 1.45; 95% CI: 1.39–1.52), diabetes (HR = 1.74; 95% CI: 1.66–1.83), and coronary artery disease (HR = 1.58; 95% CI: 1.39–1.79). If congestive heart failure develops secondary to therapy, it should be treated with cardiac medications.

Key Research Questions and Needs to Advance Care of Sexuality Issues in People with Breast Cancer or Elevated Breast Cancer Risk

1. Baseline sexual function, including breast and vulvar function in women, prior to undergoing treatment.
2. What is the most effective approach to preventing negative sexual outcomes and preserving sexuality of people with breast cancer? At what point in the cancer care continuum should interventions begin?
3. Are sexually active women and men more likely to have an earlier breast cancer diagnosis?
4. What sexuality concerns are prevalent in men with breast cancer and what interventions are effective?
5. Evidence-based guidelines for addressing sexual and reproductive concerns and outcomes in women contemplating breast cancer genetic risk testing
6. Is topical vulvar estradiol safe and effective for treating dyspareunia and provoked vulvodynia in breast cancer survivors?
7. What effect do AIs have on vulvar anatomy and sexual function in pre- and postmenopausal women being treated for breast cancer?
8. Is pelvic physical therapy effective and safe in treating dyspareunia, orgasm, and/or arousal disorders in women with breast cancer?

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Chapter 29
Gynecological Cancers

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Keywords Vulva • ovary • endometrium • cervix • chemotherapy • radiation therapy • estrogen • vaginal • dilation

General Considerations

Gynecological cancers include cancers of the vulva, the vagina, the cervix, the uterus, and the ovaries. All these cancers can affect sexual functioning in many different ways, from the psychological impact of the diagnosis to the psychophysiological impact of the disease itself, as well as the therapeutic interventions, including surgery, chemotherapy, and radiotherapy. Sometimes sexual functioning is already affected prior to the diagnosis due to bleeding, pain, fatigue, vaginal discharge, etc. Immediately after the operation, the direct impact of pain during wound healing and surgical scarring may make any sexual activity painful or impossible. In most treatment procedures of gynecological cancers, the uterus is partly or completely removed and/or the ovaries are removed. These interventions cause the loss of fertility, which is an additional general stressor with a possible negative impact on female sexual identity, femininity, and the feeling of loss of womanhood. The loss of the reproductive potential has been shown to lead to considerable distress with depressive reaction [1].

Another aspect of most of the treatment procedures is the damage to organs of the sexual response. These structures include the sensory areas of the vulva, the vestibulum, the vagina, the clitoris, the labia minora, and urethral ostium. Apart from affecting the anatomical elements of the sexual response, treatment procedures may also destroy the blood supply and the sympathetic, parasympathetic, and somatic innervation of these peripheral organs. The third important impact of genital cancer treatment involves the loss of ovarian hormone production, resulting in symptomatic estrogen, androgen, and progesterone withdrawal.

Genital cancers represent 14.4% of all the cancers that affect women. Ten percent of the mortality linked to cancers in women are due to genital cancers (the majority is attributable to cancers of the ovaries). With early diagnosis and efficient and aggressive therapy, two-third of these women survive for at least 5 years.

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The Etiopathogenetic Framework of Sexual Dysfunction in Genital Cancer Patients

Sexual dysfunction(s) of the individual patient suffering from genital cancer and the subsequent treatment are determined by three major groups of variables [2]:

(a) Preexisting sexual and relationship characteristics
   - Preexisting body image, sexual (dys)function, comorbidity, relationship resources

(b) Disease and treatment specific impact on sexual function
   - The threat (fear of death), destruction, disfigurement, dysfunction, dysregulation, disability, drugs

(c) Individual and partner coping pattern with the disease
   - Passive and active coping, changes in partner dynamics, withdrawal, depression, anxiety, etc.

Variables (a) and (c) have to be explored and studied on an individual basis (see below). We describe the disease and treatment specific impact for each type of genital cancer, taking into account that there is overlap which increases with advancing stages of each type of genital cancer [2].

Cancer of the Vulva

Impact of the Disease and Treatment Procedures

The disease itself may cause discharge and pain leading to a diminution of sexual activity before the diagnosis and treatment. Treatment usually results in the destruction of neurovascular structures at the level of the vestibule, the clitoris, and the labia minora through the removal of affected tissue. With increasing stage of the disease, the extent of the excision increases and includes removal of the inguinal lymph nodes and larger regions of the perineum in the context of a radical vulvectomy.

Prevalence and Incidence of Sexual Dysfunction and Contributing Factors

Likes et al. [3] examined 43 women with vulvar intraepithelial neoplasia (VIN) followed by vulvar excision with respect to quality of life (QOL) measured with the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire C30 EORTC QLQ-C 30 and sexual function measured with the Female Sexual Function Index (FSFI). The authors looked into the correlation of these parameters with age, size of excision, medication history, general medical findings, pathology results. They found that older age and more extensive excision were associated with poorer sexual function and QOL in women following surgical treatment for VIN.

In another study from the same group [4], the authors matched the same patients for age (±2 years) with a control group to compare sexual function and QOL. They found that women after excision had poorer scores in sexual function ($p = 0.015$) and QOL ($p = 0.003$) than nonaffected women.

Anderson et al. [5] stated in a prospective study that there was a specific disruption of the phases of excitement and resolution and to a lesser extent orgasm in women after treatment of in situ vulvar cancer. In addition to these findings, a two-third increase in the frequency of sexual dysfunction was noted and 30% of the sample was sexually inactive at follow-up.

Sexual function or dysfunction following vulvectomy was examined in a longitudinal study with 40 women after vulvectomy [6]. The authors found a significant alteration of body image following vulvectomy. Sexual frequency significantly decreased after surgery and there was significant sexual dysfunction in the categories of sexual aversion disorder ($p < 0.01$),

arousal disorder ($p \leq 0.02$), and hypoactive sexual desire disorder ($p \leq 0.001$).

In this study, however, the extent of surgery did not correlate with the degree of sexual dysfunction in any category.

In a cross-sectional study [7], 25 women following vulvectomy and 15 of their partners were examined regarding sexual function and psychosomatic reactions. More than half of the women had both sexual dysfunction and psychological problems. Their partners had no sexual dysfunction but almost half of them reported psychological problems.

Ten couples, in which the women began treatment for vulvar carcinoma, participated in a 2-year longitudinal study on sexual functioning before and after treatment [8]. Sexual functioning was measured on admission and at 6, 12, and 24 months posttreatment. Sexual functioning was operationalized in terms of current sexual behavior, sexual motivation, sexual (dis)satisfaction, and the perception of genital sensations of sexual arousal.

An age-matched nonpatient control group was added to the study, and the impact of physical variables was also evaluated. Within 1 year, all women who were sexually active before the treatment had resumed their sexual activities. At the 6-month assessment an increase in relational sexual dissatisfaction could be detected. Over the remaining observation period, the women's sexual satisfaction from their partner was not found to be different from pretreatment satisfaction levels and not different from the satisfaction in the control group, despite the physical damage and persisting poor perception of genital symptoms of sexual arousal during lovemaking. Satisfaction with sexual interaction with the partner under these circumstances appears to be more an expression of satisfaction with the intimate aspects of the sexual relationship than of satisfaction with the physiologic arousal aspects of the sexual relationship [8]. The authors [8] argued that psychological and social variables are more crucial for sexual rehabilitation than physical variables. Therefore, psychosocial issues constitute the most promising focus for intervention.

Cancer of the Vagina

Impact of the Disease and Treatment

The disease itself may cause vaginal discharge and bleeding after or during intercourse. In general, treatment involves the ablation of parts or all of the vagina (stage I and stage II). This leads either to a severe shortening of the vagina, loss of vaginal elasticity, or absence of vaginal structures.

Prevalence, Incidence of Sexual Dysfunction, and Contributing Factors

There are no specific studies looking into sexual function or dysfunction after treatment for vaginal cancer. In some of the major studies, these patients are added to the larger groups of patients with vulvar cancer and cancer of the cervix. From these limited studies, one may conclude that intercourse is either no longer possible or severely impaired, and that probably a large number of patients withdraw from sexual activities. The degree of individual suffering from these anatomical changes depends on the patient's age, relationship history, impact on body image, and the individual sexual script.

Cancer of the Cervix

Impact of the Disease and Treatment

The disease may lead to discharge and pain with a negative impact on sexual activity and possible sexual withdrawal. The impact of treatment differs between surgical procedures and radiation therapy (see Chapter on radiotherapy).

- Surgical procedures include removal of the upper third of the vagina, removal of the uterus and parametria as well as pelvic lymph nodes.
- An important feature of cervical cancer is that it often affects younger women under 45 years of age. More than 70% will be cured, resulting in a significant number of long-term treatment survivors.

Prevalence, Incidence of Sexual Dysfunction, and Contributing Factors

Quality of Life Studies

In the study of Vistad [9], the authors summarized and discussed the research findings of QOL of cervical cancer survivors based on self-report measures in terms of physical, psychosocial, and sexual well-being. They identified studies published between 1966 and 2005 and performed quality assessment regarding methodological and treatment related criteria.

The authors included 23 studies, of which eight had good methodology with validated questionnaires. They concluded that the QOL of cervical cancer survivors is reduced compared to the general female population following radiotherapy, but less so following surgery and the earliest stages of cervical cancer.

In a longitudinal study, assessment of sexual frequency, function, and behavior, as well as marital happiness and psychological distress, was performed for 61 women with early stage, invasive cervical cancer at the time of diagnosis [10]. Cancer treatment was radical hysterectomy alone for 26 women and radiotherapy with or without surgery for 37 women (26 + 37 = 63 women). Follow-up took place at 6 and 12 months after cancer therapy. Women's sexual satisfaction, capacity for orgasm, and frequency of masturbation remained stable, whereas frequency of sexual activity with a partner and range of sexual practices decreased significantly by 1 year. Women who received irradiation with or without surgery resembled women who underwent radical hysterectomy alone at 6 months. By 1 year, however, the radiotherapy group had developed dyspareunia, which was reflected in gynecologist's ratings at pelvic examination. The women receiving radiotherapy also had more problems with sexual desire and arousal, and were less likely to resume several daily life activities.

Cancer treatment modality was not related to marital happiness or stability, however.

Differences Between Treatment Procedures (Table 29.1)

Of 28 patients in a cross-sectional study treated with radiotherapy alone, 22 had developed shortening or narrowing of the vagina sufficient to interfere markedly with sexual function. Only two of the 32 surgically treated patients experienced such a sexual interference. With combined treatment, 60% showed some vaginal alterations and 33% sexual dysfunction [11]. Questioning of the patients revealed the importance of sexual function in the lives of middle-aged women. Therefore, radical surgery is preferred in the treatment of early carcinoma of the cervix, since this mode of therapy interferes minimally with sexual function.

Jensen et al. [12] examined women who had been treated for early stage cervical carcinoma with radical hysterectomy in a longitudinal study.

They reported that radical hysterectomy had a persistent and negative impact on patient's sexual interest and vaginal lubrication, whereas the majority of other sexual and vaginal problems disappeared over time. In another study, 114 women (37 surgery, 37 radiotherapy, 40 controls) were interviewed at least 5 years after initial treatment for cervical cancer. Eligible women had squamous cell tumors smaller than 6 cm at diagnosis, were currently disease free, and had either undergone surgery or radiotherapy, but not both. The two treatment groups were then compared using univariate analysis and multivariate linear regression with a control group of age- and race-matched women with no history of cancer.

Table 29.1 Impact of cervical cancer treatment on sexuality

References	Design	Sample size	Treatment	Findings	Comments
Abitbol and Davenport [11]	Cross-sectional	$N=75$	$n=28$ RT $n=32$ surgery $n=15$ combined treatment	RT associated with vaginal shorting, with combined treatment, 60% showed vaginal alterations and 33% sexual dysfunction	Radical surgery preferred in the treatment of early carcinoma of the cervix due to minimal interference with sexual function
Jensen et al. [12]	Longitudinal	$N=173$ patients and control group	$n=173$ patients with lymph node-negative, early-stage cervical carcinoma who had undergone RH and pelvic lymphadenectomy $n=$ age-matched control	Radical hysterectomy impacts patient's sexual interest and vaginal lubrication negatively	After radical hysterectomy the majority of other sexual and vaginal problems disappear over time
Frumovitz et al. [60]	Longitudinal	$N=114$	$n=37$ surgery $n=37$ RT $n=40$ controls	RT associated with sexual dysfunction	Patients with surgery can expect an overall quality of life and sexual function
Jensen et al. [13]	Longitudinal	$N=118$ patients and control group	$n=118$ patients referred for RT $n=$ age-matched control	RT associated with low or no sexual interest, severe lack of lubrication, mild to severe dyspareunia and reduced vaginal dimension	
Greimel et al. [14]	Longitudinal	$N=121$	$n=63$ surgery $n=38$ surgery/CT $n=20$ surgery/RT	Surgery/RT had the worst quality of life outcomes and sexual dysfunction	No significant differences in sexual pleasure and sexual discomfort

RT radiotherapy; *CT* chemotherapy

When compared with surgical patients and controls using univariate analysis, radiation patients had significantly poorer scores on standardized questionnaires measuring health-related QOL (physical and mental health), psychosocial distress, and sexual functioning. The disparity in sexual function remained significant in a multivariate analysis. Univariate and multivariate analyses did not show significant differences between radical hysterectomy patients and controls on any of the outcome measures.

The authors concluded that cervical cancer survivors who had been treated with surgery did not experience any severe negative impact on their QOL and sexual function, and that these patients can expect an overall QOL and sexual function not unlike that of women without a history of cancer.

The negative impact of radiotherapy was confirmed by another longitudinal study in which patients 2 years after radiotherapy had low or no sexual interest (85%), moderate to severe lack of lubrication (35%), mild to severe dyspareunia (55%), and general dissatisfaction with their sexual life (30%). Reduced vaginal dimension was reported by 50% of the patients, and 45% were never or only occasionally able to have intercourse [13].

A large study included 121 cervical cancer survivors (63 surgery, 38 surgery/chemotherapy, and 20 surgery/radiotherapy) [14]. Patients in the surgery/radiotherapy group reported significantly worse QOL outcomes (lower scores on physical, role, cognitive, and social functioning) compared to patients in the surgery group or patients in the surgery/chemotherapy group. Concerning sexual functioning, patients in the surgery/radiotherapy group reported a significantly lower sexual activity rate compared to women in the surgery group or women in the surgery/chemotherapy group ($p<0.05$). However, there were no statistically significant differences concerning sexual pleasure and sexual discomfort among the different treatment groups ($p>0.05$).

One of the interesting findings of the study was that 43.3% of the patients had not been sexually active over the past months. The main reason for sexual inactivity was that women did not have a partner, were not in an intimate relationship, or were not interested in sexual activity. Twenty to thirty percent of women reported comorbidities which may have an effect on sexuality. A number of patients (12%) reported that due to physical problems of their partners, sexual intercourse was not possible. Given these reasons, the lack of sexual activity cannot be attributed to cancer treatment alone.

Specific Physical Findings and Sexual Dysfunction (Table 29.2)

In a longitudinal study from Sweden [15], the authors focused on the impact of the treatment of cervical cancer on urinary and climacteric symptoms and sexual life.

Data were collected for 39 women by two questionnaires (before and 1 year after treatment). In order to supplement the data from the questionnaires, some data were obtained from the patient's medical records.

Voluntary micturitions, urgency and urinary incontinence, as well as climacteric symptoms had not increased 1 year after treatment. But vaginal dryness and dyspareunia had increased and sexual desire was reduced 1 year posttreatment.

In a study by Bergmark et al. [16], 332 women with a history of early stage cervical cancer were contacted and 489 women without a history of cancer as controls were asked in an anonymous questionnaire about vaginal changes and sexual function. A total of 256 patients and 350 controls answered the questionnaire. A total of 167 of 247 women with a history of cancer (68%) and 236 of 330 controls (72%) reported that they had regular vaginal intercourse.

- Twenty-six percent of the women who had cancer and 11% of the controls reported insufficient vaginal lubrication for sexual intercourse.
- Twenty-six percent of women who had cancer and 3% of the controls reported a short vagina.
- Twenty-six percent of the women who had cancer and 4% of the controls reported an insufficiently elastic vagina.

Table 29.2 Impact of cervical cancer on physical and sexual parameters

References	Design	Sample size	Measures	Findings
Lalos et al. [15]	Longitudinal	$N=39$	Two questionnaires before and 1 year after treatment of cervical cancer	Vaginal dryness and dyspareunia had increased and sexual desire was reduced
Bergmark et al. [16]	Cross-sectional	$N=606$	Questionnaires on vaginal changes and sexual function	68% of patients and 72% of controls had regular intercourse; the frequency of orgasms and orgasmic pleasure similar in the two groups
			$n=256$ patients with history of early stage cervical cancer	Cancer patients report more
			$n=350$ controls without cancer	• Dyspareunia and degree of distress caused by reduced libido • Insufficient vaginal lubrication for sexual intercourse • Shortening and inelasticity of vagina • Moderate or great distress due to vaginal changes as compared with 8% of the women in the control group
				Among the women who had cervical cancer, the type of treatment received had little if any effect on the prevalence of specific vaginal changes
Lindau et al. [17]	Case-control, longitudinal	$N=480$	$n=160$ patients with history of cancer	Sexual problems more prevalent among patients, even after 25 years following diagnosis patients suffer from complex sexual problems
			$n=320$ controls (individually matched on age and race to patients at a 2:1 ratio)	Higher prevalence of pain during intercourse and lubrication problems among survivors
				More than a third of survivors were affected by feeling unattractive because of physical appearance and by bladder infections or incontinence following sex
				Satisfaction with care for sexual problems was lower than with cancer care overall, 62% reported never discussing the effect of genital cancer on sexuality

- Twenty-six percent of the women who had cancer reported moderate or great distress due to vaginal changes as compared with 8% of the women in the control group.
- Dyspareunia was also more common among the women who had cervical cancer. The frequency of orgasms and orgasmic pleasure was similar in the two groups. Among the women who had cervical cancer, the type of treatment received had little if any effect on the prevalence of specific vaginal changes.

There are several interesting findings in this study: One finding is that orgasmic capacity seems not to be influenced by vaginal changes. Another interesting result was that in both groups with the mean age of 45 years, little or no interest in sex in the previous 6 months was the same. However, the degree of distress caused by reduced libido was higher among the women who had cancer. Thirty percent of the women in both groups reported that they had not engaged in intercourse during the previous 6 months and twice as many

controls as women with cancer reported that they had not had intercourse for at least 5 years.

Thirty-two percent of the women who had cervical cancer and 25% of the controls reported little or no satisfaction with their present sexuality.

The authors summarize that, according to the results, there is indirect evidence that the vagina may be sufficient for satisfactory orgasm and that the absence of the uterus has little effect in this regard.

Another controversial finding in this study was that the sexual complaints related to vaginal changes did not differ between the three different treatment groups. This may, however, be due to lack of sufficient sample size. The results remain difficult to interpret.

In a case–control study from the 1992, the National Health and Social Life Survey (NHSLS) [17], 221 survivors in a cancer registry were compared to a matched control group. Women were followed longitudinally for more than 25 years on average following diagnosis with clear cell adenocarcinoma of the vagina and/or cervix.

The survivors' mean age was 49 years and median survivorship was 26.8 years with a range from 5.5 to 39.7 years. Survivors and controls reported similar levels of sexual partnership and activity, but sexual problems were significantly more prevalent among survivors (mean number of problems was 2.6 vs. 1.1, $p<0.001$). For example, the prevalence of pain during intercourse and difficulty lubricating were, respectively, 7 and 3 times higher among survivors. More than a third was affected by feeling unattractive because of physical appearance and by bladder infections or incontinence following sex.

Satisfaction with care for sexual problems was lower than with cancer care overall (5.5 vs. 8.0/10, $p<0.001$). While 74% believed that physicians should discuss sex, 62% reported never discussing the effect of genital cancer on sexuality. In adjusted analysis, survivors reporting no such discussion were significantly more likely to exhibit current complex sexual morbidity (more than three concurrent sexual problems).

The study shows that even after more than 25 years following diagnosis, patients suffer from complex sexual problems, which very often are related to vulvar and vaginal changes. What is important in this study is that specific counseling and the dialog with the physician can be helpful for avoiding long-term negative consequences. The analysis shows that the conversation with the physician about the sexual effects of genital tract cancer and cancer treatment is associated with significantly fewer sexual morbidities among survivors compared to women reporting no such conversation.

Contributing Factors

To look for specific demographic, clinical, and psychosocial and physical factors which could contribute to the sexual health of cervical cancer survivors, Donovan et al. [18] examined women treated between 1 and 5 years previously for stage 0 to II cervical cancer and matched them with age and education comparable women with no history of cancer undergoing routine cervical cancer screening. All participants had a partner with whom they had been sexually active.

In the study, a total of 166 patients were approached to participate. Of these, 55 (33%) women were ineligible to participate (no current sexual partner, completion of treatment more than 5 years ago, cancer recurrence or a second cancer diagnosis, or no treatment). Of the remaining, 61 (37%) either actively declined to participate or passively declined by not returning the questionnaire after agreeing to participate, resulting in 50 (60%) women who completed their participation in the study.

Women completed measures of sexual health, vaginal changes, partner relationship quality, perceived physical appearance, and sexual self-concept.

Cervical cancer survivors reported significantly less sexual interest, more sexual dysfunction, and lower sexual satisfaction. The most consistent predictors of sexual health after treatment among survivors were time since diagnosis, receipt of radiotherapy, partner relations and perceived physical appearance, as well as vaginal changes. These variables accounted for about 50% of the variance in sexual health outcomes. The authors conclude that efforts to improve sexual health in women with a history of cervical cancer must not

be limited to the direct effects of cancer treatments on vaginal and abdominal physiology.

Sexual rehabilitation interventions should consider partner relationships, perceived physical appearance, and women's attitudes towards themselves as sexual beings in addition to vaginal changes.

In a Dutch prospective, longitudinal study [19] on the impact of early stage gynecological cancer on sexuality, women with a partner ($n=58$) completed self-report questionnaires following diagnosis but prior to treatment, and then again at 6 and 12 months posttreatment. A single assessment was also obtained from a healthy comparison group ($n=103$). Pretreatment cancer patients reported fewer and less trouble with sexual problems compared to healthy controls. Neither sexual satisfaction nor sexual activity changed from pre- to posttreatment and was comparable to that of healthy controls. Posttreatment, relatively minor sexual difficulties were shown; a notable difficulty for cancer patients concerned lubrication. At 12 months posttreatment, the sexual functioning of cancer patients was comparable to healthy controls.

Psychosocial factors were more intensively examined in another Dutch study [20]. Women faced with cervical carcinoma usually feel an increased need for support and attention, in particular from their partners, while at the same time, an important part of the partner relationship, sexual interaction, often becomes problematic. In this study, the eventuality of reduced sexual motivation in cervical carcinoma patients was investigated. It was found that sexual interaction is valued significantly less by women treated for cervical carcinoma than by women from a nonaffected control group. After treatment, no changes in overt sexual behavior occurred. Furthermore, an effort was made to identify the most important psychosexual variables underlying the reduction in sexual motivation. It was found that a considerable decrease in the appraisal of oneself as a sexual partner is generally basic to the problem. Apparently, women try to cope by conforming to the sexual demands of their partners and with that of prevailing sexual norms. It was concluded that cervical carcinoma treatment has a strong negative effect on the sexuality of the patients and that it often amplifies the already existing ambivalence towards sexual interaction in women.

In the large study from a gynecology oncology unit of a general hospital, 105 English speaking women with gynecological cancer were examined. These women had been treated for cancer of the cervix and vulva by radical vulvectomy, Wertheim's hysterectomy, and pelvic exenteration [21].

Ninety percent of the women in relationships had been sexually active prior to surgery. Of this group, 24% had no sexual difficulties postoperatively, 66% had problems more than 6 months later, and 15% never resumed intercourse, excluding those who had a colpectomy. Eighty-two percent of those aged less than 50 years who had radiotherapy suffered sexual dysfunction. Lack of desire was the most common problem and half of the women felt that their sexual relationship had deteriorated, yet only 16% felt that their marriage had worsened.

Again, in this study, the authors found that sexual dysfunction is common following a radical pelvic surgery and tends to become a chronic problem; it is notable that not only the organic causes but also strong psychogenic elements brought about by loss of fertility, disfigurement, depression, and anxiety about one's desirability as a sexual partner seem to play an important role. The presence of a stable relationship before the diagnosis of cancer helps women to cope. Thus, young single women comprise a very vulnerable group. Patients want more information on sexual issues, and the provision of sexual counseling may improve outcome in the future.

In a longitudinal study [22], radical hysterectomy for stage Ib cancer of the cervix without adjuvant treatment was analyzed with respect to short- or long-term sexual difficulties. Twenty patients with stage I cervical cancer undergoing radical hysterectomy, 18 women treated with hysterectomy for a benign gynecological condition, and 20 gynecologically healthy women were included. At 0, 4, and 8 months postoperatively, women answered a standardized questionnaire with specifically developed scales. Sexual functioning was covered in 15 specifically designed items and analyzed using Fisher's exact tests.

As a result, it was found that nonsignificant trends consistent across time and group resulted for most of the sexual variables. Preoperatively, cancer patients exhibited slightly better sexual functioning than the other two groups, but overtime this decreased slightly. Conversely, sexual functioning among the patients with benign disease showed steady improvement. These results indicate that radical hysterectomy for stage Ib cervical cancer does not entail major sexual sequelae. The authors stressed, however, that due to the limited sample size, conclusions must be drawn cautiously.

In Eastern Asian patients, there have been few studies looking at the consequences of treatment for cervical cancer on sexual function. In a study in Thailand [23] using visual analog scales on seven aspects of sexual function, 30 patients with FIGO stage Ib cervical cancer undergoing radical hysterectomy and pelvic lymphadenectomy were recruited. Patients were interviewed prior to hospital admission and then at 3 and 6 months after surgery. The mean age of the patients was 45 years. Seven patients (23%) were postmenopausal. Fourteen (46.7%) had a bilateral salpingo-oophorectomy. At 3 and 6 months after surgery, 63 and 93% had sexual intercourse, respectively. The authors concluded that radical hysterectomy using the current technique has a minimal short-term impact on sexual function.

In a study comparing radical hysterectomy by laparotomy with radical hysterectomy by laparoscopy with respect to subsequent sexual function measured by the FSFI, both interventions had a negative impact on sexual function compared with a control group, but there was no difference between the two operative procedures [24].

Endometrium Carcinoma

Impact of the Disease and Treatment

The predominant symptom of the disease is abnormal uterine bleeding, which may have an impact on sexual activity before the diagnosis is made. In general, there is no pain or any other clinical symptoms except for high stage disease. The surgical treatment includes hysterectomy and bilateral oophorectomy frequently with pelvic and para-aortal lymph node dissection. Advanced disease includes ablation of the upper third of the vagina, colpectomy, and removal of the parametria and pelvic lymph nodes. Very often at least local radiotherapy is performed (brachytherapy). Again few studies have been performed regarding the sexual function or dysfunction of the treatment of cancer of the endometrium at early stage.

In premenopausal women, removal of the ovaries will most probably have an impact on sexual function. For advanced stages, the previously described studies concerning cervical cancer can give insight into the impact of large operative procedures on the sexual life of the patients.

Prevalence, Incidence of Sexual Dysfunction, and Contributing Factors

In a retrospective study of side effects and complications of treatment, 522 patients with endometrial cancer managed in a gynecologic oncology unit were included [25]. A total of 517 patients had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH BSO). Lymphadenectomy or lymph node sampling was performed with the primary surgery in 264 and 41 cases, respectively. Postoperative radiotherapy was given as external beam or vault brachytherapy. Serious morbidity included lymphedema, hemorrhage, and vaginal stenosis. Lymphadenectomy was associated with lymphedema and lymphocyst formation in 11% of the cases. Vascular injury associated with lymphadenectomy occurred in 0.7% of the cases; however, this was satisfactorily managed through adequate surgical training and experience by staff within the unit. The incidence of vaginal stenosis (54.7%) following postoperative vault brachytherapy was a particular concern for clinical follow-up and sexual function. Although many women were not sexually active prior to treatment, those who were had high levels of

sexual dysfunction, even when vaginal stenosis was not present.

The possible impact of bilateral oophorectomy on sexual function was not especially examined in these women, but can be derived from the results seen in women who had bilateral ovarectomy for other reasons (see below).

Cancer of the Ovaries

The Impact of the Disease and Treatment

The disease manifests itself usually in more advanced ages either by increasing abdominal volume due to ascites or by abdominal discomfort. Some of the cancers may manifest themselves with vaginal bleeding. The treatment of ovarian cancer consists usually in hysterectomy, bilateral oophorectomy, and chemotherapy and all these interventions may affect sexual functioning. Furthermore in younger women there is the loss of reproductive potential, which produces severe distress. The main impact of surgical treatment is abrupt termination of the production of ovarian steroid hormones, estrogen, progesterone, and testosterone.

Prevalence, Incidence of Sexual Dysfunction, and Contributing Factors

A recent study of 200 women with ovarian cancer shows that 45% of women suffer from a sense of loss of reproductive potential, with those under the age of 55 reporting a greater sense of loss [26]. In a recent study about the long-term adjustment of early stage ovarian cancers, survivors reported good physical QOL scores and few unmet needs [27]. The main negative impact was menopausal symptoms and a negative impact on sexuality. Less than 10% of survivors reported either an interest in sex or that they were sexually active. About 56% of survivors reported fear of cancer recurrence and 59% anxiety when their tumor markers like CA 125 were tested. It seems that the major negative impact is the fear of recurrence with an important psychological distress which by itself may have negative impact on sexual function.

In a study among 232 women with ovarian cancer [28], it was shown that the disease is associated with low sexual desire (47% reported non/little desire), vaginal dryness (experience in 80% of women having sexual intercourse in the last months), dyspareunia (in 62%), and problems with orgasm (in 75%). Predictors of sexual activity were being married, being under 56 years, not receiving treatment, good self-esteem/body image, and lengths of time since end of treatment. Comparing these results to findings in breast cancer patients and healthy postmenopausal women, the authors conclude that a woman with ovarian cancer suffers from more severe problems.

In a cross-sectional study [29], 42 advanced and 58 early stage ovarian cancer patients were interviewed to compare the long-term adjustment and QOL of early and advanced stage ovarian cancer survivors (OCS). The following instruments were administered: EORTC QLQ-C30 (overall QOL) and QLQ-OV28 (ovarian specific issues), MHI-17 (anxiety, depression, and global well-being), CALGB sexual functioning, FACT Fatigue, Beck's Hopelessness Scale, Fear of Recurrence (FOR), PCL-C posttraumatic stress disorder (PTSD), Unmet Needs, FACT-Spirituality (FACT-Sp), complementary therapy (CAM use), and MOS Social Support Survey (MOS). The responses were compared between the early and advanced stage groups.

The majority of survivors scored above the medical outpatient norm for emotional status (71% of early stage and 64% of advanced stage survivors). Overall QOL, fatigue, hopelessness, spirituality, social support, degree to which unmet needs were met, and use of complementary therapy did not differ between the two groups.

No advanced stage OCS had diagnosable PTSD scores, while 6.9% of early stage survivors had scores indicative of PTSD.

Decreased sexual interest attributed to cancer and anxiety when getting CA-125 testing was of

concern for both groups. OCS used on average 5 CAM to improve their QOL.

Regardless of staging, OCS experience similarly overall positive QOL and adjustment, though PTSD, sexual problems, and fear of recurrence are still important for some survivors.

The most important factor in ovarian cancer survivors to influence their sexual life seems to be the anxiety about recurrence of the disease.

Assessment of Sexual Functioning

Careful history taking precedes the indication of specific interventions to improve sexual adaptation after gynecological cancer. Several predictors for the development of sexual dysfunction in the context of genital cancer have been identified (see earlier discussion) including physical and treatment related as well as predisposing and current psychological and relational factors. Specialized units additionally perform basic hormonal and sexual health laboratory evaluations and radiological evaluations if necessary [30].

We use the model described elsewhere to assess [2].

- Person-related preexisting factors (age, previous sexual difficulties, body image, physical and mental well-being)
- Disease and therapy specific factors (The 8 Ds): danger, destruction, disfigurement, disability, dysfunction, dysregulation, disease load, drugs
- The individual's and partner's coping pattern (affective response, coping strategies, changes in the couple's dynamic interaction)

Therapy

A Cochrane review by Miles et al. [31] evaluated the effectiveness of randomized controlled trials of interventions of any kind for sexual dysfunction following treatments for cancer in men and women. The number of studies on interventions in men outnumbers the number of studies in women strongly: only one trial from 1971 fulfilled the inclusion criteria and was included in the review. Even though there are more trials of lower quality which will be summarized below, this still mirrors the difficulties of clinical reality where recommendations are based on clinical experience rather than on scientific evidence.

Five studies were included and analyzed any outcome data relating to resumption of sexual intercourse, DSM4 diagnoses, or validated scales of sexual function. The review included thus 413 patients examining five different interventions. One trial suggested a short-term benefit for the use of vaginal dienestrol in women after pelvic radiotherapy. Psychoeducational group therapy and a couple coping intervention did not show any significant benefit. All the studies were of poor methodological quality. The authors concluded that there is no convincing evidence of supporting the use of any interventions for psychosexual dysfunction in women treated for gynecological cancer.

Amsterdam and Krychman [32] found, however, in their retrospective cohort study of 259 female cancer patients (37% had gynecologic neoplasms and the most common gynecologic malignancy seen was ovarian (27%) who attended a survivorship program at an academic medical center, that patients who received symptomatic treatment recommendations including hormone therapy alternatives, psychosexual counseling, minimally absorbed vaginal estrogen suppositories, and vaginal dilators showed self-reported improvement in their symptoms. The most frequently presented complaint was dyspareunia (72%), atrophic vaginitis (65%), hypoactive desire (43%), and orgasmic dysfunction (17%). At a median of 6 months (range 0–20), 60 patients (63%) received follow-up, and of them 42 (70%) reported improvement in their symptoms.

They concluded that the establishment of a well-structured sexual health program in a cancer setting can result in a 63% compliance rate with a 70% subjective improvement in sexual health complaints.

The interventions for the treatment of sexual dysfunction after gynecological cancer can be grouped in

- Psychological (counseling)
- Local nonhormonal and physical
- Hormonal

Psychological Interventions

There seems to be a significant lack of communication between health care professionals and women about sexual issues. A study [33] with ovarian cancer patients showed that only 9 of 43 (21%) of health care professionals discussed sexual issues and the discussion often being limited to once or twice before or after treatment.

In a recent review, Hersch et al. [34] included 22 controlled trials comparing psychosocial intervention to control condition in a gynecological cancer population. Main outcome measure was at least one QOL variable, namely social and sexual functioning, distress, depression, anxiety, attitude to medical care, self-esteem, and body image. Only five trials included interventions to improve sexual adaptation after gynecological cancer and they differ strongly with regard to structure and content, partly explaining the inconclusive results. They found substantial variability in study quality and results.

The authors concluded that information-based intervention seemed largely unable to provide meaningful benefits. Limited evidence was there in support of healing touch and cognitive behavior interventions had some positive effects. Counseling appeared to be the most promising intervention strategy for addressing QOL concerns for women with gynecological cancers.

Psychoeducational interventions have been used to enhance compliance with recommended mechanical interventions. They include information giving, motivation enhancing, and behavioral skills components. Compared to booklet on the use of vaginal dilators, this intervention was superior with regard to compliance, reduction of sexual fears, and knowledge on sexuality [35, 36]. Thus, while the regular use of vaginal dilators is generally recommended in the case of cancer treatment related vaginal tissue damage, the form of patient education seems to be crucial for compliance and, therefore, effectiveness.

Maughan and Clerk [37] piloted the use of a clinical nurse, trained in psychosexual medicine, who counseled patients before and 3 times after surgery. Counseling included information giving, emotional support, facilitation of communication, and support of coping strategies thus targeting at general and psychosexual adaptation. The intervention group was compared to a control group receiving standard nursing care. The intervention had a positive effect on women's anxiety about sex and more frequent and satisfying sex.

Caldwell et al. [38] piloted a noncontrolled 12-week group intervention for psychosexual problems in women who had been treated for gynecological cancer. Compared to baseline, women showed improvements in their sexual functioning scores after the intervention, and a trend for continued improvement at 3 months posttreatment.

Only limited data is available on the effectiveness of couple interventions [39]. Positive effects are reported for interventions which include treatment components that (a) educate both partners about the woman's diagnosis and treatments, (b) promote couples' mutual coping and support processes, and (c) include specific sexual therapy techniques to address sexual and body image concerns. Most couple interventions are not limited to sexual issues but aim at the promotion of mutual coping with the cancer illness as patient and her partner. They include cancer psychoeducation, supportive communication, partner support, and coping skills training [40]. Respectively, benefits are not limited to improved sexual adjustment but include improvements in couples' supportive communication, reduced psychological distress, and coping effort [40].

In summary, research on the effectiveness of psychological interventions is still sparse and the quality of the available studies does not

allow developing treatment plans and offering psychological treatment based on systematic scientific evidence. The limited data indicate that some women may benefit from specific interventions to improve sexual adaptation after gynecological cancer, to increase knowledge and communication on sexuality, and to improve adherence to sexuality related medical advice.

The maintenance of a positive self-image and feelings of sexuality is an issue of central importance in the provision of quality health care and contributes significantly to quality of daily living. Information about sexuality is important for the patient with gynecological cancer and many still claim that communication about sexual issues with the medical specialist is lacking [41]. Thus, besides history taking and careful sexual evaluation, Stead et al. suggest alluding to the PLISSIT model (Table 29.3) [42]. This model includes four stages of sexual counseling which increase in intensity. In the first stage, permission, the patient is offered the opportunity to talk about sexual issues. The second stage, limited information, provides the patient with general information about the sexual problem and options for interventions. The third stage includes specific suggestions with a detailed discussion about treatment options and techniques that could be used to improve sexuality. Some women may, however, beyond that need intensive therapy, which often is then being delivered by a specialist sexual counselor. This model may guide the health professional through the evaluation of sexual dysfunction and the provision of information. Table 29.3 summarizes the sexual counseling steps on the background of this model in patients with gynecological cancer.

Local Nonhormonal and Mechanical Interventions

Lubricants

If the woman complains about lack of lubrication, a lubricant can be suggested. There are water- or silicon-based lubricants available. The most widespread water-based lubricant is "KY jelly," which is available in drugstores and supermarkets. This lubricant tends to dry out quickly and needs to be reapplied. There is a water-based lubricant called "Astro-glide" which has a longer duration. Some of these water-based lubricants contain glycerine and may predispose women to vagina infections.

Silicon-based lubricants are available online or in sex stores.

Table 29.3 Use of the PLISSIT model in counseling women with sexual concerns after gynecological cancer

Counseling stage	Tasks
Permission	Give the opportunity to talk about sexual issues; include questions on sexuality repeatedly during treatment and in the years posttreatment
	Take sexual history, assess current and past sexual problems
	Refer to physical examination
Limited information	Summarize the identified biological, psychological, and relation factors, which contribute to the sexual dysfunction
	Educate about psychosexual issues in general
	Discuss treatment options
Specific suggestions	Discuss treatment options in detail
	Decide with the patient, which interventions are to be realized
	Carefully explain and monitor adherence to interventions (e.g., use of lubricants and vaginal dilators, communication of needs, etc.)
	Include partner if reasonable
Intensive therapy	Evaluate with the patient the need for more intensive sex therapy
	Evaluate options and decide on further proceeding

Vaginal Dilatation

The aim of vaginal dilatation is to maintain the patency of the vagina by breaking adhesions and fibrous filaments as they develop. Even though regular intercourse may be a way to maintain vaginal patency, the use of dilators is generally recommended. Dilators are smooth plastic tubes approximately 15 cm in length and 3 cm in diameter. There is, however, little consensus on when to begin dilatation, how often it should be performed, and for how long [43–45]. The general recommendation is to start as soon as the patient is comfortable but within 4 weeks of completion of radiation therapy. The dilator is inserted into the vagina and moved side ways and in and out for about 10–15 min per session. The intervention supports to separate the vaginal walls, to break developing scar tissue, to stretch and heal the vaginal tissues. The additional application of a lubricant or estrogen crème is most often being suggested. When Kegel exercises are used along with the vaginal dilators, it is thought that women are able to relearn to relax during intercourse. Compliance with the use of dilators upon indication is, however, rather low [35, 36]. This may be due to the lack of an established best practice and insufficient patient education and psychosexual advice [45]. The concomitant participation in a psychoeducational group intervention can increase the compliance with the regular use and practice with dilators (see above) [35, 36].

Hormonal

Local Estrogen

Women are often bothered by vaginal atrophy after radiation therapy or rapid changes in sex hormones. This will cause pain on any kind of sexual touching. The most effective treatment for vaginal atrophy is local estrogen in the form of a cream, pessary, or ring. Pitkin and Van Voorhis [46] compared a vaginal cream containing 0.01% dienestrol with a placebo cream and found significantly more women in the intervention group reporting no dyspareunia after several weeks of applying the cream 3 times a week. No differences were found in the frequency of sexual intercourse, however. Premenopausal patients with genital cancer especially those with ovarian cancer treated by bilateral oophorectomy may suffer from other hormone withdrawal symptoms due to estrogen and testosterone deficiency.

From a large number of studies in nononcological patients who had undergone ovariectomy (surgical menopause), the possible impact on libido, local atrophy of the vagina, and lubrication has been described and interventional studies have shown beneficial effects [47–51]. There are, however, very few studies about the use of estrogen replacement and testosterone treatment in gynecologic cancer patients. As far as endometrial carcinoma is concerned, the focus of the different studies dealing with estrogen replacement therapy in patients treated for endometrial cancer lies on safety.

In a study by Creasman and Henderson [52], 221 patients with stage I adenocarcinoma of endometrium were examined. A total of 47 patients received estrogen after their cancer therapy whereas 174 patients did not. The results showed that after controlling for other risk factors, the estimated distribution of time to recurrence for the two groups was significantly different ($p<0.05$) with estrogen group experiencing longer disease-free intervals. So it was concluded that the history of endometrial cancer does not appear to be a contraindication to hormonal replacement therapy in patients with stage I disease.

In another study [53], 249 women with surgical stage I, II, and III endometrial cancers were examined. A total of 130 received estrogen replacement after their primary cancer treatments and 49% received androgen in addition to estrogen. Among the cohort, 75 match treatment control pairs were identified. The hormone users were followed for a mean interval of 83 months and the nonhormone users were followed for a comparable mean interval of 69 months. There were two recurrences (1%) among the 75 hormone users compared with 11 (14%) recurrences in the 75 nonhormone users. Hormone users had a statistically significant longer disease-free interval than

nonusers ($p=0.006$). The conclusion was that estrogen/testosterone replacement therapy with or without progestin does not appear to increase the rate of recurrence among endometrial cancer survivors [54] which is inline with others [55].

Chapman et al. [55] found that there was no statistical significant difference in overall survival and recurrence rate between estrogen replacement users and nonusers in surgical stage I and II endometrial cancer survivors. Estrogen and/or androgen replacement in ovarian cancer patients who have undergone removal of the ovaries is a controversial issue.

In an older study, Eeles et al. [56] analyzed 373 patients age 50 years or younger who had undergone bilateral salpingo oophorectomy for epithelial ovarian cancer. Totally, 78 had received hormone replacement therapy starting at a medium of four after diagnosis. An outcome measure was overall survival and disease-free survival. There was no significant difference in survival between women receiving hormone replacement therapy and those not receiving it after counting for the effects of other nonprognostic factors. The authors conclude that hormone replacement therapy is not likely to have a detrimental effect on the prognosis of patients with ovarian cancer. But they indicate that to come to a final conclusion there would be a need for randomized controlled trials.

The controversy was again brought up by the publication in *JAMA* 2002 about menopausal hormone replacement therapy and risk of ovarian cancer [57]. The authors found that estrogen-only replacement therapy particularly for 10 or more years showed a significantly increased risk of ovarian cancer. Women who used short-term estrogen/progestin only replacement therapy were not at increased risk. Perdy et al. [58] found that postmenopausal estrogen replacement therapy was associated with a significant increase in risk of endometrioid or clear cell epithelial ovarian tumors. Contrary to these findings regarding a possible association between hormone replacement therapy and the development of ovarian cancer, another study by Gudrozi and Daponte [59] confirmed the previous studies that in ovarian carcinoma survivors, estrogen replacement therapy was not accompanied by an increased risk and did not have a negative influence on the disease-free interval and overall survival of ovarian carcinoma patients.

The randomized controlled trials showing an improvement of sexual function especially sexual desire in patients after surgical menopause who received testosterone was performed in patients who did not have genital cancers (this was an inclusion criterion for the study). The evidence found in these studies may be used as an indicator for the possible usefulness and benefit of such a treatment in ovarian cancer survivors [50, 51]. Safety issues and questions concerning medium- or long-term use of testosterone in these patients are, however, lacking.

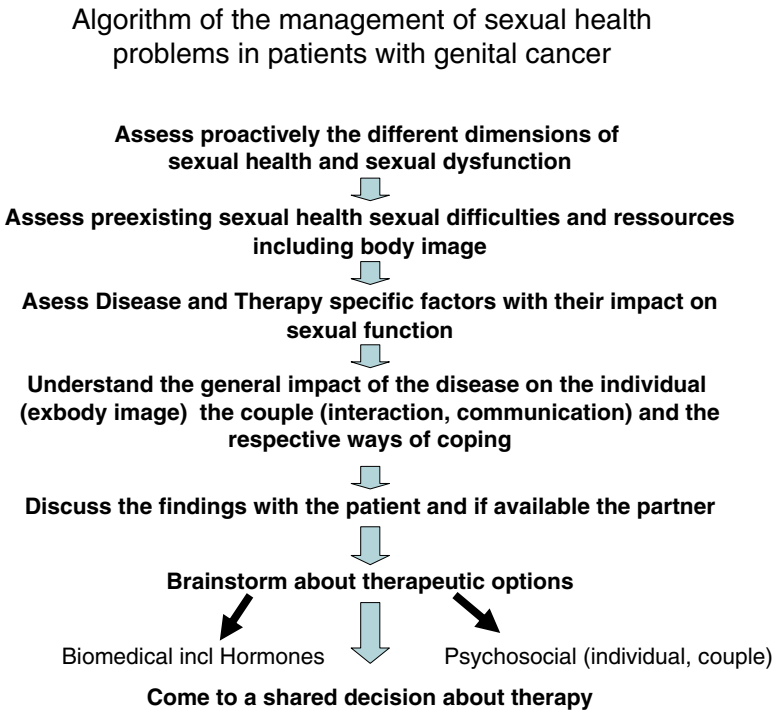
Summary and Conclusion

Women with genital cancers frequently suffer from very negative direct and indirect consequences of the disease on their sexual life. Some of these cancers have a good prognosis, so that women live after a treatment for many years and the QOL of these survivors has become more and more the focus also of oncologic treatment and care. In the first phase immediately after diagnosis and early treatment, the focus of course very often lies on survival. Later on physical and mental well-being including sexual life and sexual function become more and more important.

Good clinical practice in gynecologic oncology should therefore throughout the whole process of diagnostics and treatment be aware of the sexual health of patients and how this sexual health could be as much as possible preserved or re-established.

We propose a systematic approach which goes through several steps:

1. Assess proactively the different dimensions of sexual health and sexual dysfunction.
2. Assess pre-existing sexual health, sexual difficulties, and resources including body image.
3. Assess disease and therapy specific factors with their impact on sexual function.



4. Understand the general impact of a disease on the individual (for example, body image, pain, etc.), a couple (interaction, communication), and the respective ways of coping of the patient and the partner.
5. Discuss all the findings with the patient and if available with the partner.
6. Brainstorm about therapeutic options which reach from biomedical interventions including hormones and different drugs to psychosocial interventions including individual or couple therapy.
7. Come to a shared decision about therapy.

With this structured approach, patients should be provided with a qualified help regarding their sexual health in the context of genital cancers.

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Chapter 30
Pelvic Surgery for Urological Cancers

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Keywords Erectile dysfunction • orgasm • penile length • Peyronie's disease • climacturia

Anatomy of Erectile Function

The central functional unit of the penis is the corpora cavernosa. These dual cylindrical erectile bodies form the basis of erection. They are connected to each other for the distal two-thirds of their length. Within the corpora cavernosa are robust fenestrations resulting in significant cross-talk between the corpora. Proximally, they are connected to the undersurface of the inferior pubic rami. A thick-fibrous covering called the tunica albuginea surrounds each corpus cavernosa. As a result of cavernous nerve signals, the spongy sinusoidal spaces fill with blood and expand against the tunica albuginea compressing the subtunical venous plexuses, decreasing venous outflow. The sinusoidal spaces (lacunar spaces) are lined by vascular endothelium. The walls of these spaces are referred to as trabeculae and are composed of smooth muscle and collagen.

Arterial Supply

The internal iliac artery supplies vascular inflow to the corpus cavernosum. This artery splits into the inferior gluteal and the internal pudendal artery just proximal to the coccygeus muscle. The internal pudendal runs beneath the sacrospinous ligament and over the sacrotuberous ligament where it enters Alcock's canal. As the artery exits the canal, it gives off the perineal artery before piercing the urogenital diaphragm. The perineal artery continues its course anteriorly and superiorly to deliver blood to the ischiocavernosus muscle, aspects of the bulbospongiosus muscle and the posterior surface of the scrotum.

After the internal pudendal artery emerges from Alcock's canal, it can be referred to as the common penile artery. The common penile artery then branches into the artery of the penile bulb, urethral artery, dorsal penile artery, and the deep artery of the penis (cavernosal artery). The paired cavernosal arteries enter the tunica albuginea at the hilum of the penis. They travel down the center of each corpus giving off helicine arteries at regular intervals. These small serpentine vessels open directly into the sinusoidal spaces. It is the neuromediated relaxation of the trabeculae (wall of the sinusoidal spaces) that allows expansion of the sinusoids and the subsequent initiation and maintenance of erection.

Accessory Pudendal Arteries

Variations in pelvic vascular anatomy are not uncommon. The prevalence of accessory pudendal arteries (APAs) varies between 4 and 75% [1–4]. These arteries arise most commonly from the obturator, vesical, or femoral arteries and descend

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towards the penis. This type of APA is known as "extrapelvic." Intrapelvic APAs are visible in the periprostatic region and course parallel to the dorsal vascular complex. APAs can also be subclassified into apical and lateral APAs. The apical APA emerges through the levator ani muscle and runs for a short period before entering the penis. This may represent an aberrant internal pudendal artery [5]. The lateral APA may be seen lying anterolaterally to the prostate gland. This variant may represent the aberrant terminal branching of the internal iliac artery [5].

The APAs may provide significant component of penile vascular inflow [1, 2, 6–10]. Prior to radical pelvic surgery, Droupy performed transrectal and perineal color Doppler flow imaging before and during a pharmacologically induced erection [6]. Of the 12 study patients, APAs were found in 9 (75%). Interestingly, the accessory and internal pudendal arteries displayed similar significant hemodynamic changes after initiation of a pharmacologically induced erection. This demonstrated that APAs are important in the initiation and maintenance of erections.

More recently, Box et al. performed a prospective analysis of erectile function in 200 men undergoing prostatectomy [4]. Sexual function was assessed using the International Index of Erectile Function 5-item questionnaire (IIEF-5) preoperatively and postoperatively. All APAs were ligated and transected during the surgery. Of the 58 men without preoperative erectile dysfunction (ED), 19 had APAs. A total of 95% of these men were potent. A total of 90% of the men without APAs had recovered erectile function. The authors concluded that the presence or absence of an APA was not correlated with sexual function. Clearly, further work needs to be done to elucidate the role of the APA on sexual function.

Venous Drainage

Venous drainage of the penis loosely mirrors the arterial supply. Blood leaves the penis via three paths: deep, middle, and superficial. The deep system drains the proximal third of the penis. Emissary veins emerge from this region of the penis and link with the cavernosal, bulbar, and crural veins. Blood from this region drains into the internal pudendal vein.

The middle drainage system receives blood from the glans, corpus spongiosum, as well as the distal two-thirds of the penis. Blood draining the sinusoidal (lacunar) spaces is directed into a rich network of subtunical veins called the subtunical plexus. The plexus sends emissary veins through the tunica albuginea where they anastamose with circumflex veins. The centrally located deep dorsal vein receives blood from the circumflex veins and the retrocoronal venous plexus before continuing into the pelvis to drain into the dorsal venous complex. The superficial drainage system is largely composed of the paired superficial penile veins. They accept blood from numerous surface veins. Blood from this system ultimately ends up in the saphenous system.

Neuroanatomy

Innervation from the sacral parasympathetic (pelvic), thoracolumbar sympathetic, and somatic (pudendal) nerves is required for the generation of erection and ensuing detumescence [11–15]. Parasympathetic neurons originate in the sacral spinal cord (S2–4). They provide the major excitatory input to the penis. Excitatory signals leave the intermediolateral nuclei and travel via the pelvic nerve (or nervi erigentes) to the pelvic plexus. Here, the preganglionic fibers relay their information to the short, postganglionic cavernosal nerve. The cavernosal nerve courses along the posterolateral aspect of the prostate before exiting the pelvis [16]. As the nerves leave the pelvis, they are intimately related to the urethra. Before entering the corpus cavernosum at the crus, the cavernous nerve sends branches to the corpus spongiosum [11, 16]. Urethral reconstructive, prostate, or rectal procedures/treatments may damage the parasympathetic input of the penis thereby increasing the chance of ED.

Sympathetic innervation of the penis originates in the intermediolateral columns of the thoracolumbar spinal cord. Fibers pass through in the sympathetic chain before descending to

the inferior mesenteric and superior hypogastric plexuses. The nerve fibers then coalesce to form the hypogastric nerve en route to the pelvic plexus. From there, the sympathetic fibers reach the penis via the cavernous nerves. Additionally, sympathetic input may be accomplished through the pelvic nerve and the pudendal nerve [17].

The third component of penile neuroanatomy is the somatic system [11, 12, 18]. The afferent fibers transmit tactile information from the genitalia to the central nervous system [11]. Efferent fibers carry impulses to skeletal muscles [18]. The pudendal nerve conveys motor and sensory impulses. The cell bodies originate in the spinal segments S2–S4. The nerve courses through Alcock's canal before giving off inferior rectal, perineal, and posterior scrotal nerves. The last branch of the pudendal nerve is the dorsal nerve of the penis. It provides motor innervation for the ischiocavernosus and bulbospongiosus muscle. In the penis, this paired nerve runs laterally to the dorsal artery and communicates sensory information from the glans penis and the penile shaft to the sacral cord.

Corporal Smooth Muscle

Relaxation of the cavernosal smooth muscle cell is the biological event responsible for the erection [19–21]. As previously mentioned, the trabeculae between the lacunar spaces are occupied with a 1:1 ratio of smooth muscle and collagen [19, 21, 22]. The smooth muscle cells are composed of thin, intermediate, and thick filaments [22–24]. The most important of these are the thin (actin) and thick (myosin) filaments [23, 24].

The cavernous nerve releases nitric oxide (NO) that stimulates the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP and cAMP cause the potassium channels to open resulting in cellular hyperpolarization. The calcium channels close causing the endoplasmic reticulum to sequester intracellular calcium leaving a Ca^{2+}-poor microenvironment [25]. The calcium–calmodulin complex (which is bound to myosin light chain kinase in the contractile state) disassociates causing decoupling of the myosin/actin crossbridges [23, 24]. Smooth muscle relaxation ensues, resulting in filling of sinusoidal spaces and penile rigidity [22, 25].

Sympathetic-mediated release of norepinephrine and epinephrine sets a second messenger system on motion that increases intracellular concentration of calcium ions. The higher Ca^{2+} stimulates the formation of a calcium–calmodulin complex that binds to and activates MLCK, allowing the chain of reactions for contraction to occur.

Erectile Dysfunction Prevalence

All men experience a decrement of erectile function after prostate cancer surgery. The percentage of men who recover from erectile function during a specific time period is what is generally reported in the literature. The rates of recovery range between 20 and 86% [26–29]. The National Cancer Institute (NCI) conducted a Prostate Cancer Outcomes Study (PCOS) that revealed that 20% of the men were able to achieve erections sufficient for intercourse [29]. Bianco et al. published data from Memorial Sloan-Kettering Cancer Center indicating that erectile function is recovered in 70% of the cases after 2 years [28]. Dr. Walsh and colleagues reported that 86% of patients were potent following nerve-sparing radical prostatectomy (RP) [26]. Kundu et al. differentiated erectile function rates in men who had bilateral (BNS) versus unilateral nerve sparing (UNS) prostatectomies [27]. Men who underwent BNS reported an erectile function rate of 76% whereas those undergoing a UNS had an erectile function rate of 53% [27].

Reasons for variation in erectile function recovery rates are multifaceted and can be attributed to differences in methods of data acquisition, patient cohorts, and definitions of adequate erectile function. The gold standard questionnaire is the international index of erectile function (IIEF). Many investigators request that patients answer questions 1–5 and 15 (the erectile function domain) of this 15-question unit. Some physicians use the

Table 30.1 Erectile function after radical prostatectomy: contemporary series of open, laparoscopic, and robot-assisted radical prostatectomy

Author References	Operation type	Main outcomes
[78]	LRP – BNS	67.7% erections sufficient for intercourse
	LRP – UNS	34.1% erections sufficient for intercourse
[79]	RARP – BNS	93% intercourse rate
		51% return to baseline SHIM score without PDE5i
		22% return to baseline SHIM score with PDE5i
[80]	RARP – BNS	83% able to achieve erection for intercourse ± PDE5i
	RARP – UNS	62% able to achieve erection for intercourse ± PDE5i
[81]	ORP – BNS	54.5% able to perform sexual intercourse
	ORP – UNS	29.8% able to perform sexual intercourse
[82]	LRP – BNS	64% able to achieve and maintain erection ± PDE5i
[83]	LRP – BNS	52.5% full erections
[84]	LRP – BNS	67–76% able to engage in sexual intercourse ± PDE5i
[85]	RARP	78% potency ± PDE5i
	BNS/UNS	
[86]	LRP – BNS	64% potency rate with PDE5i
		43% intercourse rate with PDE5i
[27]	ORP – BNS	76% have erections sufficient for penetration ± PDE5i
	ORP – UNS	53% have erections sufficient for penetration ± PDE5i
[26]	ORP – BNS	86% able to have unassisted intercourse ± PDE5i
[87]	ORP – BNS	55% have full or partial erections sufficient for intercourse without PDE5i
	ORP – UNS	21% have full or partial erections sufficient for intercourse without PDE5i

RARP, robot-assisted radical prostatectomy; *LRP*, laparoscopic radical prostatectomy; *ORP*, open radical prostatectomy; *BNS*, bilateral nerve sparing surgery; *UNS*, unilateral nerve sparing surgery; *SHIM*, sexual health inventory for men; *PDE5i*, phosphodiesterase 5 inhibitors

sexual health inventory for men (SHIM), UCLA-prostate cancer index (PCI), or the expanded prostate index composite (EPIC) [30, 31]. Each of these questionnaires focuses on slightly different aspects of sexual function. The PCA and the EPIC address sexual function and bother. The SHIM does not assess the ability to perform sexual intercourse, but it just asks if the erection is firm enough for it.

Currently, no consensus exists on when to measure erectile function. Studies have reported that post-RP erectile function, while initially excellent, may nadir at 3 months before rebounding [32]. Clearly, the time point at which EF is measured can introduce significant bias into academic studies. Additionally, some reports define erectile function with or without the use of PDE5i and only rarely are the response rates segregated based on the use of these erectogenic agents (Table 30.1).

Erectile Dysfunction Pathophysiology

Three factors are involved in the evolution of ED after RP: neural injury, vascular injury, and corporal smooth muscle damage. The ability to recover erectile function depends on the severity of these factors.

Neural Trauma

Nerve handling technique is integral to postoperative nerve function. Thermal injury, traction, or even transection may result in permanent, unrecoverable nerve injury. Postoperative factors, such as edema and inflammation adjacent to the prostatic bed near the bladder neck and cavernous nerves, could negatively influence

erectile function. Data published by Katz and Bennett outline that some men respond to PDE5 inhibitors within 4 weeks after surgery but by 12 weeks no longer respond [32]. This is due to ongoing postoperative Wallerian degeneration, in part perhaps, due to perineural inflammation. Data have shown that 25% of men who were functional with or without PDE5 inhibitors within the first 3 months were nonfunctional by the sixth month [32].

Nerve-sparing status of a RP is predictive of recovery of erectile function. It follows that nonnerve sparing surgery has a very low chance of spontaneous recovery of ED. BNS and UNS surgery can be associated with robust and middling spontaneous and oral therapy-assisted recovery of erectile function, respectively [33–35]. It is imperative to recognize that the term "nerve sparing" is a macroscopic description of surgical technique. It does not refer to current nerve function, but only future potential.

The pathophysiology of ED after RP has been elucidated with the help of animal models [36–40]. Cavernosal biochemical, morphological, and functional changes occur as a result of the neuroapraxia/neurotomy. Initially, neural injury causes a lack of erection leading to decrease in cavernosal oxygenation [37]. In a hypoxic environment, corpora cavernosal penile smooth muscle cells overexpress transforming growth factor-β1 (TGF-β1) and TGF-β1 dependent endothelin-1 (ET-1). These pro-fibrotic substances encourage deposition of collagen type I and type III within the corpus cavernosum [37, 41, 42].

Corporal Smooth Muscle Alterations

In denervated animals as compared to controls, there is an increase in penile collagen content and a decrease in the smooth muscle [37, 39, 43–47]. It has been elucidated that the root origin for this transformation is apoptosis [39, 44, 47]. Apoptosis, or programmed cell death, is essential for the normal development and homeostasis of multicellular organisms. Apoptosis is stimulated by tissue denervation and hypo-oxygenation. Apoptosis is also associated with increased deposition of connective tissue, which may lead to a decrease in penile expansile capability. This pathway ends with veno-occlusive dysfunction [39, 43, 44].

Both Klein and User have explored the effect of apoptosis on ED in the post-RP setting [36, 39, 40]. Klein noticed DNA fragmentation and condensed cell nuclei characteristic of apoptotic cells in the penes of denervated rats. Sham-operated controls did not exhibit this phenomena. The authors point to an increase in TRPM-2, 2 days after cavernous nerve transection. TRPM-2 is a gene factor thought to assist in the propagation of the apoptotic cascade.

In an elegant study by User et al., penes were harvested from rats that either had bilateral, unilateral, or no cavernous nerve transection [39]. DNA content and protein content were measured. The penises from the rats that had bilateral cavernous nerve transection weighed the least compared to the rats with the unilateral cavernous neurotomy [39]. DNA content was also significantly reduced in the bilaterally denervated penes. The authors suggested that the apoptotic process involved smooth muscle cells, not endothelial cells [39].

The apoptotic process most likely involves smooth muscle and endothelial cells [48, 49]. The Memorial Sloan-Kettering Cancer Center researchers have shown that neural injury causes apoptosis in both smooth muscle and endothelium in a delayed fashion [38]. Further review of the literature allows construction of a global hypothesis for corporal cavernosal smooth muscle apoptosis. Alterations in the concentration of growth factors produced by the cavernosal nerves may induce smooth muscle fibrosis and atrophy in corporal tissue [50]. Production of cytokines and noxious agents by the damaged nerve axons may also be the causal factor of the increased early smooth muscle apoptosis, which could trigger corporal collagen deposition [43, 46].

Venous Leak

As previously mentioned, during the initiation of erection, the penile sinusoidal spaces fill with blood and expand against the tunica albuginea compressing the subtunical venous plexuses, decreasing venous outflow. This is the veno-occlusive mechanism. When the corporal smooth muscle fails to expand adequately some or all of the subtunical venules are left in a noncompressed state and this results in corporo-venocclusive dysfunction (CVOD) or venous leak, venogenic ED.

There is an increase in collagen deposition and decrease in elastin production and content in the penis as early as 2 months after prostatectomy [51]. Mulhall and colleagues studied men who had penile Doppler ultrasounds after surgery. These men had a significantly increased end-diastolic velocity on the study, which corresponds to an increase in the incidence of venous leak as time progressed after surgery [52]. The most important data from this paper is that the incidence of venous leak is 10% at 4 months, 35% at 8–12 months, and 50% after 12 months after prostate removal surgery.

Radical Prostatectomy-Associated Sexual Dysfunctions

Anejaculation

Anejaculation is the absence of seminal fluid expelled in association with a sexual climax or orgasm. Since a RP removes the prostate, seminal vesicles, and a portion of the vas deferens, these patients will experience anejaculation.

Without the expulsion of seminal fluid, it is impossible for a man to impregnate a woman in the traditional method. Sperm retrieval and subsequent sperm injection techniques are available. Testicular sperm extraction (TESE) is the method in which quantities of sperm (along with seminiferous tubules) are surgically removed from the testis. The specimen is then prepared for immediate use or frozen for later. The sperm that is harvested by TESE is then mated with the female egg using intracytoplasmic sperm injection (ICSI) [53–58].

There is a subset of men in which orgasmic quality is closely tied to the sensation of ejaculation. For this cohort, anejaculation significantly decreases satisfaction with sexual intercourse. Anejaculation may interfere with subject's self-perception of his manhood and body image.

Because prostate cancer has excellent long-term recurrence-free survival rates and men are being diagnosed at a younger age, a frank discussion about future fertility should take place before RP [59, 60]. Additionally, this conversation should cover the sexual implications of anejaculation.

Orgasm Alterations

Although the basic aspects of the physiology of orgasm have been elucidated, its intimate effect on physiological and psychogenic elements of sexual function continues to be elucidated. Ejaculation events encompass smooth muscle contraction of the accessory sex organs, buildup and release of pressure in the posterior urethra, sensation of the ejaculatory inevitability, contraction of the urethral bulb and perineum, rhythmic contractions of the pelvic floor muscles, and semen emission and ejaculation contribute to the sensation of orgasm [61].

Orgasmic perturbations can be categorized into three types:

1. Orgasmic pain (dysorgasmia)
2. Changes in orgasm intensity
3. Orgasm associated incontinence (climacturia)

Barnas et al. assessed the prevalence and nature of orgasmic dysfunction using a validated questionnaire [62]. She addressed the presence or absence of orgasm, orgasm quality before and after surgery, presence and location of orgasmic pain, as well as the consistency and

Table 30.2 Orgasmic dysfunction after radical prostatectomy

References	No. of patients	Orgasmic dysfunction type and rate
[65]	475	20% orgasmic incontinence (climacturia)
[66]	42	45% orgasmic incontinence (climacturia)
[62]	239	22% no change in orgasm intensity
		37% complete absence of orgasm
		37% decreased orgasm intensity
		4% increased orgasm intensity
		14% orgasmic pain (dysorgasmia)
[88]	17	64% orgasmic incontinence (climacturia)
		82% decreased orgasmic intensity
		14% orgasmic pain (dysorgasmia)

duration of orgasmic pain. Twenty-two percent of patients reported no change in orgasm intensity. Thirty-seven percent reported a complete absence of orgasm (anorgasm) and 37% had decreased orgasm intensity. Only 4% reported a more intense orgasm after RP than before. Pain was located in the penis (63%), abdomen (9%), rectum (24%), and other areas (4%). The pain occurred always (with every orgasm) in 33% of patients, frequently in 13%, occasionally in 35%, and rarely in 19% (Table 30.2).

It has been postulated that bladder neck/pelvic floor spasm is the origin of the pelvic pain. Based on this assumption, a prospective, nonplacebo controlled study was conducted to assess the use of tamsulosin, an alpha-adrenergic blocking agent in patients with orgasmic pain. In this study, 77% patients reported significant improvement in pain and 12% noted complete resolution of their pain with significant increase in IIEF libido score, supporting the hypothesis that orgasmic pain is related to bladder neck and/or pelvic floor muscle spasm [63].

In a study of 1,236 men treated for prostate cancer with surgery or radiation, Schover et al. found that 65% had orgasm issues. One third of these men no longer tried to reach orgasm (gave up), 17% were unable to reach orgasm, and 28% had orgasms that were unsatisfyingly weak [64].

Climacturia or urinary incontinence during orgasm may adversely affect sexual satisfaction. Choi et al. reported that climacturia occurs in one-fifth of men after radical pelvic surgery. Climacturia occurs more often after RP than radical cystectomy. This sexual dysfunction is more likely to happen within the first year following surgery and in combination with orgasmic pain and/or penile shortening [65]. In a similar manuscript, Lee et al. found a 45% prevalence of climacturia after RP. In a majority of subjects, the leakage occurred "rarely" or "only occasionally." In 21% it occurred "most of the time" or "always." The quantity of expelled urine a few drops in 58% of the men but greater than 1 ounce in 16%. Bother was also assessed in this study. Approximately 52% of patients reported "no or minimal" bother and 48% reported "significant" bother [66].

Currently, there are no effective treatment options to manage orgasmic derangements. Alpha-blocker therapy can be employed for dysorgasmia. Climacturia may be managed with mechanical devices such as penile constriction rings, behavioral modification, or pharmacologically with anticholinergic medications. The most effective approach to these issues is patient and partner education before surgery and supportive care afterwards.

Peyronie's Disease

Peyronie's disease (PD) is a scarring condition that affects the tunica albuginea of the penis. This connective tissue disorder manifests as inelastic fibrous scar tissue, which commonly causes penile curvature during erection. Other penile deformities can occur, such as indentations,

shortening, or tapering of the penis. Occasionally, PD can be associated with ED, as well as palpable areas of induration (plaques) [67].

The prevalence of PD has been quoted as 3–8%. It is believed that these figures are low as the disease is likely underreported [68, 69]. Genital and/or perineal trauma, as well as lower urinary tract surgery, has been implicated as risk factors for PD [70]. The exact etiology of PD remains unknown despite centuries of recognition and decades of study. Trauma is often cited as the cause of PD, but other theories include failure of fibrin clearance, collagen alterations, genetic predisposition, autoimmune factors, free radical production, and cytogenetic aberrations [67].

To our knowledge, there is one scientific paper in the literature that addresses the prevalence of PD following RP [71]. Of the 110 men who presented with ED after RP, 45 (41%) had penile fibrotic changes. The delineation of penile deformities was penile curvature in 93%, palpable plaques in 69%, and "hourglass" deformity in 24%.

The true prevalence of PD after RP may be higher than what is reported in the literature. Spongiofibrosis and intracavernosal injection therapy are most likely not major contributors to the development of PD. Spongiofibrosis occurs some distance from the dorsal plaque that typically develops in PD. Furthermore, improper injection technique and/or aggressive dosing of the injection medication may predispose the patient to corporal fibrosis, not tunical fibrosis (PD).

The molecular, vascular, and neural changes that lead to the development of PD after RP remain unknown [51]. Nevertheless, utmost attention should be paid to the detection of Peyronie's plaques in the postoperative setting. Early detection allows for the chance to minimize the progression of penile curvature.

Penile Length Alterations

Penile shortening occurs commonly in men who have undergone RP. Penile length changes, however small may adversely affect self body image, self-esteem, sense of manhood, and self-confidence. In 1999, Fraiman and colleagues reported that the most substantial change in penile size occurs 4–8 months after surgery [72]. The authors reported decreased penile lengths of 8 and 9% and decreased volume of 19–22% in the flaccid and erect states, respectively (Table 30.3). In similar studies, Munding et al. and Savoie et al. reported decreased penile length in 71 and 68%, respectively [73, 74]. Munding further states that 48% of these men had a greater than 1 cm decrease in penile length. Gontero and

Table 30.3 Penile length changes after radical prostatectomy

References	No. of patients	Time interval	Main outcomes
[75]	126	1 year	1.34 cm shortening – flaccid length 2.30 cm shortening – stretched length
[89]	33	6 months	No statistically significant length changes, both flaccid and erect states
[74]	63	3 months	19% had ≥15% shortening – stretched length 1.2 cm shortening – flaccid length 1.1 cm shortening – stretched length
[73]	31	3 months	13% increased stretched length 16% no change in stretched length 71% had decreased stretched length: 23% – up to 0.5 cm 35% – 1.0–2.0 cm 13% – more than 2.0 cm
[72]	100	1.7–27.6 months	8% decrease in flaccid length 9% decrease in erect length Greatest change at 4–8 months

associates have shown that postoperative RP penile shortening is independently associated with nerve preservation status and with postoperative erectile function outcome [75].

Penile volume changes can be attributed to a combination of molecular and physiological changes. At the cellular level, cavernosal hypoxia as a result of decreased erectile activity results in the upregulation of the fibrosis inducing cytokine TGF-β_1 [76]. Overtime, as corporal smooth muscle is replaced by collagen, penile volume shrinks. Fibrotic changes were seen in postoperative RP penile biopsy specimens when compared to preoperative specimens. The post-RP sampling showed increased collagen content, while elastin and smooth muscle levels were significantly decreased [51].

A second molecular cause of penile volume changes lies with changes in NO metabolism. NO is released from cavernosal nerve endings. Through a cascade of events involving the second-messenger cyclic nucleotides cGMP and cAMP, changes in intracellular calcium concentration result in penile relaxation. After cavernosal nerve injury, NO secretion is likely to be compromised resulting in a penile hypertonic state.

Physiologically, penile volume changes can be partially attributed to the unopposed sympathetic activity of the phallus. Despite the best efforts of experienced prostate surgeons, all men leave the operating room with some degree of cavernosal nerve injury. Usually this neuropraxia is temporary. As mentioned earlier, the cavernous nerve transmits parasympathetic (pro-erectile) signals to the penis. If these nerves are damaged or injured, the sympathetic nerves (antierectile) can act unopposed to cause a penile hypertonic state. Patient will refer to this as penile "shrinkage" and/or "shortening." Sympathetic hyperinnervation (competitive sprouting) refers to the rapid regeneration of sympathetic fibers in the setting of autonomic nerve injury. This results in unantagonized sympathetic tone in the end organ [77]. Any factors that result in reduced NO secretion or increased sympathetic tone, such as nerve injury after RP, may lead to decreased relaxation or distensibility of corporal smooth muscle and may lead to loss of length.

We do not yet know the exact etiology of penile volume and length changes. There may be additional causative factors for this psychologically damaging post-RP sexual dysfunction. A plausible theory is that the combination of neural injury-associated denervation resulting in smooth muscle apoptosis and cavernosal hypoxia-induced collagenization may be the underlying mechanism responsible for penile shortening and long-term erectile dysfunction.

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Chapter 31
Pelvic Radiation in Men

Luca Incrocci

Keywords Testicular cancer • penile cancer • prostate cancer • radiation • toxicity

Introduction

Despite the decrease in overall cancer incidence and mortality rates in developed countries since the early 1990s, cancer remains a major public health problem. Among men, the most common cancer affects the prostate and occurs more often in the older population [1]. Patient's quality of life, including sexual functioning, has, in recent years, come to play a more significant role in decision making about treatment type. In the 1980s and 1990s, penile prostheses and penile injections created a market for male sexual dysfunction. With the introduction of sildenafil (Viagra®) in 1998, media attention toward erectile dysfunction (ED) has made sexual problems more normative and has increased acceptance of help-seeking [2].

Methods for the Evaluation of Erectile Dysfunction

The most practical and quickest way to evaluate ED is by using a questionnaire such as the International Index of Erectile Function (IIEF) [3]. The IIEF has been translated and validated in many countries, though it has not been specifically developed for cancer patients. In the published literature on postradiation ED different questions have been used, but these have been mainly incorporated into a more general questionnaire on toxicity of radiation treatment, or quality of life in general. For an extensive review of the clinical evaluation and symptom scales for sexual dysfunction assessment, see "Definition of Potency."

Definition of Potency

A clear definition of potency is mandatory in order to make meaningful comparisons of the different studies. The Second International Consultation on Sexual Dysfunctions, held in Paris in 2003, defined ED as the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual performance [4]. Rigidity of erections, presence of spontaneous daytime erections or morning and night erections are also important issues. It is also necessary to differentiate between ED and not being sexually active, often due to reasons not related to erectile insufficiency such as absence of a willing partner, or the lack of interest in sex. Psychological factors may also play a role in postradiation ED. Many patients and their partners may think that they are contagious during radiation therapy or even radioactive, or are afraid to cause harm to the irradiated area during sexual activity. In most of the published studies, authors referred to the general terms potency or impotence

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without giving a proper operational definition. In some articles, a detailed definition of potency was provided, but it was often difficult to compare different studies. Only very recently, have studies used the IIEF questionnaire [3] or the shortened IIEF-5 questionnaire (also known as the Sexual Health Inventory for Men or SHIM) [5], although these have not been developed specifically for cancer patients.

Etiology of Postradiation Erectile Dysfunction

Most of the data available on postradiation ED come from studies in patients treated for prostate cancer. Little is known on the mechanisms of postradiation ED in other cancer types, although the etiology in patients treated for bladder and colorectal cancer is similar to that of patients treated for prostate cancer.

An extensive and critical review on postradiation ED in prostate cancer patients has been published previously [6–8]. A study by Zelefsky and Eid concluded that the predominant etiology of radiation-induced impotence was arteriogenic [9]. Several, more recent, clinical studies investigated the relationship between the radiation dose to the neurovascular bundles, the penile bulb and the penile bodies and postradiation ED [10–25], presenting contradictory results (Tables 31.1 and 31.2; Figs. 31.1 and 31.2). Most studies have only analyzed small numbers of patients and statistical power should be questioned. Postradiation ED has more likely a multi-factorial etiology, and is not only based on the radiation dose to one single anatomical structure. If this is the case, it is much harder to find a correlation between ED and the dose to a specific structure. Furthermore, it is very likely that the structure responsible for ED has not been investigated yet (i.e. internal pudendal arteries). To date, no final conclusions can be drawn whether or not the radiation dose to the penile structures correlates with postradiation ED in patients treated for prostate cancer [26]. Even in a prospective, randomized trial such correlation was not found [24].

Incidence of Erectile Dysfunction After Radiotherapy for Prostate Cancer

In recent years, the number of patients diagnosed with prostate cancer has increased dramatically because of the widespread use of prostate-specific antigen testing and the possibility for cure of early disease. Standard treatments are surgery, external-beam radiotherapy (EBRT), brachytherapy, hormonal therapy, or observation.

Incidence of Erectile Dysfunction After External-Beam Radiotherapy

An extensive review on the topic has been published previously [27]. Only studies that prospectively evaluated erectile functioning, using validated questionnaires and using a proper definition of potency are useful to draw conclusions on the incidence of postradiation ED [28–34] (Table 31.3). In general, this reaches about 60–70% in prospective studies. Two recent prospective trials have shown an incidence of ED in 30–40% of the patients treated by EBRT [33, 34]. Time elapsed since radiation is important: prospective studies show an increase of ED between 1 and 2 years after radiotherapy, but it does not seem to change after 3 years [33, 34].

Incidence of Erectile Dysfunction After Brachytherapy

Brachytherapy was originally introduced not only to limit the detrimental effects of EBRT on bowel and urinary function, but also to help preserve sexual function. The introduction of sophisticated 3D computer-assisted dosimetry, and the availability of intra-operative transrectal ultrasound after the 1990s, led to more accurate

Table 31.1 Correlation between radiation dose to the penile bulb and erectile dysfunction

References	Other structures than PB	Prospective ED evaluation	*n*	Radiation technique	Follow-up (months)	Significant correlation	Findings
Fisch et al. [15]	No	No	21	3D-CRT	24	Yes	Median D70 of the PB with a 70-Gy cutpoint
Merrick et al. [12]	No	No	46	BT	35	Yes	Minimum D25, D50, D70, D75, D90 and D95 of the PB
Merrick et al. [13]	Crura	No	60	BT	26–79	Yes	Minimum D50 of the PB
Merrick et al. [14]	Crura	Yes	128	BT	13–42	No	Minimum D50 of the proximal crura
Kiteley et al. [16]	NVB	Yes	50	BT	24–45	No	No significant correlations
Wright et al. [20]	NVB, crura	No	41	BT	12–41	Yes	Minimum D90 with a 10% cutpoint of the prescribed dose. Paradoxal result in NVB analysis
Selek et al. [17]	Penile bodies	No	28	3D-CRT	≥24	No	Paradoxical result: potent patients had a higher dose to penile base structures
Roach et al. [18]	No	Yes	158	3D-CRT	n.a.	Yes	Median dose to the penile bulb ≥52.5 Gy
Wernicke et al. [19]	No	Yes	29	3D-CRT	18–42	Yes	Median dose to D30, D45, D60 and D75
MacDonald et al. [21]	No	Yes	226	BT	≥24	No	No significant correlations
Mangar et al. [22]	No	Yes	51	3D-CRT	24	Yes	Mean D90 with a cutpoint of 50 and 60 Gy
Brown et al. [23]	No	Yes	32	IMRT	24	No	No significant correlations
Van der Wielen et al. [24]	No	Yes	96	3D-CRT	24	No	No significant correlations

PB penile bulb, *NVB* neurovascular bundles, *3D-CRT* three-dimensional conformal radio therapy, *BT* brachytherapy, *Dxx* dose delivered to xx% of an anatomic structure, *n.a.* not available, *IMRT* intensity modulated radiotherapy

Table 31.2 Correlation between radiation dose to the neurovascular bundles and erectile dysfunction

References	Other structures than NVB	Prospective ED evaluation	*n*	Radiation technique	Follow-up (months)	Significant correlation	Findings
DiBiase et al. [10]	No	No	14	BT	n.a.	n.a.	Maximal NVB doses exceeded average values in three patients with postimplant impotence
Merrick et al. [11]	No	Yes	54	BT	37	No	No significant correlations
Merrick et al. [12]	No	Yes	34	BT	13	No	No significant correlations
Kiteley et al. [16]	Pb	Yes	50	BT	24–45	No	No significant correlations
Wright et al. [20]	PB, crura	No	41	BT	12–41	No	Paradoxal result: decreased ED risk with a higher dose to the right NVB

NVB neurovascular bundles, *PB* penile bulb, *ED* erectile dysfunction, *BT* brachytherapy

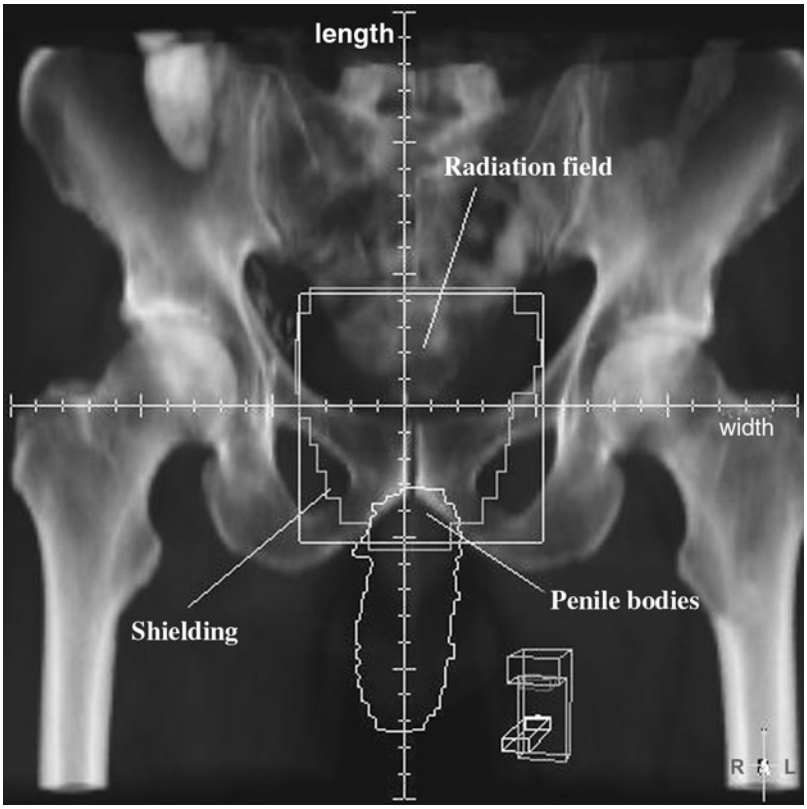

Fig. 31.1 External beam radiotherapy for prostate cancer. Example of a radiation field and its relation to the penile bodies

and reproducible implants. In general, after permanent seed implantations, ED rates have ranged from 5 to 51%, with the highest percentages found after the combination brachytherapy and EBRT [35–45]. The highest ED rates, ranging from 29 to 89%, have been reported combining the temporary Iridium-192 implants with EBRT [35, 38, 40, 44].

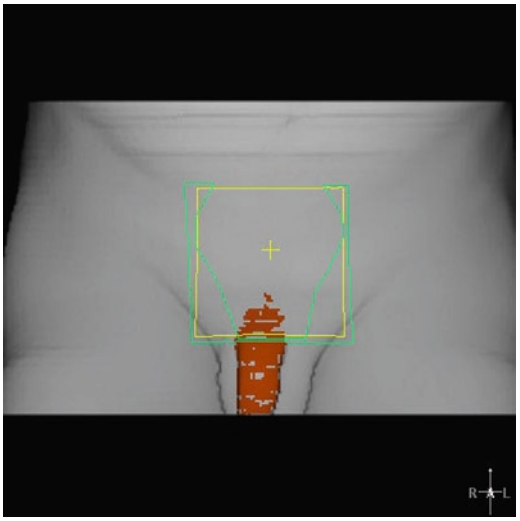

Fig. 31.2 External beam radiotherapy for prostate cancer. Example of a radiation field and its relation to the penile bodies. Three-dimensional anterior view

Incidence of Erectile Dysfunction After Radiotherapy for Bladder Cancer

Bladder cancer is the fourth most common cancer in men. If the tumor does not spread beyond the bladder mucosa (superficial bladder cancer) it is treated locally, with resection and adjuvant intravesical chemotherapy or immunotherapy. The optimal treatment for patients with invasive bladder cancer is surgery (radical cystectomy in women and cystoprostatectomy in men). In some patients, radiotherapy might be the first treatment choice depending on the patient's age, condition, and comorbidities. The general opinion is that survival following cystectomy is greater than that following radiotherapy, but no randomized trials have been performed to confirm this opinion. Radical cystectomy is associated with changes in the physiological and the psychological patient's well-being. Although radiotherapy preserves the bladder, its function is likely to be altered following the treatment with changes resulting in urinary frequency and urgency. Either treatment modality is associated with a high percentage of sexual dysfunction [46]. To our knowledge, there are no prospective studies that report on the sexual

Table 31.3 Erectile dysfunction after external-beam radiotherapy (EBRT) for prostate cancer: prospective studies

References	Patients (*n*)	Mean age[a] (years (range))	Patients potent prior to EBRT (*n* (%))	Mean follow-up (months (range))	ED (%)
Pilepich et al. [28]	230	71[b] (49–84)	102 (44)	54[b] (n.a.)	72
Beckendorf et al. [29]	67	68 (54–84)	40 (60)	n.a. (8–12)	33
Beard et al. [30]	121	n.a.	69 (57)	n.a.	57 at 3 months 64 at 12 months
Borghede et al. [31]	184	67 (46–83)	134 (73)	46 (24–96)	7
Turner et al. [32]	290	69 (44–82)	182 (63)	23[b] (n.a.)	38 at 12 months 59 at 36 months
van der Wielen et al. [33]	174	68[b] (48–60)	139 (72)	27 (6–36)	27 at 12 months 38 at 36 months
Pinkawa et al. [34]	123	71[b] (53–84)	54 (44)	16 (12–22)	73 at 16 months

n.a. data not available

[a]Mean age for entire group

[b]Median

Table 31.4 Erectile dysfunction after brachytherapy (BT) for prostate cancer

References	EBRT	Patients (*n*)	Mean age[a] (years (range))	Patients potent before BT (*n* (%))	Mean follow-up (months (range))	Incidence (%)
Martinez et al. [35]	Yes	59	n.a.	n.a.	19 (4–36)	38
Arterbery et al. [36]	No	51	n.a.	35 (69)	n.a.	13 at 6 months
Koutrouvelis [37]	No	130	71[b] (49–90)	n.a.	n.a. (6–24)	5
Joly et al. [38]	Yes	71	68 (51–82)	n.a.	n.a.	89
Sharkey et al. [39]	No	434	73 (52–83)	n.a.	28 (12–60)	15
Kestin et al. [40]	Yes	161	69[b] (n.a.)	n.a.	34[b] (5–86)	29
Sánchez-Ortiz et al. [41]	No	114	69 (n.a.)	81 (71)	23 (4–72)	51
Sharkey et al. [42]	No	299	73 (48–88)	n.a.	n.a.	15
Zelefsky et al. [43]	No	248	65[b] (45–80)	221 (89)	48[b] (12–126)	29
Potters et al. [44]	Yes	1166	69 (n.a.)	482 (41)	34[b] (6–92)	31
Stock et al. [45]	No	416	66[b] (41–83)	313 (75)	31[b] (12–92)	21 at 36 months 41 at 72 months

EBRT BT in combination with external-beam radiotherapy, *n.a.* data not available

[a]Mean age for entire group

[b]Median

functioning of patients receiving radiation therapy for bladder carcinoma.

In a retrospective study of 18 patients (56–75, median 70 years old) treated with EBRT, 13 (72%) recalled being sexually active and having good erections before treatment [46]. Of these, only six patients (56%) were active after treatment; three had ED and four reported a decrease in the quality of their erections. Eight out of 17 patients reported that their sexual life had worsened after EBRT. In a more recent and controlled study, higher percentages of ED were reported in 62 irradiated patients (median age 77 years) than in a control group of healthy men [47]. Sixty-five percent of both the patients and the controls were not sexually active at the time of the study; 87% of the irradiated patients had ED, but only 52% of the men in the control group [47].

Cystectomy and bladder substitution also have significant effects on sexual function. These procedures resulted in ED in 84% of the patients; 63% reported abnormal orgasm and 48% diminished sexual drive [48]. In another study, Bjerre et al. reported on 76 patients, 27 of whom underwent an ileal conduit diversion and 49 a bladder substitution [49]. Preoperatively 82% had normal erections whereas postoperatively, only 9% did. Postoperatively, 38% achieved normal orgasm and 26% were sexually active with intercourse. Of the nonsexually active men, 77% had ED, 29% decreased libido, 13% had partner refusal, and 20% felt less sexually attractive. There was no statistically significant difference between those treated through ileal conduit diversion vs. those treated with bladder substitution. In either case, the effects of the treatment for bladder cancer on sexual functioning were found to be quite severe.

Incidence of Erectile Dysfunction After Radiotherapy for Penile Cancer

Carcinoma of the penis is a rare malignancy, and accounts less than 1% of all male cancers in Western countries (Fig. 31.3). It is an important health problem in some developing countries where it can reach 10% of cancers in South African and South American countries. Although it is a disease of older men, it is not unusual in younger men [50]. The conventional treatment for this cancer is partial or total penile amputation, or radiation. Radiation therapy provides good results in superficially infiltrating tumors, although it may have negative cosmetic and functional effects, often resulting in psychosexual dysfunction [51].

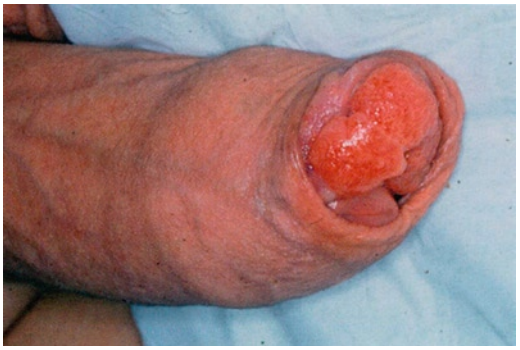

Fig. 31.3 Penile cancer. (Courtesy of Dr. W. Kirkels)

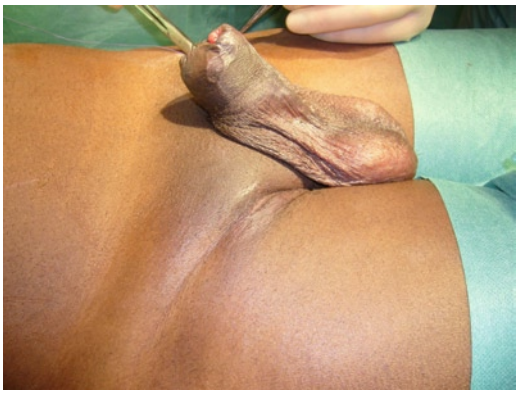

Fig. 31.4 Penile cancer. Partial amputation. (Courtesy of Dr. W. Kirkels)

Opjordsmoen et al. reported on the sexual function of 30 patients (28–75, mean 57 years) after different treatment modalities for low-stage penile carcinoma [52]. Using a global score for overall sexual functioning based on sexual interest, ability, enjoyment and satisfaction, identity, and frequency of intercourse, they reported that penectomy patients had lower scores than either radiation or local surgery patients. Patients who had undergone only partial penectomy were also dissatisfied and, interestingly, did not function sexually substantially better than patients after total penectomy [52] (Fig. 31.4). Based on such results, radiotherapy, laser beam therapy, and local incision might provide the better options for penile cancer when preserving sexual function is important. Regarding the use of laser beam therapy, for example, Windhal et al., in a retrospective analysis, reported on 67 patients treated from 1986 to 2000 with laser beam therapy [51]. Of these, 58 were still living, and 46% of them agreed to participate in the interview. Eighty-seven percent of the participating patients reported being sexually active; 72% had no ED, though 22% had a decrease in sexual function (but 6% indicated improved sexual function); and 50% were satisfied with their sexual life. Thus, it appears that most patients with penile carcinoma can still enjoy a sexual life if laser treatment is used; more invasive procedures such as surgery or radiotherapy reduce this likelihood [52].

Incidence of Erectile Dysfunction After Radiotherapy for Testicular Cancer

Germ cell tumors of the testis are relatively rare and account for about 1% of all male cancers, although the reported incidence appears to be increasing over the last two decades [53, 54]. Testicular malignancies can be classified histopathologically into seminomas, nonseminomas, and combined tumors. Following a diagnostic orchiectomy, most seminomas are often treated by radiotherapy to the para-aortic lymph nodes and most nonseminomas by platinum-based chemotherapy, in case of nodal disease of metastases. About one-third of the nonseminoma patients undergo retroperitoneal lymph nodes dissection (RPLND) that can affect ejaculatory function. The long-term survival for early disease detection approaches 100%. Since most patients undergo treatment during the most sexually active period of their life, the impact of therapy on the quality of life in general, and on sexual functioning, fertility, and body image in particular, is very important. Self-report measures of sexual function conducted soon after treatment indicate high levels of dysfunction that tend to improve over time, in general 3–6 months after treatment [55]. Limited research data on sexual functioning are available in long-term survivors of testicular seminoma treated with orchiectomy and radiotherapy.

Following radiotherapy, deterioration in sexual functioning has been reported in between 1 and 25% of the patients treated for testicular cancer [56–60]. Tinkler et al. reported on 237 patients after orchiectomy and abdominal radiotherapy and compared these data with 402 age-matched controls [58]. On almost all parameters studied, including erection, ejaculation, and libido, patients scored lower than controls (reduction in orgasm, in libido, and in interest in sex). Caffo et al. evaluated toxicity and quality of life of 143 patients treated for early-stage testicular cancer [59]. Twenty-three percent reported decreased libido, 27% had problems reaching orgasm, and 38% had ejaculation disturbances. A decrease in sexual desire, in orgasm, and volume of semen was negatively correlated with age [56]. Jonker-Pool et al. reported on three groups of patients with testicular cancer after one of three conditions: radiotherapy, wait-and-see, or chemotherapy [57]. Radiotherapy patients reported decreased libido in 22% compared to 12% in the wait-and-see group and 30% in the chemotherapy group. Decrease (or absence) of ejaculate was reported in 15, 7, and 21% in the three groups, respectively; decreased orgasm in 15, 12, and 30%, respectively [57]. Although the differences were not statistically significant, the radiotherapy group exhibited higher ejaculation and orgasm disturbances than the wait-and-see group. Similar results have been reported by Arai et al. [61].

Nazareth et al. have published an excellent review on sexual function in patients after treatment for testicular cancer [62]. Although some findings were difficult to interpret since they were based on uncontrolled samples, non-validated questionnaires, or patients who had received a variety of treatments, the authors concluded that, in general, treatment of testicular cancer often results in sexual dysfunction. Significantly more ED occurred in patients treated for testicular cancer than in healthy controls, and sexual drive (sexual desire and frequency of sexual intercourse) was significantly reduced [62]. Ejaculatory function worsened in all studies where a non-nerve-sparing RPLND was performed. In studies without control procedures, sexual dysfunction reached even higher levels [62].

Of these dysfunctional outcomes, the effect on ejaculation is perhaps most readily explained. Ejaculation is achieved by neural impulses conducted via the sympathetic trunk, postganglionic nerve fibers, and hypogastric nerves, all of which are closely connected with the retroperitoneal lymph nodes. During RPLND, performed in case of residual tumor mass after chemotherapy, these nerves are difficult to recognize and might be damaged, resulting in decreased semen volume or dry ejaculation. Sympathetic nerve-induced contraction of the internal bladder sphincter prevents passage of semen into the bladder. As a result of careful anatomical studies, the technique of the RPLND has now been modified to include a nerve sparing procedure so that antegrade ejaculation is now maintained in 80–100% of patients [55]. Polychemotherapy induces loss of libido, decreased arousal, and potentially decreased erectile function in patients with testicular cancer [63]. Chemotherapy has a major effect on the hormonal, vascular, and nervous systems, all important for normal sexual functioning. In more than half of testicular cancer survivors, Leydig cell dysfunction occurs, as indicated by low plasma testosterone and elevated luteinizing hormone levels [63]. Decreased amount of semen is also reported significantly more often by chemotherapy-treated patients than those simply under observation, possibly caused by lower testosterone levels.

Given the potential deforming effects of treatment for testicular removal, several studies have addressed issues of body image following treatment of testicular cancer [58, 60, 64]. More than half of testicular cancer patients reported that their body image had changed after treatment (orchiectomy and radiotherapy) [65]. Yet only about half of the patients reported being informed by their urologist about the availability of testicular implants [60, 64] (Fig. 31.5). As expected, body image has been reported to improve after implantation of a testicular prosthesis [64–67].

In conclusion, controlled studies indicate that sexual dysfunction persists for about 2-year

Fig. 31.5 Testicular prostheses

posttreatment in testicular cancer patients and may be due to a combination of biological and psychological factors. However, before concluding that sexual dysfunction is a frequent and serious outcome of treatment of testicular cancer, more evidence is needed from controlled studies that include greater numbers of patients.

Incidence of Erectile Dysfunction After Radiotherapy for Colorectal Cancer

Colorectal surgeons are becoming more aware of the details of the neurovascular anatomy around the rectum and pelvic structures, and as such, have made significant progress in their attempts to spare sexual and other functions. Rates of ED after surgery only for rectal cancer vary from 0 to 73% and ejaculation disorders have been reported in up to 59%; however, the studies generating these data included only small numbers of patients. Furthermore, it remains difficult to compare rates of sexual dysfunction across studies because of the different questionnaires used. The main cause of sexual dysfunction after proctectomy appears to be injury to the autonomic nerves in the pelvis and along the distal aorta and anterior surface of the rectum. Dysfunction is more common after abdominoperineal resection than after low anterior resection. In 1992, total mesorectal excision (TME) was introduced for the treatment of rectal cancer, a procedure that preserves autonomic nerves.

Radiation therapy has become an important part of the multimodality treatment of locally advanced rectal carcinomas. The addition of preoperative radiation appears to increase the percentage of patients complaining of sexual dysfunction, in both males and females [68, 69].

Nesbakken et al. prospectively assessed sexual functioning in patients undergoing a total or partial TME procedure without previous radiotherapy [70]. A visual analogue scale assessing libido, sexual activity, potency, and ejaculation was administered before and 6 months after surgery. Six of 24 men reported a decrease in erectile function, one was fully impotent, and two reported retrograde ejaculation. Pocard et al. reported on 20 patients, of these 13 were males (42–76, mean 57.5 years) [71]. Of the 13 men, nine (69%) were sexually active both pre- and postoperatively. One reported retrograde ejaculation. After 3 months, four patients reported less rigid erections but these normalized at 1 year after surgery. The authors concluded that TME and autonomic nerve preservation spares sexual functioning in patients with rectal cancer, at least in the patients without preoperative radiotherapy [71]. The specific effect of radiotherapy on ED in rectal cancer patients has been addressed by Bonnel et al. who reported on 42 patients, 15 of whom had received preoperative radiotherapy [68]. No difference in erectile capacity was seen across groups, but ejaculation difficulties were higher in the radiotherapy group (2 out of 11 patients as compared to 2 of 24 patients). These authors concluded that sexual dysfunction may be due to a direct effect of radiotherapy or to the more difficult surgical procedure to visualize the autonomic nerves in the irradiated area [68]. Specifically, the inferior hypogastric plexus is responsible for erection and the superior hypogastric plexus for ejaculation, mediated by the sympathetic system, and these systems are likely to be compromised during surgery. However, a multicenter study has shown that even with a careful nerve-preservation technique, men reported impotence or were permanently unable to ejaculate (38%) [72].

Ejaculatory and Other Sexual Dysfunctions

A deterioration of sexual activity has been associated with the severity of ejaculatory dysfunction, particularly a decrease in volume or an absence of semen [73]. After radiotherapy for prostate cancer, ejaculatory disturbances vary from a reduction or absence of ejaculate volume (2–56%) to discomfort during ejaculation (3–26%) and haemospermia (5–15%). Dissatisfaction with sex life was reported in 25–60%, decreased libido in 8–53%, and decreased sexual desire in 12–58%. One study reported a decreased intensity of orgasm, decreased frequency and rigidity of erections, and decreased importance of sex [9, 10, 44, 45].

Therapy of Postradiation Erectile Dysfunction

Prior to the introduction of sildenafil, only one small study reported on the efficacy of intracavernosal injections (ICI; Fig. 31.6) in the treatment of ED after radiotherapy for prostate cancer [74]. All patients had erections sufficient for vaginal penetration with an ICI. Dubocq et al. reported a high satisfaction rate and low morbidity in 34 patients who received a penile implant after being irradiated for prostate cancer [75]. With the availability of oral drugs to treat ED, these methods of therapy are loosing popularity. The efficacy of sildenafil after radiotherapy for prostate cancer in open-label studies has been reported in up to 90% of the patients [76–80]. In the only randomized, double-blind trial performed so far, sildenafil improved erections significantly as compared to placebo; 55% of the patients had successful intercourse with sildenafil (18% with placebo) [81, 82]. Similar results have been reported in one randomized, double-blind trial using tadalafil [83, 84].

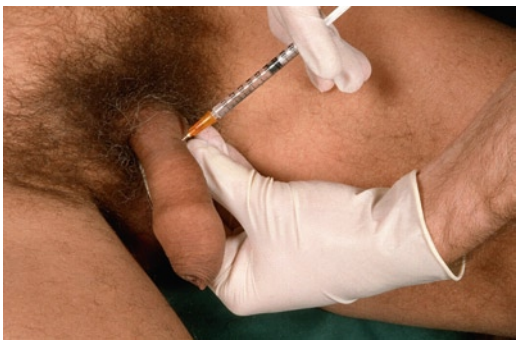

Fig. 31.6 Intracavernosal injection of a vasoactive drug

Prevention of Postradiation Erectile Dysfunction

Prevention is a difficult matter. If one accepts the hypothesis that radiation induces vascular damage, then decreasing the dose to pelvic vascular structures could decrease ED rate. As no reliable data are available to correlate the radiation dose in the penile structures and neurovascular bundles with the prevalence of postradiation ED, to date no conclusions can yet be drawn. Possibly, reduction of treatment margins, the use of fiducials to visualize the pelvic organs, more sophisticated radiation techniques as the intensity modulated radiotherapy (IMRT), all might reduce the prevalence of postradiation ED. One study on IMRT for prostate cancer showed a reduction of the radiation dose to the penile bodies but it did not investigate this effect on sexual functioning [85]. However, prospective studies with large series of patients, and the use of standardized validated questionnaires, have to investigate this hypothesis.

Recently, frequently discussed in the literature is the role of phosphodiesterase type 5 inhibitors (PDE5i) in the penile rehabilitation process for patients after radical surgery for prostate cancer [86]. This is not the case for patients undergoing radiation therapy. As PDE5i have been found effective in the treatment of ED after radiotherapy in randomized trials of prostate cancer [81–84], one may speculate that the use of these drugs might be useful in the rehabilitation process as well. Schiff et al. reported in a nonrandomized,

nonblinded study, that the early use of PDE5i after brachytherapy was associated with a significant improvement in and maintenance of erectile function compared with late use [87].

The hypothesis is that PDE5i may work in a number of fashions (1) by increasing nightly, spontaneous, and voluntary erections, can improve oxygenation of the corporal bodies, (2) preserve endothelial function and (3) and protect cavernosal smooth muscle integrity and function. These purported mechanisms may prevent fibrosis occurring in the first 6–12 months after radiotherapy by restoration and preservation of nitric oxide-mediated vasodilation in the irradiated corporal bodies and maintain erectile function of patients undergoing radiation therapy. Hopefully, ongoing studies in the USA with sildenafil and tadalafil in patients undergoing radiotherapy for prostate cancer will help verify this hypothesis.

Conclusion

The prevalence of postradiation ED is high. There are still no conclusive data on EBRT techniques, field sizes, energy used and their specific influence on ED. Although vascular damage seems to play the most important role in postradiation ED this has not confirmed so far and it is certainly not the only mechanism involved. A multi-factorial etiology has to be considered, taking into account age, comorbidity, previous pelvic surgery, drugs, pretreatment erectile function and hormonal manipulation. The definition of (im)potence advocated by the Second International Consultation on Sexual Dysfunctions should always be used [4], and ED evaluation should be standardized by using, prospectively, validated questionnaires on quality of life and sexual functioning, such as the IIEF. A better understanding of the etiology would allow for more specific therapeutic modalities. Finally, sexual counseling is an important aspect. Patients need to be correctly informed on the pelvic anatomy, on the possible sequelae of radiation on their sexual life and functioning. Sexual desire, satisfaction with sexual life, libido and frequency of intercourse have to be assessed as well. Not only a functional penis but a functional man, including his partner, has to be the goal of sexual rehabilitation after radiotherapy of pelvic cancer.

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Chapter 32
Pelvic Radiation in Women

Pernille T. Jensen

Keywords Adjuvant radiotherapy • Androgen-deficiency syndrome • Atrophic vaginitis • Baseline score • Benzydamine • Brachytherapy • Clinical meaningful difference • Dyspareunia • Epithelial damage • European Organisation of Research and Treatment of Cancer (EORTC) Quality of life core questionnaire C30 • EORTC quality of life questionnaire colo-rectal module (QLQ CR38) • EORTC quality of life questionnaire cervix module (CX24) • External beam radiation, Faeces incontinence • Female sexual dysfunction • Female Sexual Function Index (FSFI) • Fibrosis • Hormone replacement therapy • Hyperbaric oxygen therapy • Hypoactive sexual disorder • Induced menopause • Interstitial radiation • Interstitial implant • Intracavitary brachytherapy • Irradiation vaginitis • Late radiation effects • Local oestrogen, Lubrication problems • Methyl-testosterone • Normal tissue tolerance • Orgasmic problems, Pelvic radiation for anal cancer • Bladder cancer, Cervical cancer • Endometrial cancer • Rectal cancer • Vulva cancer • Perineal implant • Premature ovarian failure • Psychosexual effects • Psychosexual adjustment • Quality of life, Radiation toxicity, Radical radiotherapy • Radiotherapy, Radio-necrosis • Re-epithelisation • Response shift bias • Sexual dissatisfaction • Sexual dysfunction • Sexual enjoyment • Sexual functioning • Sexual function vaginal changes questionnaire (SVQ) • Sexual rehabilitation • Vaginal dryness • Vaginal atrophy • Vaginal mucositis, Vaginal dilator • Vaginal narrowing • Vaginal shortening • Vaginal stenosis • Vaginal vault necrosis • Vaginal adhesions • Vulvectomy • Vulvo-vaginal mucositis

Radiotherapy for Cancer in the Pelvis

Pelvic radiation represents a major therapeutic strategy, either as adjuvant or primary treatment in the management of cancer in women. This mainly concerns women with gynaecological malignancies: endometrial, cervical, vaginal, and vulva cancer; intestinal malignancies: rectal and anal cancer, and bladder cancer. Further, long-term breast cancer survivors may experience similar adverse effects after ovarian ablation accomplished by pelvic radiation. Finally, women treated with radiation for childhood cancer, e.g. Hodgkin lymphoma are at risk for ovarian failure and premature menopause; adverse effects that not only influence their fertile lifespan but also may have a negative effect on their sexual life [1]. The fact that the number of long-term cancer survivors has increased during the past 2–3 decades makes demands to health care providers to professionally handle late effects after pelvic radiation.

Pelvic radiation may be delivered as external beam radiotherapy and/or brachytherapy. Lately, technical effort progress have been made to

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determine the dose intensity pattern that will best conform to the tumour shape; e.g. intensity modulated radiation therapy (IMRT) and 3-D/4-D computed tomography (CT) or magnetic resonance (MR) images of the patient that is used in conjunction with computerised dose calculations. The main purpose is to allow a higher radiation dose to be focused within the tumour while minimising the dose to surrounding normal critical structures. Brachytherapy may facilitate this goal. For cervical cancer, brachytherapy is delivered using an applicator inserted close to or in the tumour target (Figs. 32.1a, b and 32.2). For large pelvic tumours interstitial brachytherapy with insertion of needles through a perineal template or placing flexible catheters during laparotomy may be used for coverage of large volume tumours at the pelvic side wall (Figs. 32.3–32.5).

The limiting factor for the total dose delivery of radiation is normal tissue tolerance. Hence, in managing cancer with radiotherapy, a delicate balance between cure and normal tissue tolerance have to be dealt with. In general, the occurrence of complications is dose and fractionation dependent and there may be a long latency period for many adverse late effects to emerge, probably due to scattered irradiation remaining in the organs around the tumour. However, other factors may also have an impact on the occurrence of adverse effects after irradiation. Gene expression studies have identified genes related to radio sensitivity in, e.g. subcutaneous fibroblast cell lines of breast cancer patients [2]. These findings may, in the future, enabling further individualisation of the treatment to obtain a high cure rate with fewer side-effects.

Late Effects of Radiotherapy

Radiation effect is progressive and may become symptomatic after a latent period between the end of acute effects and the development of late effects, but there may be a continuous progression from the acute oedema, mucosal and submucosal inflammation and persistent ulceration to fibrosis [3]. On the long term, excessive pelvic fibrosis may cause intestinal and ureteral stenosis, lymph oedema of the lower extremities, endothelial damage, inflammation, ischaemia and necrosis in retroperitoneal vessels and nerve plexuses. Certain risk factors predispose to susceptibility for late toxicity and include, besides genetic factors, diabetes, arterial disease, and a large tumour bulk.

The accumulated radiation dose to the pelvic organs is critical for both acute bowel, bladder, and genital toxicity [4–7]. Symptoms related to the gastrointestinal tract are common after pelvic radiation, both acute and chronic: diarrhoea, rectal bleeding and abdominal pain due to intestinal obstruction and/or intra-abdominal adhesions

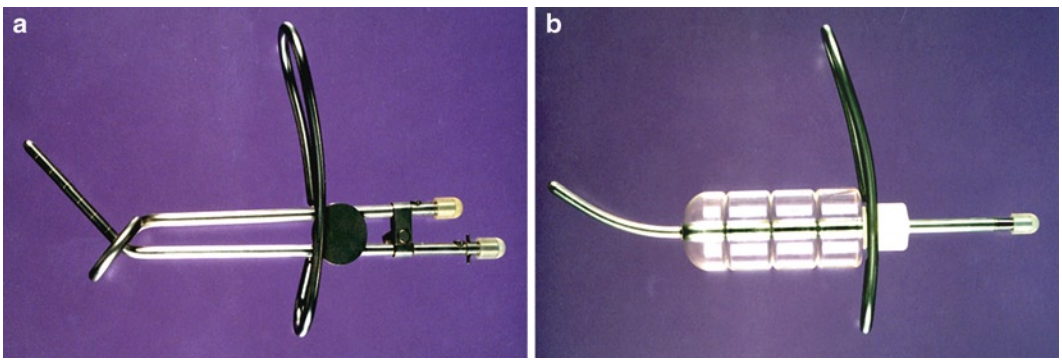

Fig. 32.1 Two different applicators for brachytherapy in cervical cancer. In (**b**) the vaginal part of the applicator is covered with plastic to reduce radiation to the vaginal wall

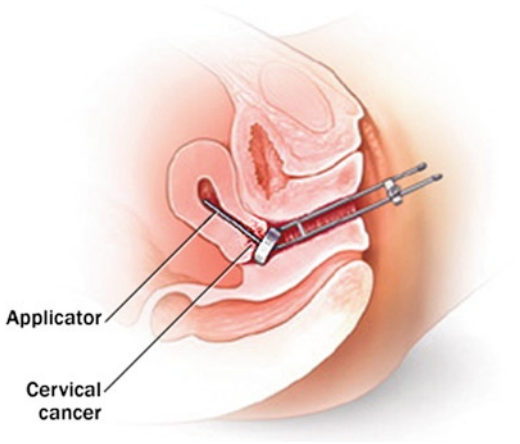

Fig. 32.2 An applicator for intracavitary brachytherapy in situ in a patient with cervical cancer Copyrighted and used with permission of Mayo Foundation for Medical Education and Research, all rights reserved

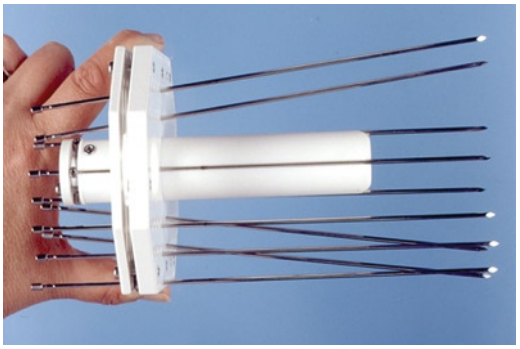

Fig. 32.3 The Martinez Universal Perineal Interstitial Template (MUPIT) with needles for implantation into the tumour bed of e.g. patients with anal cancer, advanced or recurrent cervical cancer

[4, 8–11]. Patients treated for anal or rectal cancer may experience increased gas, liquids or solid faeces incontinence, rectal emptying problems, and frequent bowel movements [9, 12].

Acute urologic radiation toxicity comprises frequency of urination, nocturia, urgency bladder spasm, dysuria, and haematuria. With a median period of 2–3 years late effects may arise as the bladder submucosa undergoes varying degrees of fibrotic change, bladder capacity reduces and telangiectasia may develop. Ischaemia from radiation-induced endarteritis obliterans gives rise to a fragile neovasculature that tends to

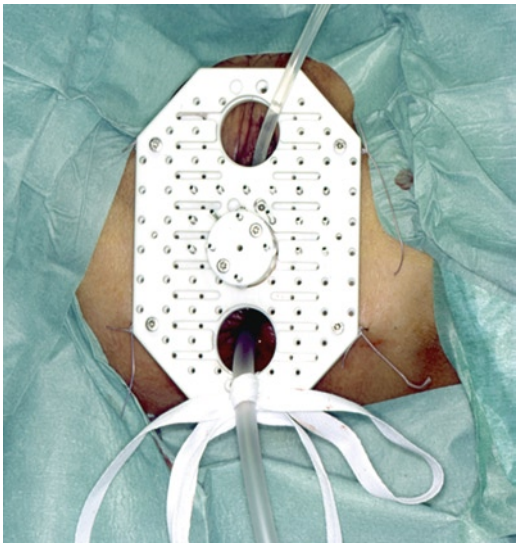

Fig. 32.4 The needles are inserted blindly into the tumour bed through the MUPIT and are in situ in a patient with recurrent cervical cancer. The template allows angling of the needles when inserted through the peripheral insertion holes thus optimising tumour coverage on the pelvic sidewall

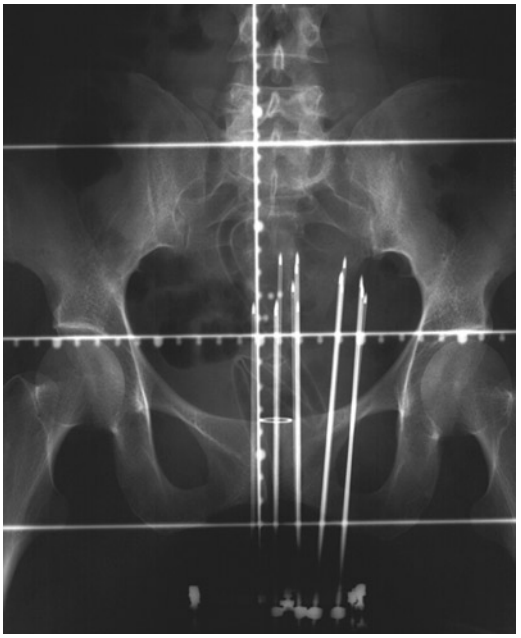

Fig. 32.5 X-ray of needles in situ in the pelvis for interstitial brachytherapy. A high-activity source will move in pulses into the needles and according to a computer-optimised dose distribution, vary the dwell times in certain positions

bleed. Potential symptoms of late effects include, besides those mentioned, contracted bladder, hemorrhagic cystitis, detrusor instability, ulceration, necrosis, and a potential for perforation and fistula formation; vesicovaginal- and rectovaginal fistulas [6, 7, 13].

The rapid cell-turnover of the vaginal and vulva epithelium makes it very sensitive to the effects of radiation. Following pelvic radiation, acute radiation effects involve vaginal erythema, moist desquamation and a confluent mucositis. Further, a fibrinopurulent exudate is often present in the area of contact with the brachytherapy source. The mucosa may demonstrate severe congestion and submucosal haemorrhage (hyperaemia). These effects usually resolve within 2–3 months after radiotherapy. In some patients, however, there is a progressive vascular compromise and tissue hypoxia may result in epithelial sloughing, ulcer formation and necrosis. On the longer term, vaginal wall thinning, adhesions, atrophia and fibrosis may occur often followed by decreased vaginal elasticity, narrowing, shortening and ultimately total vaginal stenosis [14–19]. Following surgery and/or radiotherapy vulva cancer patients may experience acute dermatitis, oedema, and ulceration. On the longer term, narrowing of the vaginal entrance, skin fibrosis, sensory alteration, or paresthesia besides itching, pain, a burning feeling, discharge, and foetor from the vulva region may arise [5, 20]. Urethral problems are also common: spraying of urine, interrupted stream, angulated stream or poor urine stream due to varying degree of urethral stenosis [20]. Reconstructive surgery may be necessary to the vulva, vagina and perineum with correction of anal and urethral stenosis and fistula repair [20].

Radiation to the ovaries initially affects the dividing granulosa cells that line the growing ovarian follicles and support maturing oocytes. With destruction of sufficient granulosa cells, the oocyte loses viability and the follicle becomes atrophic [21]. Temporary or permanent sterility occurs depending on the girl's/woman's age at the time of irradiation and the radiation dose. Fertility may return as a result of survival of primordial follicles with little or no granulosa cell proliferation at the time of irradiation. Studies of long-term survivors after radiation and chemotherapy for childhood cancer have shown a reduced ovarian reserve and thereby a potential shortened reproductive span and an early menopause [22]. This is presumably a consequence of a reduction in the total number of follicles or an accelerated rate of atresia in the remaining follicles. Furthermore, radiation effects on the uterus in childhood include a reduced adult uterine volume [23] and an increased risk for small-for-gestational age offspring [1].

Assessment of Sexual Function

Patient-related factors may have a substantial influence on subjectively reported adverse effect after pelvic radiation. It is well known that response-shift, i.e. the phenomenon that patients who are cured for a potentially fatal disease, re-conceptualise their perception of well-being and, despite considerably morbidity, report better or equal quality of life compared to persons from the general population [24]. This is one of the main challenges when interpreting quality of life results and has been shown also to apply to women's report on quality of life following treatment for cancer involving pelvic organs [25–27]. Although significant sexual dysfunction was reported following radiotherapy to the pelvis, this did not seriously affect overall measures of quality of life. Another challenge when interpreting subjective measures concerns baseline assessment. It has been suggested that a baseline score of sexual functioning in, e.g. a cervical cancer patient may be severely influenced by the patient's knowledge of her cancer diagnosis, symptoms of the cancer, e.g. post-coital bleeding or inter-menstrual bleeding episodes, and knowledge of potential treatment effects [28–30]. Hence, although hard to obtain, the desirable value for comparison with post-treatment effect is a pre-cancer score rather than a pre-treatment score. As an example, the study of Pieterse et al. found a significant lower level of sexual activity, low sexual interest and a higher prevalence of

dyspareunia among women with cervical cancer immediately before treatment when compared with age-matched control women [31]. In line with this, Jensen et al. found no differences between cervical cancer patients and age-matched controls when asking the women treated for cervical cancer at 3-month post-treatment to retrospectively report their sexual functioning *before* the cancer diagnosis [14, 32].

Psycho-sexual Effects of Pelvic Radiation

Although still perceived as a sensitive topic, the impact of cancer and its treatment on sexual functioning receives nowadays more attention both in the research field and in the clinical setting. This is probably due to the increasing awareness and acceptance of the importance of a continued sexual function as part of the rehabilitation process for cancer patients [26, 33–36].

Gynaecological cancer patients have given a clear indication that they perceive a continued sexual function as important [33–35]. In the study of Ekwall et al. gynaecological cancer patients rated their sexuality as one of three issues of central importance for the quality of their daily living [35]. Studies have documented that the level of communication between the health care professional and the patient about potential sexual problems are low and insufficient from the patient's point of view [33–35]. Long-term survivors of gynaecological cancer have expressed a great need to talk with their doctor or a nurse about their sexuality and sexual difficulties, and claimed that this need was often ignored or simply not addressed in the clinical setting [35]. They felt that the staff mainly gave information of biomedical character but never related it to the potential effect on their sexual life. As an example, one woman was informed that after brachytherapy her vagina would shorten, however, no information was given regarding potential difficulties in completing sexual intercourse or being intimate with her partner [35].

To evaluate key issues of post-treatment psycho-sexual adjustment after surgery or combined surgery and adjuvant radiotherapy for early-stage endometrial or cervical cancer, Juraskova et al. conducted in-depth interviews with 25 patients [33]. Objectives of the study also included assessment of the impact of post-treatment sexual functioning on the overall quality of life and evaluation of the psychosocial needs of the women and their partner [33]. Although the small sample size did not allow any firm conclusions regarding quantitative analyses, the authors mentioned that the women interviewed substantiated the results obtained from larger quantitative studies. Women who received radiotherapy, particularly combined external pelvic radiotherapy and brachytherapy, reported the greatest difficulties related to sexual activity and sexual satisfaction post-treatment [33]. The qualitative results were divided into patient–partner issues and patient–doctor issues. The patient–partner issues pointed towards qualitative differences between women in childbearing age and women who were menopausal. Alterations in the perception of femininity emerged as an important aspect of sexual readjustment for the pre-menopausal women. They regarded treatment, especially radiotherapy, as having had a significant negative influence on their femininity, on their partnership, on their body-image and on their self-esteem. Obviously, these findings were more common in younger women who identified their femininity with their ability to bear children [33]. Regarding their partnership, most women found that their partner had difficulties coping with the diagnosis of cancer and that their partner was afraid to resume sexual intercourse. The partner, on the other hand, expressed fear of causing pain or further physical damage while the women reported fear and insecurity regarding their sexual relations. The women indicated that after treatment for cancer their sexual satisfaction was to a greater extent related to intimate aspects; sensuality, disclosure and reassurance. They did, however, also indicate a need, despite their own difficulties, to provide their partner with what they thought he wanted, i.e. sexual intercourse. In general and in

parallel to the results of Ekwall et al., all women expressed a great need for comprehensive information about their disease, especially regarding organs involved in their treatment and possible side-effects particularly in relation to sexual matters [16, 33, 35].

Assessing distressful symptoms after treatment of cervical cancer, Bergmark et al. found that sexual functioning was the primary source of distress [18]. Especially dyspareunia and reduced orgasm frequency caused most distress. Very few patients had any recollection of sexual problems being mentioned by their doctor. This is in accordance with several studies including the comprehensive study of Hendren et al. who noted that only 9% of female rectal cancer patients remembered discussing sexual effects of treatment with the health care professionals before treatment [26].

As it appears, sexual dysfunction following pelvic radiation for malignancies in the pelvic organs is multi-factorial in origin. The occurrence of physical symptoms and the negative impact of cancer and treatment on psycho-social and relationship matters will place these women at risk for developing sexual problems. When summarising results from available studies of sexual problems it should be noted that only a few of the studies have included measures of personal sexual distress. Current knowledge of the complexities related to female hypoactive sexual desire, arousal and pain sexual disorders has prompted recommendation of a classification system based on physiological as well as psychological pathophysiology, and a personal distress criterion for most diagnostic categories [37, 38]. This includes a re-definition of sexual interest to include the concept of receptivity and sexual arousal disorders are separated into genital and subjective subtypes, while the definition of dyspareunia reflects the possibility of pain precluding intercourse. The anticipation and fear of pain characteristic of vaginismus is noted while the assumed muscular spasm is omitted given the lack of evidence [37, 38]. Very few measures of female sexual dysfunction have included these comparatively new conceptual considerations.

Sexual Problems After Pelvic Radiation

In the following, studies reporting different aspects of sexual problems after pelvic radiation are summarised. It should be noted that most studies report from study populations who have received multi-modality treatments, i.e. surgery + external beam radiation and/or brachytherapy and with or without chemotherapy. There is considerably more data on female sexual dysfunction after radiotherapy for gynaecological cancer [14–17, 39–46] than after colorectal [9, 26, 27, 47, 48], anal [12, 25], and bladder cancer [49–51]. This reflects a paucity of research in the area of sexual dysfunction in patients with rectal, anal, and bladder cancer rather than actual differences of the impact of radiation on sexual functioning in these patient groups.

Gynaecological Cancer

The longitudinal study design assesses changes over time. The repeated observation at the individual level makes this study design more powerful than cross-sectional observational studies, by virtue of being able to exclude time-invariant unobserved individual differences, and by virtue of observing the temporal order of events. This is especially relevant when reporting effects of radiotherapy since adverse effects of pelvic radiation may change over time and late effects may emerge after an asymptomatic period.

Flay et al. assessed short-term sexual functioning after radiotherapy with or without primary surgery in 16 patients with stage I–III cervical cancer [43]. Women were assessed on four occasions: prior to radiotherapy, at the end of radiotherapy and at 6 and 14 weeks after radiotherapy. The results obtained prior to radiotherapy were considered as a baseline score although more than one-third of the sample had had primary surgery at this assessment point. In line with later studies of radiation effects on the vaginal mucosa, a large proportion of the women

experienced vaginal dryness, shortening, and narrowing increasing over time during the first 14 weeks following radiation. A surprisingly high proportion of the women (37% pre-treatment, 47% at 6 weeks follow-up and 43% at 14 weeks follow-up) reported concern that sex would cause recurrence while almost one-third of the patients constantly reported concern that sex would aggravate the cancer [43]. At 14-month post-treatment several reasons for changes in sexual activity were mentioned: dyspareunia (43%), concern of causing bleeding (36%), low back pain (29%), vaginal dryness (43%), vaginal shortening (64%), and vaginal narrowing (43%) [43].

Schover et al. assessed long-term effects on sexual functioning over time in 63 early-stage cervical cancer patients [17]. She included and compared patients who were treated by surgery only and patients treated by combined modalities; surgery plus external beam radiation and external beam radiation plus brachytherapy. The Sex History Form [52] and the Brief Symptom Inventory [53] measures were used for self-assessment at the beginning of treatment and 6- and 12-month post-treatment. Scores were compared to objective ratings of the vaginal mucosa and pain during gynaecological examination [17]. No differences in any measures were observed between the two groups receiving combined modality treatments; hereafter named the radiotherapy group. By 1 year, sexual desire and sexual activity had declined significantly and responsibility for initiating sexual relations had shifted to the partner for 58% of the patients compared to 39% before the cancer and significantly more prevalent in irradiated women [17]. While no significant findings concerning sexual arousal were observed across treatment groups and across time, significant differences were observed regarding specific sexual complaints. By 1-year post-treatment irradiated women reported more painful sexual intercourse (50%), post-coital bleeding and that pain diminished sexual pleasure compared to patients treated by surgery only (10%). There was a trend towards more vaginal narrowing, shortening, and post-coital soreness in the radiotherapy group [17]. Scores from vaginal examination did not change over time but differed significantly between treatment groups: while patients treated with surgery only had normal vaginal mucosa, normal vaginal size and no pain during examination, most irradiated women had mild changes in mucosal appearance, mild reduction in vaginal size and some had mild pain [17]. At 1 year, a positive correlation was found between objective measures of vaginal changes and the patients' subjective assessment of dyspareunia. The study confirmed the potential of late-onset radiation adverse effects and also demonstrated that women receiving radiotherapy either as part of or constituting their treatment for early-stage cervical cancer are at higher risk of experiencing sexual problems and vaginal changes than patient treated by surgery only [17].

Jensen et al. included 118 patients with locally advanced cervical cancer in their longitudinal study of sexual problems and vaginal changes. A minor part of the sample constituted of patients who had radical hysterectomy and pelvic lymphadenectomy as their primary treatment and adjuvant external beam radiation due to high-risk histological factors [14]. No differences could be detected between the two groups in any measures and results were therefore reported for the group as one. Results were compared with those of an age-matched control group over time and for seven key issues results in the patient group were compared with retrospectively assessed pre-cancer values. Patients were assessed repeatedly six times over a 2-year period after treatment with a validated questionnaire; the Sexual function and Vaginal changes Questionnaire (SVQ) [54]. The patients reported persistent sexual dysfunction from the first assessment 5-week post-radiation throughout the first 2 years after radiotherapy with no indication of improvement (see Table 32.1). Compared with control women patients reported a significant persistent pattern of low or no sexual interest, moderate to severe lack of lubrication, orgasmic problems, dyspareunia, and sexual dissatisfaction [14]. Patients with dyspareunia and lack of lubrication reported a high level of distress from these sexual dysfunctions unlike the control group who only

Table 32.1 Sexual dysfunction in women with advanced cervical cancer after radical or adjuvant radiotherapy

	5 weeks	3 months	6 months	12 months	18 months	24 months
Low or no sexual interest	90% (RR 1.5)			87% (RR 1.5)		84% (RR 1.4)
Lack of lubrication Quite a bit – very much	28% (RR 5.3)			40% (RR 7.3)		28% (RR 5.3)
Dyspareunia Quite a bit – very much	27% RR 7.4			17% (RR 4.8)	15% (RR 4.6)	
Orgasm Never – occasionally	67% (RR 1.6)			62% (RR 1.5)		63% (RR 1.6)
The size of vagina bothering during intercourse because it felt too small	49% (RR 5.6)			29% (RR 3.6)		42% (RR 4.8)
Able to complete sexual intercourse Never – occasionally	61% (3.5)			50% (2.9)		43% (2.4)
Dissatisfied with sex life	30% (RR 2.0)			31% (RR 2.1)		28% (RR 1.8)
Not sexually active	50% (RR 2.0)			47% (RR 2.0)		
Low or no partner sexual interest	53% (RR 1.3)					

The straight line indicates the time course with significant differences between the patient group and the healthy age-matched control women. The percentage indicates the incidense of the particular problem in the patient group while the RR indicates the Relative Risk for the patient group of experiencing the particular problem compared with the control women.

reported mild distress. Vaginal shortening bothersome during sexual intercourse was reported by 40% of the patients and 45% of the patients were never or only occasionally able to complete sexual intercourse. As a group, the patients had an increased risk of becoming sexual inactive, however noticeable, despite considerable sexual and vaginal problems, 63% of the patients who were sexually active before treatment became sexually active again 12 months after treatment although with a reduction in sexual activity frequency from once to twice weekly to once to twice monthly. The patient's assessment of changes since before the cancer diagnosis confirmed the findings of the patient versus controls: significant less sexual interest, increased dyspareunia, increased difficulties achieving orgasm and decreased ability to complete sexual intercourse. Patients receiving hormone replacement therapy had a lower risk of having reduced sexual interest and of becoming sexual inactive. Only temporary effects were observed regarding the partner's sexual interest and his ability to achieve an erection [14].

Several cross-sectional studies have been published regarding quality of life and sexual functioning and vaginal changes in cervical cancer long-term survivors [15, 16, 44]. The patient sample in these series mainly constitutes long-term survivors with early-stage disease. All three studies report substantial sexual and/or vaginal dysfunction following radiotherapy with or without surgery. However surprisingly, Bergmark et al. report significant increased risk of both vaginal shortening, vaginal elasticity and insufficient vaginal lubrication after surgery only compared to all other treatment regimes including radiotherapy [15]. These findings are hard to explain but may represent results after extensive radical surgery method with extended resections of the vaginal vault and very broad and deep excisions of the parametrium during radical hysterectomy. Other reasons have been proposed: use of a non-validated questionnaire, inclusion of old women with a high risk of vaginal atrophia, and no attempt to control for hormonal status [44]. As a group, the patients in the study of Bergmark et al. reported a high relative risk of moderate to severe dyspareunia (relative risk = 8.5) and a high degree of distress if the problems would persist [15].

Cull et al. assessed psychosocial and sexual outcomes after surgery only or radiotherapy with or without surgery in 83 early-stage cervical cancer patients at a mean follow-up of 97 weeks (range 17–171 weeks) [16]. Non-validated rating scales were used for sexual relationship assessments but supplemented with face-to-face interviews evaluating present and past sexual functioning. As for the patients' physical functional status, only 40% of the sample had resumed their full pre-morbid range and level of activity. The most common complaints, reported by 40–50% of the sample, was persistent tiredness, lack of energy, depressed mood, and anxiety [16]. Of the total sample 91% had worries concerning disease recurrence, 39% reported self blame and 37% reported a loss of self confidence. Almost half of the sample reported deterioration in their sexual function post-treatment. All phases of the sexual response cycle were affected and all the differences between the premorbid and post-treatment ratings were highly significant. All ratings on sexual difficulties were highly correlated with the total score of physical symptoms and with the psychological distress scores. Radiotherapy patients were more likely to report pain during intercourse and loss of sexual pleasure after treatment. Sexual/relationship worries comprised feeling less sexually attractive (29%), worries that sex causing recurrence (37%) or pain (60%), and blaming partner for disease (29%) [16]. The study highlights important psychosocial, sexual and physical aspects of being a cervical cancer survivor. As stated by the author: "while some physical morbidity may be an inevitable and acceptable price to pay for curative therapy, it may be questioned whether the functional outcome could be improved by relief of some of the patients' psychological distress." A very high degree of worries and anxiety related to the cancer, potential recurrence and the women's general health were reported. Further, a substantial proportion related sexual activity to their cancer and risk of recurrence. Access to accurate information and support may relieve some of the psychological distress and, on the longer term, followed by improved physical and sexual functional outcome [16].

Frumovitz et al. compared quality of life and sexual functioning in long-term survivors with early-stage cervical cancer after radical surgery or radiotherapy with control women [44]. Validated questionnaires were used including the Female Sexual Function Index (FSFI) [55] and the Brief Symptom Index-18 [56]. While no differences were observed in any measures of quality of life and sexual functioning in patients treated with surgery and controls, significantly poorer quality of life, more somatisation, anxiety, and depressive symptoms were reported by the irradiated patients [44]. Irradiated women reported more dyspareunia, more difficulty becoming sexually aroused, with lack of vaginal lubrication, in reaching orgasm, and in achieving sexual satisfaction. Radiation persisted as an independent prognostic factor for sexual dysfunction after accounting for tumour size, histology and grade [44]. The results of Frumovitz et al. are in agreement with a similar study of Greimel et al. who compared cervical cancer long-term survivors after surgery or surgery with adjuvant radiotherapy or surgery with adjuvant chemotherapy [57]. Patients who had adjuvant radiotherapy reported significant lower frequency of sexual activity and more vaginal problems than did those treated with surgery with or without chemotherapy as measured by the European Organisation of Research and Treatment of Cancer (EORTC) quality of life cervical cancer module CX-24 (QLQ CX24) [58].

The majority of patients with endometrial cancer present themselves in stage I where surgery is the treatment of choice. Pelvic and paraaortic lymphadenectomy disclose those patients with more advanced stages. Adjuvant radiotherapy has been shown to reduce the risk of locoregional relapses, however, with no evidence of a survival benefit [59]. There is a severe paucity of data on the effect of surgery and adjuvant radiotherapy on the sexual functioning in patients with endometrial cancer although adjuvant radiotherapy, both as external beam radiotherapy or as vaginal brachytherapy, has been and still is widely used in patient with early-stage disease and presence of histological high-risk factors or

advanced stage. Lately, studies have emerged evaluating the effect of multimodality therapies on the risk of late effects and/or the quality of life of endometrial cancer patients [4, 59–67], but only a few studies included data on sexual functioning [65–67]. Sexual functioning was not the primary outcome in any of these three studies. They all assessed patients in stage I only, and they used non-validated questionnaires or items [66, 67] or scales/items related to other cancer diagnoses (prostate or ovarian cancer) [65].

Nunns et al. assessed vaginal morbidity and sexual functioning in a subset of patients (75 patients out of 252) who had postoperative brachytherapy ($N=32$) or external beam radiation and brachytherapy ($N=43$) [66]. The overall incidence of vaginal stenosis was 54.7% of which most (75%) were confined to the upper third part of the vaginal. In addition, vaginal vault scarring was found in 63%, vaginal adhesions in 53%, telangiectasia in 60%, and mucosal atrophia in 61% with no difference between those who had additional external beam radiation besides brachytherapy. Only 20 out of 75 women were sexually active prior to treatment. Of these, 13 women (65%) reported reduced sexual interest and activity post-treatment and 12 women (60%) reported dyspareunia [66].

A Dutch multicentre trial (Portec 2) evaluated postoperative quality of life after adjuvant external beam radiation or brachytherapy. Baseline scores of quality of life issues and sexuality were obtained 3–4 weeks after surgery and were therefore prone to be influenced by the surgical trauma. Therefore, the authors' findings of improvement in sexual activity and sexual interest over the first 6 months after radiotherapy may merely represent expected improvement after a "false" baseline score obtained shortly after surgery and not actual improvement compared to before the cancer. No attempt to compare with age-matched normative data was done [65]. At a mean of 8 years post-treatment, van de Poll-France et al. found no difference in sexual activity and sexual interest or vaginal dryness in 25 long-term endometrial cancer survivors after surgery with or without adjuvant external beam radiation [67].

Although substantial surgical modifications have been made during the past decade in the treatment of vulva cancer, considerable sexual dysfunction is reported after treatment of this rare gynaecological cancer [20, 68–74]. The primary treatment in early-stage vulva cancer comprises a combined surgical procedure to the vulva and the groin(s). Adjuvant radiotherapy may be given to the vulva region in case of close resection margins and to the groins and the external iliac region in case of positive inguinal and/or pelvic nodes. If the sentinel node procedure is used, the latest evidence suggests that adjuvant inguinal radiotherapy is used only in case of two or more intra capsular lymph node metastases or in case of extra capsular spread [75]. Preoperative or radical radiotherapy should be considered only if the vulva cancer is considered advanced and either unresectable or if complete resection will endanger function of the urethra and/or anal sphincter.

Studies on sexual dysfunction following treatment of vulva cancer mainly concern dysfunction related to the surgical procedure. A few studies have included a sub-group of patients who received adjuvant radiotherapy [72, 74], mainly inguinal, but due to small sample sizes, no conclusion was drawn regarding the impact of radiotherapy on the women's sexual functioning. Since most patients will present themselves with resectable tumours, results regarding their sexual disruption are presented here, and although not documented in the literature, radiotherapy to the vulva region and/or the groins and the pelvic region is suggested to add on the existing knowledge on sexual disruption in this patient group. As it appears from Fig. 32.6, the disfigurement of the vulva region after surgery is further aggravated by adjuvant radiotherapy.

Andersen et al. conducted a study of 15 patients who underwent surgery for a vulva malignancy [68]. Besides reporting psychosocial distress and mild depression, the vulvectomy patients experienced significant sexual disruption. The women reported very limited capacity for sexual arousal, considerable sexual anxiety, and a 50% reduction in sexual activity frequency [68]. The longitudinal study of Weijmer Schultz

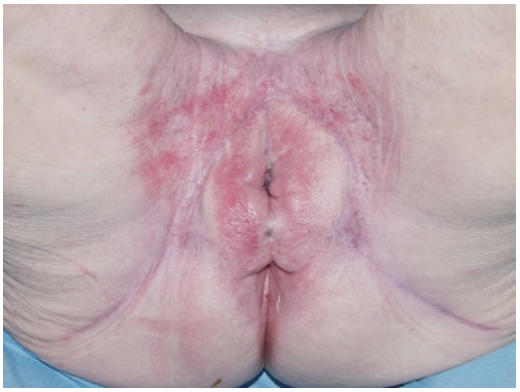

Fig. 32.6 Late radiation effects with telangiectasia, narrowing of the vaginal entrance, skin fibrosis, and sensory alterations after vulvectomy and adjuvant radiotherapy

et al. add to this a high risk for stenosis of the vaginal entrance and a serious reduction in the perception of positive genital sensations during sexual arousal and orgasm with no recovery taking place over time [74]. Green et al. also reported significant global sexual dysfunction, sexual aversion disorder, hypoactive sexual disorder, and sexual arousal disorder after vulvectomy, more prevalent in the older women. Those women who were sexually active before vulvectomy and who ceased sexual activity after surgery were more likely to report disturbances in body image, dyspareunia, orgasmic disorder, arousal, hypoactive sexual disorder, and sexual aversion disorder [70].

In summary, gynaecological cancer patients are at great risk of experiencing sexual disruptions following pelvic radiotherapy. From the single study of patients with advanced cervical cancer, it appears that the risk for severe persistent sexual dysfunctions and vaginal changes is high with no recovery over time. For early-stage cervical cancer, patients who are given adjuvant or primary radiotherapy are at greater risk of experiencing sexual disruption than patients treated with surgery only. There is no available data supporting a common claim that combined treatment with surgery and adjuvant radiotherapy results in more severe sexual dysfunction or other adverse effect compared to radical radiotherapy (external beam pelvic radiation combined with brachytherapy).

There is a serious paucity of data regarding sexual functioning in endometrial cancer patients. No studies have used validated questionnaires designed to evaluate sexual dysfunction and sexual dysfunction was never the primary outcome. Conclusions regarding sexual functioning in endometrial cancer patients should therefore be drawn very cautiously. It has been suggested that sexual functioning does not play a great role in the lives of endometrial cancer patients since they are old [67]. However, this view represents a preconceived discriminative notion that older women are not interested in sex and should not preclude further studies in the field.

Rectal Cancer

Comparatively less data are available concerning the impact of radiation on the sexual functioning of patients with rectal cancer. Preoperative (chemo)-irradiation is recommended in T3-T4 [tumour extending through the lamina muscularis (T3) or if the tumour extends to the peritoneal surface with local pelvic spread to organs or the pelvic wall (T4)] due to a significant effect on the local recurrence rate [76]. It is questionable whether preoperative radiotherapy has a positive effect on long-term survival; at present, the effect is limited but may improve with optimised chemo-irradiation in the future [76, 77]. For earlier stages of rectal cancer preoperative radiotherapy has also demonstrated a positive effect on the loco-regional recurrence rate, however, this did not turn into a convincing survival effect. There is evidence that preoperative (chemo)-irradiation is *not* followed by an increase in sphincter-conserving procedures and causes significant more pelvic and perineal wound infection besides late rectal and sexual dysfunction [9, 76]. Like gynaecological cancer patients, most patients who undergo treatment for rectal cancer, prefer being confronted with a risk of sexual problems prior to the treatment. In the study of da Silva et al. 81.4% of the women

stated it to be extremely or somewhat important, when asked about the importance of discussing sexual issues [78].

Lange et al. did a longitudinal study to determine the prevalence of and identify risk factors for sexual dysfunction after rectal cancer treatment [47]. They included 990 patients of whom 365 were women. They all had resectable tumours and were assessed before treatment and thereafter repeatedly up to 24-month post-treatment. Fifty per cent of the patients had preoperative radiotherapy and 73% of the patients had a temporary or definite stoma. A non-validated questionnaire was used. Before treatment, 51.7% of the women were sexually active, dropping to 32.5% 3 months after treatment and a further decrease to 18.4% being sexually active at 2-year post-treatment. Increasing age was the only negative prognostic factor for being sexually active. Sixty-two per cent of the women reported either newly developed sexually dysfunctions or aggravation of pre-existing sexual dysfunctions after treatment. Preoperative radiotherapy was the only significant risk factor. For nearly 60% of the women, both dyspareunia and vaginal dryness either developed or worsened compared to before treatment with the presence of a stoma being the only significant risk factor [47].

Similar deterioration in sexual functioning was reported in the cross-sectional study of long-term survivors of rectal cancer by Hendren et al. [26]. Despite the use of nerve-sparing surgery and just under 40% of the women having had adjuvant pelvic radiotherapy, 29% of the women reported that "treatment made their sexual life worsened" with adjuvant radiotherapy being significantly associated with this statement. Women, who reported that treatment made their sexual life worsened, mentioned several reasons: they were afraid that the ostomy would make noise, they were ashamed of their body, they believed their partner was reluctant to have sex, they believed that their partner found them less attractive and was afraid of hurting them, and 94% of the women reported a loss of sexual spontaneity [26]. Fifty-three per cent of the women reported "new" sexual problems arising after treatment that were not present before treatment. Thirty-one per cent of the patients responded positively that they had been sexually active during the past 4 weeks compared to 63% before the treatment of their rectal cancer. The sexually active women reported superior quality of life than those not being sexually active. The FSFI was used for assessment of sexual functioning [55]. Compared to scores from control women in validation studies of the FSFI [55, 79], the women who underwent treatment for their rectal cancer reported considerably more sexual dysfunction in all domains; desire, arousal, lubrication, orgasm, satisfaction, and pain with even lower scores than those women who were included in the validation study with established sexual dysfunctions [26]. Lubrication problems was reported by 56%, orgasm problems by 35%, libido problems by 41%, arousal problems in 29%, and dyspareunia by 46% with even higher prevalence in the selected group of 16 women who reported new sexual problems arising after treatments [26].

Marijnen et al. examined the impact of short-term preoperative radiotherapy on quality of life and sexual functioning in 365 women with rectal cancer over time up to 24 months after surgery with or without preoperative radiotherapy [27]. In both groups an improvement was reported regarding being sexual active over time. However, while 90% of those treated with surgery only returned to being sexually active, this was the case for 72% of those who received adjuvant radiotherapy. For the latter group, sexual functioning as an overall measure was significantly worse for all time points compared with the non-radiated group. However, due to the use of a non-validated questionnaire, very limited details regarding specific sexual dysfunctions were reported [27].

Pietrzak et al. reported no differences in quality of life as measured by the EORTC Quality of Life Questionnaire C30 [80] between short-term radiotherapy and long-term chemo-radiation for rectal cancer. However, compared with Danish female population-based norms, provided by the EORTC [81] and adopting a conservative interpretation of a clinical significant differences with at least a 10-point difference on a 0–100 scale [82], significant deteriorations was found in both radiation groups regarding global quality of life,

physical, role, emotional, and social function, besides significant more fatigue, insomnia, appetite loss, constipation, diarrhoea, financial difficulties [48]. Sexual functioning was assessed with one non-validated item: "Did your health status and/or treatment cause your sexual life to decline?" Thirty-eight per cent of the patients in the chemoradiation group responded "a lot" while 15% in the short-course radiation group did so.

As it appears, although data are still limited in female rectal cancer patients, there is a clear indication that women who undergo treatment for rectal cancer are at risk of developing severe sexual dysfunctions and that adjuvant pelvic radiotherapy add negatively to this risk. Lately, the EORTC quality of life group has revised the EORTC Quality of Life Questionnaire Colo-Rectal module (QLQ-CR38) [83] into a short-form module; the CR-29 [84]. Only two items assess sexual functioning in this questionnaire: one item on the extent of sexual interest and one item on pain/discomfort during sexual intercourse. The authors suggest using an additional, more comprehensive questionnaire on sexual dysfunction in studies of treatment effects to obtain more valid results on sexual dysfunction [84].

Anal Cancer

Although some discussions exist about the optimal treatment of very small anal tumours, there is agreement that the introduction of primary radical radiotherapy and concomitant chemotherapy for anal carcinoma has had a survival benefit besides conserving the sphincter [85–87]. The sphincter-conserving approach was also assumed to improve quality of life. However, since hardly any data exist on quality of life issues from the period where abdominoperineal resection was the treatment of choice for anal cancer this assumption will never be proved. At present, there are conflicting data regarding the impact of radiotherapy on the anal cancer patient's quality of life including sexual functioning [12, 25, 86, 88–90]. Further, while some centres prefer treatment with combined external beam radiation with external boost to the perineal or pelvic region, other centres prefer to use perineal implants and interstitial irradiation [25, 91]. Irrespective of the boost modality, pelvic organs are at risk for late radiation adverse effects in anal cancer patients. No prospective studies have evaluated the impact of radical radiotherapy and concomitant chemotherapy on the sexual functioning in female anal cancer patients using well-validated questionnaires designed to assess female sexual dysfunction in details. In the following, results from three small studies will be summarised [12, 25, 90]. Assessment of sexual functioning was done using single items on sexual interest, sexual enjoyment, vaginal dryness and pain at intercourse as part of the EORTC QLQ-CR38 [83].

Jephcott et al. compared a selected group of 50 (37 women and 13 men) long-term anal cancer survivors with age- and gender-matched volunteers [12]. All patients were treated with external beam radiation and external boost with concomitant chemotherapy. Results were not separated on gender except for sexual functioning. Significant and clinical relevant differences were reported in several quality of life domains; physical, role, and social functioning besides global quality of life scores and fatigue, appetite loss, constipation, diarrhoea, dyspnoea and financial difficulties. While sexual interest and extent of sexual activity resembled the scores of the volunteers, severe deterioration was reported regarding sexual enjoyment, vaginal dryness and pain during sexual intercourse [12]. Although no attempt was done to account for treatment effect or late adverse effects, the results compare very well with the clinical impression of late effects affecting the vaginal mucosa, the vaginal entrance and the perineal region in female anal cancer patients and impacting negatively on several aspects of the woman's sexual life.

Allal et al. included 41 selected long-term anal cancer survivors (35 women and 6 men) and compared them with population-based female norms from the literature [25]. Most patients had interstitial brachytherapy adjuvant to external beam pelvic or perineal radiation and concomitant chemotherapy. A very high prevalence of grade 2–4 complications were observed and the

severity of late complications significantly affected the quality of life of the patients in several aspects, e.g. social and role functioning, diarrhoea and financial difficulties. Compared to the scores of the volunteer sample in the study of Jephcott et al. very low scores on sexual interest and activity was reported in the study of Allal et al. [25]. However, very few patients responded to the items on the sexual enjoyment, vaginal dryness and pain (8 of 35 women). Hence, these results seem unreliable which is also noted by the authors. In the study of Oehler-Jänne et al. 61 women with stage I–IV anal carcinoma were included [90]. They compared toxicity between external boost and interstitial brachytherapy and did not find any differences in late adverse effects between the two groups. They concluded that both radiotherapy modalities were well tolerated, however, no norm data were included for comparison. Comparing the results of Oehler-Jänne et al. with responses from the healthy controls in the study of Jephcott et al., it is obvious that patients reported significant deterioration in several quality of life aspects that presumably can be ascribed to radiotherapy. Again, taking a conservative interpretation for a clinical meaningful difference of 10 points on a 0–100 scale in the functioning and symptom scales of the EORTC modules used, significant deterioration in sexual enjoyment, vaginal dryness and dyspareunia were reported in both groups [90].

Hence, although there is very sparse valid information regarding the impact of radiotherapy on the sexual function of female anal cancer patients, it seems evident that anal cancer patient should be considered at risk for severe disruptions in her sexual life.

Bladder Cancer

Radiotherapy in combination with chemotherapy is used as an organ-sparing approach for invasive bladder cancer at some institutions. There is agreement that patients should be selected carefully and that candidates for bladder preservation with the highest success rate are patients with solid T2 tumours or early T3 tumours. A trimodality approach with trans-urethral bladder resection preceding radiotherapy and chemotherapy is recommended [92, 93]. A radical surgical approach is still considered as the standard treatment for invasive bladder cancer at most institutions. In women, an anterior exenteration may be performed, including the bladder, urethra, uterus and the ventral vaginal wall although the genitals can be spared in selected cases. Further, urinary diversion is done with a segment of bowel and a continent or non-continent conduit is performed. While there is evidence that men experience severe sexual disruptions after radical cystoprostatectomy for bladder cancer, the literature concerning female sexual dysfunction after both surgery and radiotherapy is sparse. Here, the focus is on the few women included in studies of quality of life after bladder-conserving radiotherapy for bladder cancer [49–51, 94, 95]. No studies have focused especially on female bladder cancer patients and their quality of life and the number of women included is unfortunately often too small to make any conclusion.

Zietman et al. and Caffo et al. included 12 and 6 women, respectively, in their studies of quality of life in long-term survivors after trimodality treatment of bladder cancer. Only two and three women, respectively, completed the sexual function items so both authors concluded that the results were inadequate. Both studies reported better quality of life after the bladder-conserving approach than after conventional surgery [50, 51]. Fokdal et al. did not either include a sufficient number of female patients in their study of quality of life after radical radiotherapy for bladder cancer [49]; seven women of whom only two were sexually active. Five of seven women reported lack of sexual desire and two reported that radiotherapy had a moderate impact on their present sexual life [49]. Henningsohn et al. included a large number of patients in their cross-sectional study of long-term bladder cancer survivors; however, only 45 women were treated with cystectomy and 13 women were treated with irradiation [94, 95]. Both studies concentrated on distressful symptoms following either surgery or radiotherapy. However, the majority (62%) of those patients who underwent surgery had preoperative pelvic

irradiation although to a lower total dose. In women, the genitals were only removed in case of macroscopically local spread of the bladder cancer. Again, very limited information regarding the sexual functioning of the women included could be extracted: Ten out of ten women responding and treated with radiotherapy reported no or low sexual interest and none were sexually active. Severe sexual disruptions were reported for the male patients after both treatments; more severely after surgery. Substantial distress was related to the sexual limitations [94, 95].

As it appears, due to underreporting no conclusion can be drawn regarding the impact of pelvic radiation on female sexual dysfunction in female bladder cancer patients. However, urologists and oncologists should pay attention to the literature on the impact of pelvic radiation in other female cancer patients and inform their patients accordingly.

Intervention for Female Sexual Dysfunction

Sex therapy for female sexual dysfunction is described elsewhere. Here, a summary on the physical aspects of sexual dysfunction in women following pelvic radiotherapy is given [19]. Interventions mainly relate to both acute and chronic effects of radiation on the vaginal wall and the vulva/perineum. However, attention should also be drawn to radiation-induced ovarian failure which, in premenopausal women, may result in decreased vaginal lubrication and vulvovaginal atrophia and hence further aggravate the effect of radiation. Further, women with induced premature menopause report a significantly higher rate of hypoactive sexual disorders than their age-matched controls.

Premature Ovarian Failure

The existence of an androgen-deficiency syndrome in younger women with induced menopause as a result of surgery, radiation and/or chemotherapy is discussed in the literature. Several randomised controlled studies in women with induced menopause and hypoactive sexual disorders have shown that combined treatment with oestrogen and methyl-testosterone significantly improved both degree and frequency of the women's sexual interest and enjoyment compared to women who received oestrogen only [96–100]. Although these studies are mainly done in women with surgically induced menopause, results may very well adapt to women with premature ovarian failure as a result of pelvic radiation.

Hormone Replacement Therapy

While several studies have found a positive effect of hormone replacement therapy (HRT) on sexual problems in menopausal women [101–104], very few studies have evaluated the effect of HRT following pelvic radiation for cancer. In the prospective observational study of Jensen et al. those women receiving HRT after radiotherapy for their cervical cancer, had a lower risk of having reduced sexual interest and of becoming sexually inactive [14]. This may be taken as an indirect indication of a positive effect of HRT. Ploch et al. found that HRT improved the quality of life and reduced vaginal discomfort in irradiated cervical cancer patients without having a negative influence of their risk of recurrence or survival [105].

Post-irradiation Vaginitis/Vaginal Mucositis

Oestrogen

Following radiation of the vagina there is a loss of virtually all epithelium in the areas receiving the maximal surface radiation. This loss persists through the first 3–6 months after radiation and is followed by a period with early epithelial replacement consisting of a thin and incomplete layer of basal cells. The epithelial covering becomes progressively more complete while inflammatory changes gradually diminish and

by 2 years the epithelium assumes a nearly normal structure. The use of oestrogen following completion of radiotherapy is thought to have a significant effect on the epithelial regeneration. While there is clear evidence that local and systemic oestrogen have a significant positive effect on atrophic vaginitis, vaginal dryness and dyspareunia in the healthy menopausal woman [103, 104, 106], the literature concerning women with cancer is limited [107–109] and no intervention studies could be identified from the past two decades. In the two small randomised studies of Pitkin et al. the effect of 0.01% dienestrol, one application three times a week, were evaluated in women who had undergone primary radiotherapy for cervical carcinoma. The maturation of the vaginal epithelium was evaluated with smears, the degree of bleeding during intercourse and dyspareunia was evaluated by interview and the vaginal calibre was assessed clinically. The odds ratio for improvement in dyspareunia in patients compared with placebo was 3.81 (95% CI 1.19–12.16) favouring the oestrogen cream [19]. It is concluded that local oestrogen accelerate the regeneration of the vaginal epithelium especially with long-term use, it decreases the incidence and severity of dyspareunia and decreases the risk of vaginal narrowing while no effect on vaginal bleeding was found [107, 108].

Benzydamine

This anti-inflammatory compound for topical use has a documented anti-septic positive effect for head and neck radiation reactions. It acts by stabilising cells and lysosomal membranes and by inhibiting the synthesis of prostaglandins. It is absorbed well and reaches a higher concentration in the underlying inflamed tissue. In addition it has analgesic, anaesthetic and antimicrobial effects. In gynaecological use benzydamine is applied as a vaginal douche once or twice daily in a 0.1% concentration or as with the sales name "Tantum Rosa" powder, diluted with water and application of a soaked tampon in the vagina for 15–30 min. Four small studies have evaluated the effect of benzydamine on the effect of acute radiation-induced vaginitis in cervical cancer patients [110–112]. They all found a significant effect on the vaginal adverse affects; burning sensation, vaginal tenderness, oedema, and pruritus after 15 days of use and in the study of Kanaev et al. also found a significant effect 2 months after completion of the treatment. The odds ratio for the resolution of acute radiation vaginal mucositis with the use of benzydamine versus placebo was 12.31 (95% CI 3.13–48.48) [19, 110, 111].

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy acts to stimulate collagen formation at the wound edges through elevation of local tissue oxygen tension. The repair of a radio-necrotic area is limited by the reduced blood supply. Hyperbaric oxygen therapy provides a rich capillary bed in surrounding radiation-damaged tissue and thereby allows re-epithelisation to occur. Three small studies have evaluated the effect of hyperbaric oxygen therapy on radio-necrosis of the perineum and the vagina after radiotherapy for gynaecological, anal, rectal, or bladder cancer [113–115]. All patients had failed to respond to conservative therapies. In two studies there was a marked positive effect of hyperbaric oxygen therapy, especially on vaginal vault necrosis and fistula [114, 115] whereas the effect on perineal lesions was less convincing. In one study of 12 gynaecological cancer patients no healing response was observed [113]. Treatment with hyperbaric oxygen has a sound theoretical basis; however, the results are essentially based on weak evidence from small selected series. Hyperbaric oxygen therapy remains a treatment option that is worth trying in selected cases especially with vault necrosis resistant to conservative treatment.

Vaginal Dilators

Stenosis of the vagina occurs as a result of adhesion formation together with the circumferential

fibrosis of the upper vaginal tissue. Adhesions occur as a result of epithelium damage after vaginal brachytherapy. This leads to contraction of the vaginal vault and a shortened vagina. Vaginal stenosis may induce sexual problems especially related to sexual intercourse as observed in the study of Jensen et al. [14] and may ultimately preclude sexual intercourse due to complete vaginal stenosis [61]. As a means of preventing vaginal stenosis and treating established stenosis, a suggestion to resume sexual intercourse or to use a vaginal dilator together with lubricants is recommended after pelvic radiation especially if brachytherapy is applied either as intracavitary or as interstitial implants. The clinical experience is that compliance with the use of a vaginal dilator is usually low. Two studies have evaluated the effect of vaginal dilation on the risk of developing or preventing vaginal stenosis after intracavitary radiotherapy for gynaecological cancer [116, 117]. In the study of Decruze et al. the intervention group was introduced to a vaginal stent and advised to use it daily even if they were sexually active [116]. The odds ratio of developing vaginal stenosis following use of the stent was 0.1 (95% CI 0.030–0.033) compared to advice of regular sexual intercourse. The effect was maintained for a follow-up period of 1 year. Robinson et al. randomised patients to an intervention group with a psycho-educational program based on the "information-motivation-behavioural skills" model of behavioural change to increase the rate of compliance with use of a vaginal dilator. The non-intervention group received a dilator and had a brief introduction and written information [117]. Younger women attending the experimental program (44.4%) were significantly more likely to follow recommendations for vaginal dilation than those who received the control intervention (5.6%). Women, regardless of age, who received the experimental intervention, reported less fear about sex after cancer treatment. The older women who received the experimental intervention gained more sexual knowledge. There was no evidence that the experimental intervention improved global sexual health [117].

Conclusion

There is strong evidence that pelvic radiation in either modality place the woman at risk for experiencing sexual dysfunction. At present, no data can support a hypothesis of increased risk of and severity of adverse effects after combined surgery and adjuvant radiotherapy compared to radical radiotherapy alone neither in gynaecological, rectal, anal or bladder cancer patients. Women with advanced cancer have an increased risk of severe permanent sexual disruptions following radical radiotherapy. Even long-term survivors treated for early-stage cancer with adjuvant or radical radiotherapy report substantial chronic psychosexual problems influencing their relationship. There is evidence that radiotherapy is a negative prognostic factor for sexual functioning in both cervical and rectal cancer patients and that being sexually active has a positive influence on the quality of life. There is very limited knowledge concerning the impact of radiotherapy on the sexuality of female bladder and anal cancer patients. This should not be taken as evidence of a reduced risk of sexual disruptions in these patient groups as rather it reflects a severe paucity of research in the area. Only few and small series of intervention studies for sexual problems after radiotherapy have been conducted. They document an effect of vaginal oestrogen, benzydamine, vaginal dilators, and hyperbaric oxygen therapy on acute and late vaginal radiation effect. However, as pointed out by the patients themselves, information about and communication with the patient and her partner about potential sexual problems following pelvic radiation may be the first and most important step towards sexual rehabilitation after cancer treatment.

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Chapter 33
Impact of Chemotherapy and Hormone Therapy on Female Sexual Health

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Introduction

In both sexes, diagnosis and treatment of cancer have a crucial impact on each dimension of quality of life and well-being, including sexuality [1]. Facing a cancer is a major distress and it is absolutely normal that sexual difficulties may occur during the early course of the disease. However, the strong improvement of the survival rate raises the issue of managing long-term consequences for patients and their partners. Human sexuality encompasses much more than sexual function and is highly dependent on sexual identity and relationship during the entire life span. The burden of cancer has, indeed, a multidimensional impact on sexuality because it affects not only the biological substrates of sexual response, but also intrapersonal and interpersonal aspects which are essential for feeling intimacy in a relationship [2]. Previous experiences and socio-cultural norms may also modulate the clinical relevance of sexual symptoms and the level of distress. On the other hand, preserving sexual and emotional intimacy may reduce the negative impact of cancer favoring the patient's positive attitude toward the awareness of being a day by day survivor, without experiencing a sense of guilt, shame, betrayal, loss of hope, etc. [3–5].

The sexual side effects of cancer in women are multifactorial depending not only on the type, stage and prognosis of the disease, but also mostly on treatment modalities which include surgery, radiation and chemotherapy. Physical and mental impairment, body image concerns, mood disorders, loss of fertility and femininity, lack of pleasure in an ill body, as well as personal history, previous self-esteem and satisfaction with sexuality, coping strategies, family and couple dynamics, partner's and social support, quality of the relationship with the health care provider and other psychosocial issues have a strong influence on sexual function in women of any age, but especially in younger patients who have still to fulfill life cycle stage-related goals [6, 7].

Here, we will focus our attention on the impact of chemotherapy and other hormone therapies on female sexual health with particular regard to breast and gynecological malignancies. In addition, we will summarize the most relevant management strategies for female sexual symptoms related to chemotherapy and hormone therapy.

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Impact of Chemotherapy on Female Sexual Health

Advances in the diagnosis and treatment of cancer from childhood to adult age have greatly increased the life expectancy of premenopausal women. Chemotherapy can cause premature ovarian failure resulting in adverse effects of hormone deficiency [8]. The ovaries are, indeed, very sensitive to cytotoxic treatment, especially to alkylating agents, in addition to taxanes, and to higher cumulative doses. Treatment with cyclophosphamide (CYC) confers up to a 40% risk of ovarian failure in women of reproductive age. The probability that a woman will enter menopause as a result of chemotherapy increases dramatically at the age of 35 and it can be roughly estimated that each month of chemotherapy translates into 1.5 years of lost reproductive life. It is difficult to predict the degree of ovarian damage from a particular chemotherapy regimen and, even though chemical markers of ovarian reserve are promising, large prospective studies are needed before we can predict the maintenance of reproductive capacity in cancer survivors [9–13].

Reproductive function protection requires close cooperation between oncology departments and assisted reproduction centers. Based on the available studies, premenopausal women facing chemotherapy should be counseled about ovarian preservation options including the use of GnRH agonists (GnRHa) which appears to improve ovarian function and the ability to achieve pregnancy following chemotherapy, even though results are still inconclusive [14, 15]. Indeed, the only established method of fertility preservation is embryo and/or oocytes cryopreservation according to the Ethics Committee of the American Society for Reproductive Medicine (2005), but this option requires the patient to be of pubertal age, have a partner or use donor sperm, and be able to undergo a cycle of ovarian stimulation, which is not possible when the chemotherapy has to be initiated immediately or when stimulation is contraindicated according to the type of cancer. For patients who need immediate chemotherapy, cryopreservation of ovarian tissue for future in vitro maturation, autotransplantation or xenotransplantation is the only possible alternative [16].

The sudden loss of ovarian hormones from chemotherapy and of course from surgery, as it occurs in the treatment for many gynecological cancers, especially ovarian in origin, significantly contributes to sexual dysfunction [17]. In addition, some aggressive surgical techniques, such as radical hysterectomy, bowel resections and anterior/posterior exenterations for advanced gynecologic malignancy can result in the impairment of neurovascular and neuromuscular substrates of the sexual response and significantly affect self-esteem. Moreover, pelvic radiation may be indicated in the treatment for cervical and some endometrial cancers causing skin fibrosis and vaginal narrowing and shortening [1].

Oncological surgeons are starting to consider not only fertility issues but also sexual health concerns in women. Therefore, surgical techniques are becoming less aggressive without impact on survival. However, nerve-sparing approach and other strategies to preserve the biological substrate of the sexual response are still in their infancy and further studies are needed to understand their utility in minimizing long-term negative sexual consequences [18].

According to the National Cancer Institute, research shows that approximately half of women who have been treated for breast and gynecologic cancers experience long-term sexual dysfunction [1, 19].

It is worth remembering here that the study of female sexual health is a rapidly evolving field in which sensitive diagnostic instruments to identify the main outcome sexual measures have been only recently developed [20]. That being so, experts in the field of sexual medicine are under the impression that the clinical relevance of sexual symptoms in women with cancer is higher than that reported in trials investigating the impact of specific compounds on quality of life and sexual functioning because of the lack of appropriate sexual assessment tools [21]. In any

case, the major insult to sexual function as a consequence of chemotherapy derives from the loss of sex hormones, both estrogens and androgens, which are of paramount importance for genital receptivity, mental desire and awareness, and general responsiveness [22]. In addition, neuroendocrine adaptation due to the deficiency of sex hormones involves a complex rearrangement of a vast array of neurotransmitters, neuromodulators and other relevant neuroactive mediators namely to thermoregulation, mood, pain threshold and cognition [23]. Indeed, estrogens and androgens exert both organizational and activational effects at multiple levels of the nervous system, and their actions are mediated by nongenomic as well as direct and indirect genomic pathways. In addition to affecting the hypothalamus and other brain areas related to reproduction, sex hormones are involved in a multitude of nonreproductive brain functions and therefore, hormonal withdrawal after natural or surgical menopause can lead to a host of changes in brain function and behavior [24].

Menopausal symptomatology, such as hot-flushes, night sweats, chronic fatigue, etc., may be variably expressed in every single woman and may also include sexual symptoms such as modification of sexual desire, impairment of central arousal and reduced perception of orgasm and satisfaction. On the other hand, estrogen deficiency significantly contributes to uro-genital and vaginal involution by reducing epithelial cell proliferation, paracellular permeability, smooth muscle content and by inducing vascular remodeling and changes in innervation. Vaginal pH shifts from acidic to alkaline and vaginal secretion are reduced contributing to genital symptoms of dryness, irritation/burning, pruritis and recurrent vaginitis. In addition, urinary symptoms, such as frequency, urgency, nocturia, dysuria, incontinence and post coital/recurrent urinary infection, may be present. Over time, vaginal vault becomes pale in appearance and less elastic with loss of rugation and tissue friability followed by progressive shortening and narrowing, while the clitoris gets fibrosed and the vulvar and labial tissues lose fullness [25]. When uro-genital atrophy is present, sensation, vasocongestion and lubrication are highly damaged; thus, in sexually active postmenopausal women genital arousal may be impaired and sexual pain disorders (dyspareunia and vulvodynia) may frequently occur.

Estrogen highly orchestrates the entire hemodynamic process leading to vaginal vasocongestion and increased lubrication by affecting independently, or in association with androgens, the complex cascade of mediators involved in genital arousal [26–28]. The inadequate hormonal-dependent genital receptivity is likely to cause other sexual symptoms which contribute to amplify pain during coital and non-coital activity. Indeed, it is extremely common to observe a lack of mental arousal and a decline in sexual desire following a history of sexual pain; the consequent reduction of orgasmic capacity may, then, reduce sexual satisfaction which, in turn, negatively influences sexual motivation, activity and the couple's relationship. That being so, there is a high degree of comorbidity among sexual symptoms in menopausal women and it is important to timely recognize the "leader" symptom to avoid such cascade of negative events and to establish appropriate treatments. Indeed, if hypoactive sexual desire disorder (HSDD) is present, as a result of androgen insufficiency related to the removal of the ovaries or to chemotherapy, it is likely that the entire sexual response may be compromised, regardless of the entity of uro-genital symptoms [29]. Finally, it is likely that the "domino" effect of other menopausal symptoms, namely hot flushes and mood swings, can modulate the clinical expression of sexual symptoms [30, 31].

That being so, the impact of cancer treatments on sexual function is not only related to the direct effects of chemotherapy, surgery and radiotherapy on the neuroendocrine, neurovascular and neuromuscular components of sexual response, but it is also the results of the indirect effects on mental and physical well-being, including climacteric syndrome, weight gain, negative cosmetic side-effects, loss of attractiveness, coping strategies to the disease, emotional distress, adverse effects of psychotropic or pain medications, etc. [32–34].

As far as breast cancer therapy on women's sexuality is concerned, a study conducted some years ago in a sample of 50 Italian women, disease free and sexually active, who have undergone surgery (58% mastectomy and 42% quadrantectomy) at least 1 year previously and have completed chemotherapy and/or radiotherapy showed that 90% of the women continued sexual activity after treatment, but there was an increase in the incidence of sexual problems which resulted in a slight reduction in the quality of their sex lives. Sixty-four percentage of the women experienced an absence of sexual desire and 48% low sexual desire, while 38% had dyspareunia, 44% frigidity and 42% lubrication problems. Vaginismus, brief intercourse and female orgasmic disorder were reported by 30% of the subjects. Thirty-six percentage suffered from sexual dysfunction before treatment, which worsened in about 27%, while in 49% of women sexual problems arose mainly after chemotherapy (26%) or surgery (12%). About half of them experienced changes in the relationship with their partner [35].

In general, conservative surgical interventions and immediate breast reconstruction after mastectomy seem to be associated with a better sexual function overtime by ameliorating self-esteem, sense of femininity and couple's satisfaction. Breast insensitivity following reconstruction is reported as distressing for desire and mental arousal. However, beyond the first year after diagnosis, a woman's quality of life is more likely influenced by her age or exposure to adjuvant therapy than by her breast surgery [36–39].

Impact of Hormone Therapy on Female Sexual Health

Endocrine chemotherapy in hormone-dependent breast cancer is the key to successful intervention by reducing recurrences [40]. However, the use of GnRH analogues, tamoxifen and third-generation aromatase inhibitors (AIs), including anastrozole, letrozole and exemestane, has a short- and long-term impact on sexual function which have been difficult to quantify due to the complexity of variables conditioning human sexuality [41]. Sexual complaints after the diagnosis of breast cancer, occurring alone or in combination, are relatively common including all sexual complaints in 30–100%, desire disorder in 23–64%, arousal or lubrication concerns in 20–48%, orgasmic concerns in 16–36% and dyspareunia in 35–38% [35, 42]. Even though there are some evidences supporting a negative role of treatment-related effects, survivors' levels of relationship distress, depression and age rather than hormonal levels have proved the most significant variables affecting arousal, orgasm, lubrication, satisfaction and sexual pain [5, 43]. In any case, experiencing abrupt menopause as a result of chemotherapy or ovarian suppression with GnRH analogs at young age is a risk factor for sexual problems, and the rates of dysfunction are greater than that would be expected in a healthy, community sample of women of the same age range [44–49].

Tamoxifen, a first-generation selective estrogen receptor modulator, is prescribed to block estrogen receptors in the breast, but it also acts as a weak estrogen agonist on the uterine lining requiring monitoring for adverse endometrial effects. Tamoxifen results in a spectrum of abnormalities involving the genital tract, including pain, burning or discomfort during intercourse [50] in spite of its ability to increase the vaginal maturation index [51]. In addition, mild decrease in sexual desire in women given tamoxifen has been reported but negative sexual side effects were not confirmed in women over 50 years [52–54]. A randomized study conducted to compare the effect on sexual activity of a GnRH agonist alone and in association with tamoxifen showed that combination therapy was less negative supporting the estrogenic action of tamoxifen on the genital tract [55]. On the other hand, in premenopausal women adding hormone therapy with tamoxifen or GnRH analog to chemotherapy does not seem to further impair sexual function, while after termination of endocrine therapy sexual dysfunction diminished in those women without chemotherapy [48].

Postmenopausal women with breast cancer are increasingly treated with third-generation AIs because they produce profound suppression of estrogen in all tissues by blocking the cytochrome P450 aromatase complex that converts androgens to estradiol, which underlies the estrogen receptor-positive mammary carcinogenesis. In addition, AIs induces less gynecological adverse events in comparison with tamoxifen. However, the complete prevention with AIs of any estrogen production in the female body exacerbates menopausal symptoms and induces intense vaginal dryness and moderate to severe dyspareunia with subsequent loss of sexual desire in many women [56]. A highly elegant review has recently summarized the impact of AIs on sexual functioning underlying that to date only five studies have investigated such crucial topic for quality of life of breast cancer survivors [57]. A randomized controlled study comparing exemestane with tamoxifen showed that 48% of women in the AI group reported significantly reduced vaginal lubrication, compared to those women using tamoxifen (52%) [58]. Similarly in the MA17 trial the reported sexual outcomes were significantly poorer in the AI (letrozole) group, compared to the placebo group, but no specific information on vaginal lubrication and dyspareunia was assessed [59]. The ATAC trial found significantly increased levels of vaginal dryness, dyspareunia and a reduction in libido among women receiving an AI (anastrozole), compared to tamoxifen, without reporting differences in quality of life between the two groups [60]. These findings are consistent with the results obtained comparing the acute effects of tamoxifen and third-generation AIs (letrozole/anastrozole) on menopausal symptoms including dyspareunia which increased after 3 months in women receiving an AI compared to tamoxifen [52]. At variance, the Intergroup Exemestane Study (IES) found no significant differences in quality of life and sexual functioning in women receiving an AI but the validity of these findings are questioned by the switchover to exemestane after receiving 2–3 years of tamoxifen [61]. Collectively, since the use of AIs is increasing, these results support the need to perform rigorous studies to assess the impact of the use of AIs on sexual functioning using suitable validated instruments in order to identify the more vulnerable women for effective management and long-term compliance to endocrine chemotherapy.

Management Strategies for Female Sexual Symptoms Related to Chemotherapy and Hormone Therapy

There is currently a paucity of therapeutic interventions to address sexual problems related to chemotherapy and hormone therapy. An accurate sexual history and a focused clinical evaluation are essential to understand the potential causes and, eventually, to establish tailored strategies to manage the complexity of contributors driving sexual response cycle.

Very elegant and comprehensive reviews on the crucial topic of "how to manage" women in order to mitigate sexual problems related to cancer underlined counseling as an imperative step at any stage of the disease [1, 8, 42, 56]. Any kind of interventions appeared to be most effective when started near the time of diagnosis and initiation of treatment. Education and lifestyle interventions coupled with physical therapy including pelvic floor exercises, medical devices and other strategies to learn new sexual expertise are mandatory together with individual and couple-based psychosexual interventions for cognitive reconstruction [56, 62–64].

Recently, Brotto et al. used a brief, three-session psycho-educational intervention (PED) in 22 women with early stage gynecologic cancer who had arousal disorder and found a significant positive effect of the PED on sexual desire, arousal, orgasmic satisfaction, sexual distress, depression and overall wellbeing, and a trend toward significantly improved physiologic genital arousal and perceived genital arousal [64].

Finally, a recent meta-analysis reported that the strongest positive effects in women with cancer were couple focused and included educating

both partners about the woman's diagnosis and treatment, promoting couples' mutual coping and support processes, and including specific therapies to address sexual and body image concerns [65].

As far as pharmacological treatments are concerned, options are limited especially in women with premature ovarian failure and hormone-dependent malignancies. In general, non-hormonal treatments are the first-line recommendation to improve vaginal dryness and dyspareunia. Commercial vaginal moisturizers and lubricants with different characteristics are available and may be very helpful [8, 56]. In a comprehensive menopausal assessment intervention program designed to assess and alleviate the three main menopausal symptoms, hot flushes, vaginal dryness and stress urinary incontinence, the use of moisturizers and lubricants was included in an individualized plan involving education, counseling, pharmacologic/behavioral interventions and psychosocial support. Vaginal dryness was reported as a problem by 71% of women with breast cancer at baseline. Following the completion of the intervention, sexual functioning improved significantly across all domains of sexual functioning (sexual attractiveness for self and partner, interest in sex for self and partner, frequency of sex, arousal, lubrication and orgasm) suggesting that the improvement of vaginal dryness can be beneficial to several dimensions of the sexual response [66]. Another innovative intervention study involves the use of olive oil as a lubricant during intercourse, pelvic floor muscle relaxation exercises to manage dyspareunia and a vaginal moisturizer to ameliorate vaginal dryness and thus alleviate sexual difficulties experienced following adjuvant treatment for breast cancer. If followed for 12 weeks, such physical approach has the potential to improve the symptoms of vaginal dryness and dyspareunia, specifically in women on AIs [67]. These women may be more problematic. Indeed, even low-dose topical vaginal estrogens are contraindicated due to the small but significant increase of circulating plasma estradiol levels, at least in the short term, and their use is a patient-centered decision in consultation with the oncologist [68, 69]. The prescription of local vaginal DHEA may offer promising results for women treated with AIs which prevents the intravaginal accumulation of estrogens. Indeed, in a phase III randomized controlled trial of 216 postmenopausal women without breast cancer, DHEA improved all domains of sexual function by increasing maturation of epithelial cells and decreasing vaginal pH without significantly increasing serum estrogen or testosterone levels, with all steroid values remaining in the range seen in postmenopausal women [70–72].

However, it is important to keep in mind that topical estrogen therapy with conjugated equine estrogen cream, estradiol tablets, pessaries and rings, estriol cream and suppositories, not available in the US market, at the recommended doses to avoid significant systemic absorption may be used in all the other women who suffer from vulvo-vaginal atrophy [73]. In addition, survivors with premature menopause who had a non-hormonal dependent cancer have to be treated with hormone replacement therapy (HRT) at least until the mean age of natural menopause and unwarranted cancer fears should be avoided. Indeed, with the exception of meningioma, breast and endometrial cancer, there is no biological evidence that HRT may increase the recurrence risk [44]. By contrast, the "Hormonal Replacement Therapy after Breast Cancer is it safe?" trial (HABITS) investigating the use of HRT in women with a history of breast cancer was terminated after a median of just 2.1 years because of a statistically significantly higher recurrence of breast cancer in the treated group [74]. Although subsequent studies have not replicated this finding [75, 76], the HABITS trial [74] and a more recent trial with tibolone (LIBERATE), a special kind of hormonal replacement [77], have discouraged the use of HRT in women with a history of breast cancer. Therapeutic non-hormonal alternatives may be proposed to cancer survivors with severe climacteric symptoms [8, 78].

In light of early studies suggesting a protective role of androgens in breast cancer women, the use of testosterone can be hypothesized to treat survivors with hypoactive sexual desire disorder (HSDD) and some cases of women

treated with androgens have been reported in the literature [79, 80]. However, the safety of androgen replacement in the breast cancer population and in women with other malignancies has not been adequately studied. A recent randomized placebo-controlled phase III crossover clinical trial randomly assigned 150 partnered postmenopausal women with a history of cancer who were reporting a decrease in sexual desire to a 10-mg equivalent testosterone dose in a cream base [Vanicream (PSI, Rochester, MN, USA), 2% testosterone] or placebo for 4 weeks each. It was demonstrated that women who were on active testosterone cream had higher serum levels of bioavailable testosterone than did the women on placebo, but the average intra-patient sexual desire change from baseline to weeks 4 and 8 was similar in both arms [81]. Other potential non-hormonal treatments to relieve HSDD may involve neuroactive compounds acting on the balance of neurotransmitters with a prosexual effect. However, the safety of buproprion, a compound with both dopamine and norepinephrine reuptake inhibition, to relief HSDD in women with cancer is not established [82]. In order to improve intensity and duration of genital stimulation for women with arousal and orgasm problems several types of vibrators are available. The Eros Clitoral Therapy Device (UroMetrics, St. Paul, MN, USA), a small clitoral vacuum pump used for women with and without arousal disorder to increase sensation, vaginal lubrication, orgasmic attainment and greater overall sexual satisfaction, has been approved by the US Food and Drug Administration (FDA) and may be beneficial in selected women [83].

In conclusion, the recognition that sexual symptoms are fairly common following a cancer diagnosis and are often exacerbated by adjuvant hormonal and non-hormonal treatments is an important part of the oncologic care and it is not a neglected area anymore [84]. Given the multifaceted components of women's sexuality and the multitude of variables related to cancer diagnosis and treatment, the ideal approach to sexual function and dysfunction remains to be established. However, there is no doubt that the increasing knowledge in the field of sexual health will soon lead to the development of multidimensional strategies for individualized care of women and their partners. Increasing the quality of life after having increased the life expectancy appears to be the best wish for future generations of patients and health care providers.

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Chapter 34
Impact of Androgen Deprivation Therapy on Men's Sexual Health

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Keywords Androgen Deprivation Therapy • Mechanism of Action • Sexual Side Effects • Testosterone • Production • Production Suppression • Androgen Insensitivity • Sex-Determining Region (Sry) • Testis-Determining Factor (TDF) • Sertoli Cells • Leydig Cells • Dihydrotestosterone (Dht) • 5(Alpha)A-Reductase • External Genitalia • Hypogonadism • Testosterone Levels • Physiology Of Testosterone • Hypothalamus-Hypophysis-Testicle Axis • Gonadotropin-Releasing Hormone • Luteinizing Hormone • Adrenal GlAnd • Dehydroepiandrosterone • Dehydroepiandrosterone Sulfate • Androstenedione • Progesterone • Pregnenolone • 17-Hydroxyprogesterone • 17-Hydroxypregnenolone • Medical Castration • Surgical Castration • Lhrh Agonists • Antagonists • Anti-Androgens • Androgen Receptors Blockers • Bilateral Orchiectomy • Ketoconazole • Aminoglutethimide • Medical Adrenalectomy • Erectile Function • Penile • Structural Damage • Girth • Length • Corpora Cavernosa Structural Damage • Penile Veno-Occlusive Dysfunction • Penile Prosthesis • Ejaculation • Premature • Delayed • Ejaculatory Dysfunction • Libido • Decreased • Loss of • Genital Changes • Late-Onset Hypogonadism • Intermittent Androgen Deprivation Therapy • Continuous Androgen Deprivation Therapy • Penile Rehabilitation • Phosphodiesterase Type 5 Inhibitors (Pde5i) • Vacuum Erectile Device (VED) • Venous Leakage

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Introduction

The importance of androgens in the maintenance of homeostasis in a male has been well established. Even in the earliest stages of embryological development, androgens play a vital role in sex differentiation. This is most evident in patients who lack androgen receptors or have decreased androgen sensitization, leading to sexual dimorphism [1]. The association of aging with a decline in sexual health has been acknowledged since the nineteenth century, when Brown Séquard began to inject himself with a mixture of dog and guinea pig testicular extracts to "rejuvenate himself" [2]. He claimed this mixture would improve his physique as well as his mental capacity. This background generated enormous interest in finding the "fountain of youth." It was not until 1935 that Butenandt, Ruzicka, and Gyula successfully and independently synthesized a hormone named testosterone, for which Butenandt and Ruzicka received the Nobel Prize of Medicine in 1939 [3]. Public interest grew in the applications of this new "silver bullet" for a wide range of ailments, ranging from sexual dysfunction to age reversion. Around the same time, an astute clinician/researcher, Charles B. Huggins, reported that "prostatic epithelium undergoes atrophy when androgen hormones are

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greatly reduced in amount." He then concluded that "significant improvements should occur in the clinical condition of patients with far advanced prostate cancer subjected to castration" [4]. For his pioneering works, he was awarded the Nobel Prize in Medicine in 1966 [3]. Since then, numerous studies have confirmed these findings. Androgen deprivation therapy (ADT) has since been a powerful treatment option for those with prostate cancer.

It is estimated that more than 189,000 new cases of prostate cancer are diagnosed each year [5]. Around 10% of patients will receive ADT at some point during their disease course [5]. Despite its effectiveness in battling prostate cancer, ADT is a double-edged sword as its side effects are numerous, ranging from cognitive deficits to sexual dysfunction. This chapter aims to elucidate the impact of ADT on male sexual health.

Role of Testosterone on Male Sexual Health

Since its discovery in the 1930s, much has become known about the integral role of testosterone in the development and maintenance of homeostasis of the male. Testosterone involvement ranges from the embryological differentiation and masculinization of the male phenotype as well as maintenance of cognition, memory, and sexual function. Many of these have been learned through observation of babies who were born with androgen insensitivity and men who display physiological or acquired hypogonadism. Despite these findings, more research is still needed to define the complex and intertwined involvement of testosterone in the male homeostasis.

From the embryological standpoint, developmental commitment to a male body habitus begins with the fertilization of a Y chromosomal sperm with an X oocyte. Within the Y chromosome, a sex-determining region (SRY) which codes for the testis-determining factor (TDF) drives a series of embryologically sex-differentiated changes that ultimately results in a male phenotype. On the other hand, males with Y chromosome or SRY region deletions are phenotypically females. TDF induces the migration of mesonephric cells into the testis, which later differentiate into Sertoli and Leydig cells. The Sertoli cells organize to form testis cords, which at puberty undergo canalization to form seminiferous tubules. It also secretes Mullerian-inhibiting substance (MIS) to cause the regression of the Mullerian ducts, the future predecessor of female genitalia. In response to SRY influence, the mesenchymal cells of the urogenital ridge differentiate into Leydig cells during week 9–10. These cells secrete testosterone stimulating the Wolffian ducts to differentiate into the vas deferens, epididymis, and seminal vesicles, whereas prostate and bulbourethral glands develop in response to dihydrotestosterone (DHT) [6, 7]. DHT is the product of the enzymatic action of 5α-reductase on testosterone and has a tenfold affinity for androgen receptors [8]. In the setting of DHT deficiency, prostate growth and development are severely compromised. During puberty, in responding to the elevated level of testosterone, the prostate grows significantly [9]. Other factors that play an important role in the development of prostate include estrogenic compounds, paracrine mesenchymal factors such as Hox transcription factors, activin A, follistatin, insulin-like growth factor, and urokinase plasminogen activator [10–14].

Not only does DHT play an integral role in prostate development, it also plays an essential role in the development of external genitalia. It influences the masculinization of the male external genitalia by inducing the elongation of the urethral tubercle, canalization of the urethral plate, and fusion of the urethral folds. Mice exposed in-utero to antiandrogenic compounds or 5α-reductase inhibitors have hypospadias as well as scrotum malformation [15]. Complete insensitivity or loss of androgen receptors leads to feminization of the external genitalia.

As stated above, testosterone plays a vital role in the maintenance of cognition, memory, and sexual function. This is most evident in men with physiological or acquired hypogonadism, such as is the case with those on ADT. In males, symptoms of hypogonadism include decreased libido, decreased erectile quality, loss of vigor, decrease in the size of genitalia

and testicular volume, delayed ejaculation, and erectile dysfunction via impairment of nitric oxide system and potentially erectile tissue structural changes (Table 34.3). Other symptoms include decreased cognitive function, depressed mood, lack of motivation, sleep disturbances, decreased muscle and bone mass, vasomotor symptoms, and changes in lipid profiles. In an analysis of 343 patients, Zitzman et al. demonstrated a wide spectrum of symptoms associated with low testosterone level [16]. At total testosterone levels of 12–15 nmol/L (345–432 ng/dL), there were complaints of loss of libido and loss of vigor or energy level; whereas at levels of 10–12 nmol/L (288–345 ng/dL), there were increasing complaints of obesity. At levels of 8–10 nmol/L (230–288 ng/dL), a higher rate of type II diabetes mellitus and lack of concentration were reported, along with disturbed sleep, and depressed mood. Finally, at levels <8 nmol/L (230 ng/dL) vasomotor symptoms (hot flushes) and erectile dysfunction were reported.

Physiology of Testosterone

The testicles are the main organs responsible for androgen production in males, secondarily, the adrenal glands produce about 5% of the body's testosterone. In order to understand the effects of androgen deprivation therapy on male homeostasis, it is important to appreciate how testosterone and androgens are produced. Table 34.1 shows androgens produced by testicles and adrenal glands.

Table 34.1 Androgen production by testes and adrenal gland

Testes	Adrenal gland
Testosterone	Dehydroepiandrosterone (DHEA)
Androstenediol	Dehydroepiandrosterone sulfate (DHEAS)
Androstenedione	Androstenedione
Dehydroepiandrosterone (DHEA)	Progesterone (weak androgenic effect)

Hypothalamus-Pituitary-Testis Axis

Testosterone synthesis starts in the hypothalamus, where neurons in the preoptic area secrete gonadotropin-releasing hormone (GnRH) to the hypothalamo-hypophyseal plexus. The stimulation of GnRH on gonadotropin-secreting cells causes the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate Leydig and Sertoli cells in the testicles, respectively. Leydig cells account for >95% of total body production of testosterone; in turn, FSH stimulates Sertoli cells for spermatogenesis. Testosterone subsequently acts as a negative feedback on hypothalamic secretion of GnRH and hypophyseal secretion of LH; whereas, estradiol (the metabolite of testosterone after aromatization) acts as a negative feedback on hypophyseal secretion of FSH [17].

Testosterone is then metabolized in the prostate by 5α-reductase to dihydrotestosterone (DHT), a potent androgen. However, only 2% of total serum testosterone is metabolized to DHT by the prostate, and it is responsible for growth, differentiation, and function in the prostate (Fig. 34.1).

Production of Androgens by the Adrenal Gland

Androgens produced by the adrenal cortex include dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione. DHEA is the precursor of testosterone, and is produced in both the testicles and the adrenal glands. Cholesterol is the substrate from which all androgens originate (iadrenal and testicular). Conversion of cholesterol to pregnenolone is the first metabolic step. DHEA production can originate from two different metabolic pathways: pregnenolone can be metabolized to progesterone, then to 17-hydroxyprogesterone and finally to DHEA; in another pathway, pregnenolone is metabolized to 17-hydroxypregnenolone, and subsequently to DHEA [17]. In the adrenal glands, DHEA is then metabolized to androstenedione (Fig. 34.2).

Although testosterone may also derive from DHEA produced in the adrenal glands, this only accounts for <1% of total serum testosterone. Also, androstenedione may be converted peripherally to estrogens via aromatization, but it cannot be directly converted to DHT. Even though adrenal androgens may stimulate prostatic growth in certain conditions, significant growth is not observed under normal conditions [17].

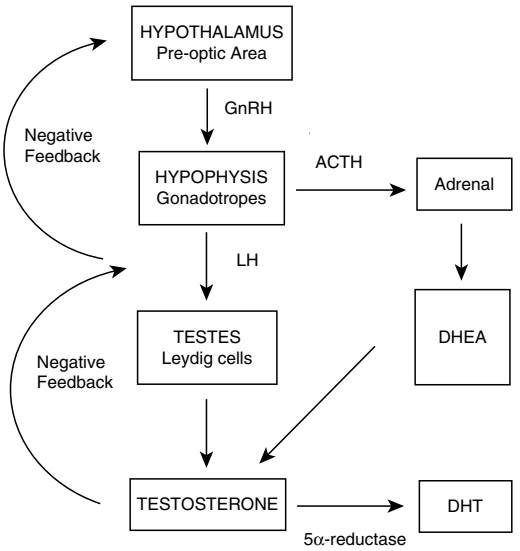

Fig. 34.1 *Testosterone production*. Testosterone produced by the hypothalamus-hypophysis-testicle axis is metabolized in the prostate to DHT by 5α(alpha)-reductase. DHEA produced in the adrenals may also be metabolized to testosterone; however, adrenal androgens weakly influence prostatic growth without conversion to testosterone. *GnRH* gonadotropin-releasing hormone; *LH* luteinizing hormone; *DHT* dihydrotestosterone; *DHEA* dehydroepiandrosterone; *ACTH* adrenocorticotropin hormone

Mechanism of Action of Androgen Deprivation Therapy

The main goal of ADT is to block the interaction between androgens and prostate, either by decreasing androgen production, blocking androgen receptors, or a combination of both. The most commonly used therapeutic strategy is to decrease testosterone production by means of castration, either medically or surgically. Table 34.2 shows an array of drugs that have been utilized for pharmacological castration.

Medical Castration

Medical castration is achieved by suppressing testosterone production by the testicles with agents acting at the pituitary level. In normal

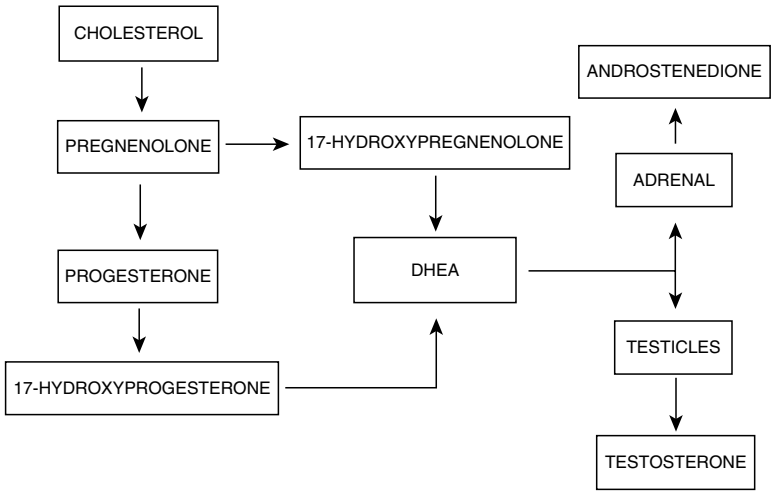

Fig. 34.2 *Dehydroepiandrosterone production and metabolic pathways*. Cholesterol is the starting substrate for androgen production in the testicles and the adrenal glands. *DHEA* dehydroepiandrosterone

Table 34.2 Medical castration agents

Luteinizing hormone acting agents		Antiandrogens		Inhibitors of androgen production
Agonists	Antagonists	Hormonal	Nonhormonal	
Leuprolide Histrelin Triptorelin Goserelin	Abarelix Citrorelix	Cyproterone	Flutamide Bicalutamide Nilutamide	Ketoconazole Aminoglutethimide

physiologic conditions, the hypothalamus stimulates the pituitary to secrete LH in a pulsatile manner via GnRH. LH in turn will stimulate Leydig cells to produce testosterone. LH-RH agonists exploit the desensitization of LH-RH receptors in the pituitary after chronic exposure to LHRH to suppress testosterone production. Initial exposure to LH-RH agonists will result in a flare of LH and testosterone; therefore, antiandrogens are usually co-administered for the first 21–28 days.

LH-RH antagonists are agents that competitively bind to LH receptors in the pituitary, effectively reducing LH concentration within 24 h. The advantage of this approach eliminates the need for co-administration of antiandrogens [61].

Surgical Castration

Bilateral orchiectomy consists of removing both testicles surgically. Three surgical techniques are available, including simple orchiectomy, epididymis-sparing orchiectomy, and subcapsular orchiectomy. After bilateral orchiectomy, serum levels of testosterone start decreasing within 24 h.

Antiandrogens

Antiandrogens competitively occupy androgen receptors. These agents can be hormonal and nonhormonal. When antiandrogens are used for ADT, there is no suppression of testosterone production, and therefore, they are mostly used in combination with an LH-RH agonist or antagonist. These medications are rarely used as single therapy for ADT [61].

Inhibition of Androgen Synthesis

Ketoconazole inhibits the production of androgens by blocking the conversion of cholesterol to lanosterol; this, in turn, decreases the overall hormone production by the adrenal cortex. Ketoconazole also interacts with the enzyme desmolase, which metabolizes 17-hydroxypregnenolone and 17-hydroxyprogesterone to dehydroepiandrosterone [17, 20]. By inhibiting desmolase, ketoconazole contributes to a cessation of androgen production by the adrenal glands [61]. Aminoglutethimide inhibits adrenal androgen production by preventing the conversion of cholesterol to pregnenolone [61] (Fig. 34.3). Ketoconazole and aminoglutethimide have extremely potent suppression effects on the adrenal cortex function, and their effects are considered equivalent to a medical adrenalectomy. Therefore, cortisone replacement is required when using ketoconazole and aminoglutethimide as ADT agents [61].

Androgen Deprivation Therapy Effects on Sexual Function

Androgen deprivation therapy is targeted to suppress testosterone effects on the prostate. Without testosterone, prostate cells undergo apoptosis. Even when testicular production of

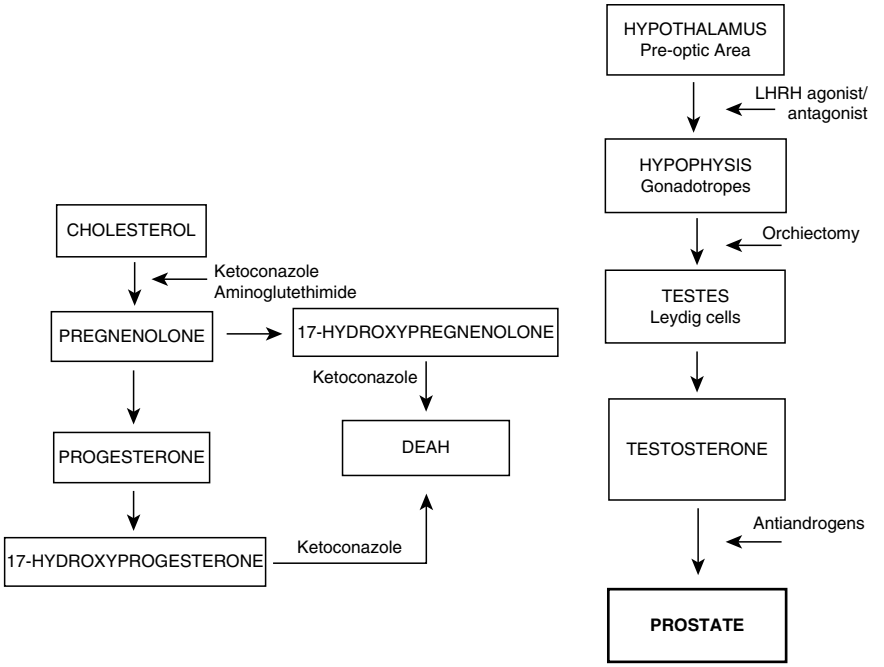

Fig. 34.3 Mechanism of action of androgen deprivation therapy agents. *LHRH* luteinizing-hormone releasing hormone; *DHEA* dehydroepiandrosterone

testosterone can be suppressed by castration, androgens can still be produced by the adrenal cortex, although in much less quantity. However, androgens made by the adrenal cortex have weaker effects and minimal influence on the prostate in comparison to testosterone. In the absence of testosterone, androgens produced by the adrenal gland are physiologically insufficient to support sexual function.

Since testosterone regulates several aspects of sexual function, castration will cause significant side effects involving erectile function, anatomical changes in the male genitalia, libido, and ejaculation (Table 34.3).

Table 34.3 Sexual side effects related to androgen deprivation therapy

Sexual function	Side effect
Erectile function	Venous leakage
	Decreased arterial flow
	Impaired PDE5 and nitric oxide regulation/expression
Ejaculation	Premature ejaculation
	Delayed ejaculation
	Decreased ejaculatory volume
Libido	Decreased libido
Genitalia	Decreased penile length and girth
	Decreased testicular volume

Erectile Function

Penile erection involves a complex interplay of hormonal secretion, vascular patency, and neural inputs (both central and sensory). Testosterone plays an important role in erectile function, and therefore, ADT has deleterious effects as multiple papers have demonstrated [18–23]. Androgen influence on erectile function involves regulation of phosphodiesterase type 5 and α-adrenergic receptors, smooth muscle cell growth and response to vasodilators, endothelial and nitric oxide synthase regulation and expression, neural structure and function, extracellular matrix deposition, and connective tissue metabolism [18, 19]. Nocturnal penile tumescence is also regulated by testosterone [21, 23].

Structural damage within the corpora cavernosa has been demonstrated in animal models, and a consequence of this damage is venous leakage. These changes can be found at very early time-

points after castration [20]. Aversa et al. also demonstrated impaired relaxation of cavernous endothelial and corporeal smooth muscle cells with low testosterone levels [22, 23].

In addition, decreased arterial flow and up to 50% decrease in erectile response from cavernous nerve stimulation has been described in rats [24]. Androgen deprivation causes increased responsiveness of α-adrenergic receptors in penile smooth muscle, increased apoptosis in cavernosal smooth muscle in rats, and reduction of trabecular smooth muscle in rabbits. Veno-occlusive dysfunction has also been described as a consequence of impaired response to vasculogenic stimuli, which leads to decreased blood flow, and ultimately alteration of the fibroelasticity of the corpora cavernosa.

Unfortunately, these structural changes may be irreversible. All these changes (structural and functional) lead to multi-factorial erectile dysfunction (vasculogenic, neural, and hormonal erectile dysfunction), which along with decreased libido, is a therapeutic challenge in patients on ADT as only a handful of treatment options are left available. 5-phosphodiesterase inhibitors are the first line of treatment for erectile dysfunction; however, impaired regulation on 5-phosphodiesterase and nitric oxide synthase regulation/expression along with the vascular/structural changes make sildenafil citrate and similar agents relatively ineffective. In fact, veno-occlusive dysfunction and venous leakage may also contribute to vacuum erectile device and intracavernosal injection therapy failure. Implantation of a penile implant has been shown to improve quality of life more than any other treatment in men on androgen deprivation therapy [24].

Ejaculation

Testosterone plays an important role in regulating seminal vesicle (SV) function, and it has been demonstrated that their secretory activity increases when endogenous testosterone levels increase [25]. In fact, it has been demonstrated that the secretory activity of seminal vesicles is influenced by the endogenous level of testosterone. Other hormones have been linked to seminal vesicle function regulation. For example, gene expression of luteinizing hormone and human chorionic gonadotropin (hCG) receptors has been found in the SV, but their exact physiologic influence is yet to be elucidated [26].

Ejaculatory dysfunction has been correlated with hypogonadism; however, there is limited information investigating the influence of ADT on ejaculatory function, even when men on ADT are in a profound testosterone-suppression state. Hypogonadism as a cause of ejaculatory dysfunction is controversial, and either premature or delayed ejaculation has been reported. Cohen described premature ejaculation as a consequence of hypogonadotropic hypogonadism in 12 patients [27]. However, in a larger series of patients, Corona et al. found that patients with higher than normal levels of testosterone had premature ejaculation, and patients with lower than normal levels of testosterone presented delayed ejaculation [28]. Among their explanations for delayed ejaculation in patients with hypogonadism, they propose that decreased levels of testosterone may cause a reduction in the volume of ejaculate, which in turn decreases prostatic and SV stimulation [28–30]. In order to clarify the specific effects of ADT on ejaculatory function, further research is needed.

Libido

By far, this is the most deleterious sexual function side effect in men on ADT. Testosterone regulates sexual interest, frequency of sexual acts, and penile tumescence at night. Loss of libido has been reported in many men on ADT [31–33]. Potosky et al. [34]. reported that ADT affects negatively on sexual function, regardless of castration method. However, this group also found that patients on chemical castration reported having a bigger problem with their sexual function compared to those who had undergone orchiectomy, irrespective of their pretreatment sexual

function [34]. They also found that those without diabetes mellitus and younger than 70 years old were more prone to report ED after initiation of ADT. The same group reported that men with good pre-ADT sexual function had large declines in libido, frequency of sexual activity, and erectile function [35, 36]. Not all patients will lose their libido, and Kumar et al. [37] reported that age, testosterone level before treatment and physical fitness are factors that affect variation in libido in patients receiving ADT.

Unfortunately, these side effects last as long as ADT continues. Nevertheless, after cessation of ADT, testosterone levels return to normal in the vast majority of patients. Several papers have addressed the question of how long testosterone takes to return to normal levels and different results have been reported [51, 66–74]. The shortest length of time for testosterone to reach normal levels was reported by Goldenberg [66] at 8 weeks after ADT cessation, but periods of up to 8.2 months [67] have been reported. Factors that negatively influence testosterone recovery include age (older than 65 years) [65–67], low pretreatment testosterone levels [68] and duration of ADT [69].

Genital Changes

ADT causes genital changes that include decreased size of the phallus and decreased testicular volume. Although less commonly reported, loss of penile length and girth is a well-known side effect from ADT possibly related to erectile tissue structural changes [37]. As mentioned above, several changes occur with the absence of androgens, including apoptosis of smooth muscle in the corpora cavernosa, reduction of trabecular smooth muscle, decreased arterial flow, and alteration of the fibroelastic properties of the corpora cavernosa. Limitation of arterial blood flow to the penis has in fact been related to decreased oxygenation of the penis and ultimately, fibrosis of the penis.

Testicular volume has also been described to be affected with the use of ADT. Although this is reversible once ADT is stopped, it is unclear how long it takes for patients on ADT to develop irreversible testicular atrophy. Histological changes including several tubular atrophy, collagenization and fibrosis of the interstitium with Leydig cell atrophy has been described by Hadziselimovic et al. [75]. While concluding that these histological changes were irreversible, the tissue samples obtained for analysis were from patients under active ADT for a mean time of 13.8 months. Contrarily, Huhtaniemi et al. [76] found no changes on Leydig cells in patients on ADT for 6 months, but Sertoli cells and tubular atrophy were found. Further studies with histological analysis are needed to answer this subject.

Assessment of Patients on Androgen Deprivation Therapy

In 2006, the International Society of Andrology (ISA), the International Society for the Study of Aging Male (ISSAM), the European Association of Urology (EAU), the European Academy of Andrology (EAA), and the American Society of Andrology (ASA) convened to redefine recommendations on the diagnosis, treatment, and surveillance of late-onset hypogonadism (LOH), in view of growing interest from general practitioners and urologists alike [38]. These recommendations were published in major scientific journals. The term LOH is defined as a syndrome composed of both clinical and biochemical evidence of testosterone deficiency [38]. While LOH is physiological, ADT impact on sexual health is equivalent to an acquired profound hypogonadism. The general clinical picture of either physiological or acquired hypogonadism is quite complex with broad variation in symptoms including lack of motivation, inability to concentrate, loss of energy, erectile dysfunction, loss of libido, and muscular atrophy. Often, these symptoms may be mistakenly attributed to other causes.

When assessing for ADT impact on sexual health, it is necessary to integrate a thorough history and a meticulous physical exam coupled with any complementary biochemical workup and imaging. The history should be focused on

patient's libido, sexual desire and satisfaction, ability to achieve or maintain erection, frequency of sexual intimacy, firmness of erection, and vasomotor symptoms. Questionnaires such as the Morley ADAM (androgen deficiency of the aging male) questionnaire, Aging Male Survey (AMS), and the new Massachusetts Male Aging Study (MMAS) have been developed as an assisting tool for assessment. Among them, the ADAM has been validated and shown to have the highest sensitivity and specificity of 88 and 60%, respectively, for the diagnosis of hypogonadism [39, 40]. In the Prostate Cancer Outcomes Study, 413 men received either orchiectomy or ADT, the deleterious impact on sexual health was noted. The rate of those men who reported no sexual interest increased from 30 to 60%, whereas those who reported inability to achieve an erection increased from 35 to 75%. Lastly, the proportion who reported no sexual activity increased from 45 to 80% [41].

Physical examination should be tailored to define decreased muscle mass, changes in genitalia size, increased body fat, changes in body habitus, and loss of pubic and body hair. In addition, a biochemical assessment of testosterone is necessary to confirm the diagnosis. The ISSAM guidelines suggest that when the values of free or total testosterone are >2 standard deviations from the norm, this can be considered hypogonadism [42]. It is recommended that blood samples obtained to measure testosterone levels should be drawn in the morning, and in multiple times on different days to allow for variations in hormone production. At our center, in addition to total and free testosterone level measurement, assessment of other hormones is also performed, including prolactin, LH, estradiol, and thyroxine in order to rule out other endocrine abnormalities that may be aggravating or contributing to the hypogonadism. In those with severe erectile dysfunction, Doppler ultrasound of the genitalia may be beneficial in anticipation for penile prosthesis implantation.

In conclusion, assessment for the deleterious impact of ADT is problematic and should be achieved through a combination of thorough and meticulous history and physical coupled with supportive laboratory testing and imaging.

Therapeutic Strategies for Patients on Androgen Deprivation Therapy

Intermittent Versus Continuous Androgen Deprivation Therapy

Aside from sexual health effects, other effects from ADT include alteration in bone metabolism, psychological and metabolic syndrome, among others. In an attempt to prevent these side effects, intermittent androgen deprivation therapy (IADT) has been proposed as an alternative in several studies.

Benefits from IADT include recovery of libido and potency during off-treatments in patients who were previously potent; other advantages include prevention of depression, osteoporosis and muscle atrophy [43]. Hot flashes, sense of well-being, and energy level are other improvements noticed when patients are off-treatment [44]. Therefore, IADT has been proposed as a better alternative to continuous therapy, especially in young patients with good sexual function. Although quality of life has been reported to improve in men on IADT [45], contrarily, a phase III study from the South European Uro-Oncological Group [56] found that there was no statistical difference in overall quality of life between patients on IADT versus those on continuous ADT; however, sexual function was comparable to pretreatment levels on IADT. Because decreased testicular volume is a concern with ADT, a potential benefit from IADT may include limitation of genital changes and/or testicular atrophy, although whether IADT in fact limits these changes has yet to be elucidated.

Whether IADT is a safe alternative regarding cancer control compared to continuous therapy has been a topic of debate; however, multiple studies have suggested that progression or survival is not compromised on IADT when compared to continuous therapy [46–54]. Though patients on continuous androgen deprivation therapy may present with androgen resistance within 2 years [55], this is not the case for IADT. In fact, Kurek et al. [48] found that patients on IADT were able to remain off-treatment for an average of 27 months with a PSA of <3.0 ng/ml; also, at a

mean follow-up of 48 months none of the patients developed androgen-resistant tumors.

One of the downsides of IADT is that its benefits do not last for long as off-treatment periods shorten overtime [46, 53, 57–59]. Also, some authors have expressed concerns regarding possible androgen surges when deprivation therapy is re-initiated [60].

In summary, IADT continues being a topic of debate. However, its advocates state that it is a safe therapeutic alternative for young patients with good sexual function, and for patients who wish to limit ADT side effects.

Penile Rehabilitation

Penile rehabilitation currently refers to strategies directed to prevent permanent damage to the corpora cavernosa, with the objective of maximizing the chance to restore patients' preoperative level of erectile function. Multiple therapeutic options exist to achieve this goal, including phosphodiesterase type 5 inhibitors (PDE5i), vacuum erectile device (VED), and injection therapy. These options could be used individually or in combination to maximize their therapeutic effects.

Protection or regeneration of corporal smooth muscle, cavernous nerves, and corporal endothelium are the main objectives of penile rehabilitation. Lack of "oxygenation" to the corpora cavernosa has been hypothesized as a cause for most of the devastating molecular changes in the penis. By creating an artificial erection, either with the VED or PDE5i, "oxygenation" to the corpora cavernosa tissues is restored, hoping to avert permanent structural damage [62, 63].

The concept of penile rehabilitation was originally considered for patients undergoing radical prostatectomy, in whom it is recommended to start early postoperatively, as venous leakage (a consequence of corporal smooth muscle fibrosis) may develop [64, 65]. Some authorities suggest that such rehabilitation may be of benefit to men on ADT (Mulhall, personal communication 2010). In fact, Muller et al. [77] reported improvement of erectile function in two groups of castrated rats that were injected with sildenafil citrate for 7 days and for 28 days, respectively, starting immediately after castration. Histological findings included a higher smooth muscle–collagen ratio in the group of rats receiving sildenafil for 7 days. Despite these promising findings, when erectile function from both groups was compared to that of a control group of noncastrated rats, it remained statistically significantly lower in the castrated rats group.

It is thus recommended that all patients on androgen deprivation therapy learn about these therapeutic strategies, as most of the morphologic changes in the penis may be prevented, and possibly reversed, with penile rehabilitation therapy. Also, in patients whose libido is not affected by ADT, all available treatment modalities for erectile dysfunction should be offered for sexual intercourse.

Conclusions

Androgen deprivation therapy has deleterious sexual side effects, with a heavy impact on patient's quality of life, especially in young patients with good pretreatment sexual function. Intermittent androgen deprivation therapy is a promising alternative to minimize these side effects. The concept of penile rehabilitation is a good therapeutic strategy to prevent permanent penile morphologic changes due to lack of testosterone.

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Chapter 35
Colorectal Cancer

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Keywords Colon • rectum • mesorectum • chemotherapy • radiation • stoma • body image

Overview of Treatment of Colon and Rectal Cancer

Colorectal cancer is a huge health problem with an estimated worldwide incidence of about one million patients and about 529.000 cancer deaths annually. It is estimated that 2.8 million people survive at least 5 years after their diagnosis of colorectal cancer [1]. The disease affects slightly more males than females. In the US, lifetime risk of developing colorectal cancer is about 1 in 20, and the median age at diagnosis is 72 years [2].

The basis of treatment of colon and rectal cancer is radical surgical resection of the primary tumor and the draining regional lymph nodes. For colon cancer large segmental resections of the colon are performed: right hemicolectomy, transverse colectomy, left hemicolectomy or sigmoid resection. These resections may be performed through a midline or transverse incision of the abdominal wall (laparotomy) or minimally invasive through key-hole incisions (laparoscopy). Depending on the clinical stage, up to 60% of patients develop metastatic disease in follow-up, predominantly in the liver. Adjuvant chemotherapy has been shown to reduce this risk by eliminating micrometastatic disease. The Int 0035 trial showed this benefit for the first time, using a scheme of 5-FU and levamisol: a 16% absolute reduction of mortality (33% relative reduction) [3]. The MOSAIC study showed an additional benefit of oxaliplatin to 5-FU with an additional 4% increase in 6 year overall survival [4]. Current guidelines advise adjuvant chemotherapy (5-FU combined with oxaliplatin) in case of positive lymph nodes or adverse pathological features to reduce recurrence and increase survival.

Due to the confined anatomical space of the pelvis, resection of rectal cancer is more demanding than resection of the colon. Improved insight in the anatomical structure of the rectum has led to the surgical concept of the mesorectum and total mesorectal excision (TME) [5]. The mesorectum may be regarded as an integral package, containing all regional lymph nodes of the rectum inside a fatty layer which has clear dissection planes in its circumference. As the majority of rectal cancers are limited to the mesorectum, intact resection of the mesorectum will result in an adequate resection with low percentages of local recurrence.

Major surgical resection of rectal cancer includes two strategies: (1) Low Anterior Resection in which a total mesorectal excision is performed through a laparotomy or by laparoscopy. An anastomosis can be made between sigmoid colon or descending colon and the rectal stump. In many cases a temporary diverting stoma on terminal ileum or transverse colon is created to protect the anastomosis. (2) Abdominoperineal Resection in which a total mesorectal excision is performed as

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in low anterior resection followed by resection of the anus and distal rectum. A permanent end colostomy is unavoidable in this operation. In experienced hands and in selected cases, low anterior resection or abdominoperineal resection may also be performed laparoscopically assisted [6]. Laparoscopic operations may be associated with less morbidity and a faster recovery [7, 8].

Minor surgical resection of rectal tumors includes transanal techniques, e.g., Transanal Endoscopic Microsurgery (TEM). These techniques induce little morbidity but are only suitable for limited lesions (T1).

Neoadjuvant treatment is given as short course radiation therapy (five daily doses of 5 Gy) or long course radiochemotherapy (28 daily doses of 1.8 Gy) dependent on tumor stage and local protocol. Reduction of local recurrence is the main goal of both schemes. In the Dutch TME study patients were randomized to 5×5 Gy radiation versus no radiation. All patients underwent total mesorectal excision. After a median follow-up of 6.1 years local recurrence was 5.6% in the radiation therapy group versus 10.9% in the surgery only group. No benefit in survival was observed [9]. Based on these results short course neoadjuvant radiation therapy is the standard of care in large parts of Europe, especially in the Netherlands and Sweden. Long course radiochemotherapy followed by a waiting period is given with the aim to reduce local recurrence in locally advanced tumors. In these cases downsizing of the tumor is necessary to obtain negative circumferential margins during resection.

In France the FFCD 9203 study compared neoadjuvant chemoradiation with radiation therapy only (45 Gy radiation with or without 5-Fu) in patients with clinically resectable T3 or T4 tumors. Local recurrence was significantly reduced in the chemoradiation group: 8.1 versus 16.5% [10]. In the EORTC 22921 trial it was also demonstrated that chemotherapy, whether given before or after surgery, and neoadjuvant radiation therapy for resectable T3 or T4 tumors reduced the percentage of local recurrence (7.6–9.6% for the chemotherapy groups versus 17.1% for the radiation only group [11].

In a randomized controlled trial the German Rectal Cancer Group compared long course chemoradiation (28 fractions of 1.8 Gy, total 50.4 Gy, combined with 5-Fu), given preoperatively or postoperatively. Local recurrence was significantly reduced in the preoperative radiation group [12].

The creation of a stoma occurs frequently in rectal cancer treatment and infrequently in colon cancer treatment. In distal rectal cancer, preservation of the anal sphincter is often not possible. In these cases an abdominoperineal resection is performed resulting in a permanent end sigmoid colostomy, usually in the lower left quadrant of the abdomen. In some cases with a tumor in the mid- or upper rectum, an end colostomy may be created because of contraindications to make an anastomosis between sigmoid colon and rectal stump. These contraindications include poor sphincter function and a high likelihood for anastomotic leakage (poor condition of the patient, co-morbidity, etc.). When after a low anterior resection an anastomosis is made, a temporary loop ileostomy or transverse colostomy may be warranted to reduce the chance of anastomotic leakage and to increase the likelihood of anastomotic healing. These defunctioning stomas have been shown to reduce the incidence of anastomotic leakage [13]. Patients who experience anastomotic leakage after surgery are very likely to undergo a relaparotomy with dismantling of the anastomosis and the creation of a permanent colostomy. After resection of colon cancer, stomas are infrequently used. Usually this will only be done in an emergency situation with distended bowels and in patients with poor condition. Healing of an anastomosis cannot be relied upon in these cases.

The Impact of Colorectal Cancer Diagnosis on Psycho-Sexual Functioning

The diagnosis and subsequent treatment of colorectal cancer is a major life event to many patients and may cause significant psychological

distress. Worster and Holmes performed a phenomenological study into patients' preoperative experiences: fear, questions, isolation and uncertainty were found to be major themes [14]. In a study by Goldzweig et al. psychological distress, coping and social support were investigated among middle-aged colorectal cancer patients and their spouses. The level of social support was found to be inversely correlated to the levels of psychosocial distress. Men were found to be more distressed than females although husbands received more support from their wives than vice versa [15]. Northouse et al. studied patients' and spouses' adjustment to colon cancer using validated questionnaires. A decrease in family functioning, social support and emotional stress was found in patients and in spouses from diagnosis to 1 year afterwards. Marital satisfaction also declined, but was not measured at the time of diagnosis. Women, both patients and spouses, reported more distress and less marital satisfaction [16].

Houldin performed semistructured interviews of caregivers of patients diagnosed with stage III or stage IV colorectal cancer. Caregivers experienced a total disruption of life, tried to stay positive but attempted to maintain life normal, especially for the children. On sexuality, both positive and negative effects were found. Some caregivers lost desire because of their own high stress levels, other caregivers' sexual relation intensified, attributed to an increase in bonding [17]. In a model study of Manne and Badr the adaptation of a couple to cancer is looked upon from a relationship perspective (12). Spouses can be regarded as partners instead as patients or caregivers: the intimate connections between them may bring strength and support and lead to a closer emotional bond. This may function as an opportunity to relationship growth. The consequences to sexual functioning are not described however [18]. Hagedoorn et al. draw some interesting conclusions in a meta-analysis of distress in couples coping with cancer [19]. First, women report more distress, regardless of their role as partner or patient. Second, there is a moderate correlation between distress in patients and partners, suggesting that couples react as an emotional system. Third, at most only a modest rise in distress is observed in couples coping with cancer (13).

The Impact of a Stoma on Sexual Functioning

It is evident that no person in good health wishes to have a stoma. It is a bodily mutilation, which requires daily care. Accidents and leakage may occur, skin irritation is a frequent problem and flatulence is without control. If a stoma is not made at an appropriate site, leakage and skin irritation are more prevalent. Ileostomy patients may experience dehydration and sodium depletion. Long-term problems include stenosis, prolapse and parastomal hernia [20]. Finally, a stoma has a negative impact on physical attractiveness [21].

Jenks et al. prospectively studied the influence of a stoma on body image in patients with cancer using the Body Cathexis Scale, the Draw-a-Person technique and structured interviews [22]. Interestingly, body image scores were not different before and after treatment in this study. Persson and Hellström performed open-ended interviews with nine patients 6–12 weeks after their ostomy operation (16). Significantly altered body image was a repeated theme in the interviews and all patients reported a decrease in attractiveness [23]. In a prospective study on female sexuality after colorectal surgery by da Silva et al. body image amongst others was assessed using a Body Image Scale [24]. Again, body image improved over time. A tendency to a worse body image was seen in stoma patients, although this was not significant (16). The rise in the perception of body image is explained by Jenks et al. by the initial negative influence of the cancer diagnosis and pending stoma on body image, and a rise after the operation (15). On the other hand, coping and acceptance with the situation after surgery, using humor and emphasizing the positive aspects of a stoma (including a relief of symptoms, control over bowel function, the possibility to undergo restoration of continuity, normalization of life and a status of having undergone curative treatment for cancer) may in fact be beneficial to the acceptance and overall body image [25].

Krouse et al. studied 599 cancer and noncancer patients with colostomies using a Quality Of Life-ostomy questionnaire [26]. On the dimension of psychological well-being and social/sexual well-being, 37 and 25% of cancer patients reported a low score. However, from this study it is not clear what the impact of the colostomy is apart from the impact of the cancer diagnosis and treatment. Manderson performed unstructured interviews with 18 patients with a stoma [27]. Most of these patients had stoma surgery 5 years or longer before the interview. Many patients expressed feelings of discomfort and embarrassment with the stoma. Some patients left their partner or were left by their partner because of the stoma. Partners were in general supportive and acceptant to the stoma. Some patients reported a lack of desire or a lack of desire by their partners. Many patients continued intimate and sexual relations, although often after a long period of inactivity (20).

Preoperative education of the patient and stoma site marking is important to reduce anxiety, to answer questions and to enhance acceptance of the stoma by the patient [28]. Furthermore, it will give the opportunity for ostomy nurses to build a relationship with the patient and his or her partner in which sexuality can be openly discussed [29].

The Impact of Treatment of Rectal Cancer on Male Sexual Functioning (Table 35.1)

Erectile dysfunction (ED) and ejaculatory dysfunction (EJD) are well-known problems after total mesorectal excision for rectal cancer. These problems are related to damage to pelvic autonomic nerves caused by preoperative radiotherapy and iatrogenic surgical injury [30, 31]. According to several studies, ED and EJD rates after TME vary from 11 to 25% and 19 to 54%, respectively [32–35].

It is difficult to identify the contribution of each treatment component in the development of sexual dysfunction. Sexual dysfunction after radiotherapy is a multifactorial problem, involving fibrosis, vascular toxicity, neurotoxicity and psychological factors [36]. Radiation damage to the cavernous arteries may result in ED (add reference). Furthermore, the seminal vesicles may be damaged after irradiation, resulting in EJD [37]. Only a few studies describe the late side effects of preoperative short-term radiotherapy in TME patients. Lange et al. analyzed 990 patients (497 in the radiation + TME group and 493 in the TME only group) in terms of risk factors for long-term sexual dysfunction after rectal cancer treatment using nonvalidated questionnaires. An increase in general sexual dysfunction, ED and EJD was reported by 76.4, 79.8 and 72.2% of male patients, respectively. In this study radiotherapy was not an independent risk factor for ED or EJD and therefore the authors concluded that sexual dysfunction is mainly caused by surgery [38]. In another randomized trial comparing three reconstructive procedures functional outcome was assessed. Until 12 months after surgery sexual functioning was comparable in patients with or without Radiation therapy. However, a significantly decline in male sexual functioning was observed after 24 months in patients who underwent radiation therapy suggesting delayed damage [39].

The pelvic autonomic nerves may be damaged at a number of points during rectal surgery (Figs. 35.1 and 35.2). The superior hypogastric plexus, containing pure sympathetic nerves, is situated just below the aortic bifurcation. Two sympathetic hypogastric nerves run caudally from this superior hypogastric plexus: medial to the ureters between the endopelvic fascia and the pelvic peritoneum. Damage to the superior hypogastric plexus and hypogastric nerves could lead to disturbed ejaculation. The hypogastric nerves unite the superior hypogastric plexus with the inferior hypogastric plexus. Parasympathetic fibers emerge from the second, third and fourth sacral spinal nerves as the pelvic splanchnic nerves and join the hypogastric nerves to form the inferior hypogastric plexus. Disruption of the parasympathetic nerves could lead to ED. From the inferior hypogastric plexus, nerves to the sexual organs run in the neurovascular bundles at the lateral border of Denonvillier's fascia at the

Table 35.1 Prevalence of sexual dysfunction after colorectal surgery

References	Study design	Procedure			
Male studies					
Han [74]	Retrospective study	LAR – TME	8/37	22%	Impotent
			29/37	78%	Retrograde ejaculation
Asoglu [35]	Retrospective study	"Open" TME	6/17	35%	Erectile dysfunction
			5/17	29%	Unable to ejaculate
		Laparoscopic TME	1/18	6%	Unable to ejaculate
			1/18	6%	Erectile dysfunction
Jones [45]	Retrospective study	Laparoscopic TME	4/101	4%	Retrograde ejaculation
			2/101	2%	Erectile dysfunction
Morino [75]	Retrospective study	Laparoscopic TME	14/50	31%	Erectile dysfunction
			11/50	24%	Absence of orgasm
			17/50	38%	Unable to ejaculate
Jayne [41]	Randomized trial (CLASSIC)	Laparoscopic TME	23/55	41%	Severe change in sexual functioning
		"Open" TME	6/26	23%	
		Laparoscopic colonic resection	2/46	4%	
Ameda [76]	Retrospective study	TME – ANP	$n=28$	12%	Erectile dysfunction
Sterk [77]	Prospective study	"Open" TME	8/29	28%	Impotent
			2/29	7%	Retrograde ejaculation
Bonnel [31]	Retrospective study	TME + ANP	11/15 preop RT	73%	Sufficient erection for penetration and normal ejaculation
			20/26 no preop RT	77%	
Kim [78]	Prospective cohort study	TME + ANP	20/68	29%	Intercourse satisfaction sustained
			9/68	13%	Retrograde ejaculation
Quah [32]	Randomized trial	Laparoscopic TME	6/15	40%	Erectile dysfunction
			6/15	40%	No ejaculation
		"Open" TME	3/22	14%	Erectile dysfunction
		Laparoscopic TME	1/22	5%	No ejaculation
Female studies					
Han [74]	Retrospective study	LAR – TME	1/35	3%	Dyspareunia
Asoglu [35]	Retrospective study	"Open" TME	5/10	50%	Dyspareunia
			5/10	50%	Vaginal dryness
			5/10	50%	unable to achieve orgasm
		Laparoscopic TME	1/14	7%	Dyspareunia
			1/14	7%	Vaginal dryness
			1/14	7%	Unable to achieve orgasm
Tekkis [54]	Prospective study	APR	$N=18$	50%	Dyspareunia (1 year postop)
			$N=20$	45%	Unable to achieve orgasm
		LAR	$N=63$	33%	Dyspareunia (1 year postop)
			$N=65$	23%	Unable to achieve orgasm
			7/35	20%	Diminished lubrication
Platell [59]	Retrospective study	TME + ANP	4/22	18%	Dyspareunia
			5/22	23%	Vagina too short or inelastic
		Colonic resection	0/19	0%	Dyspareunia

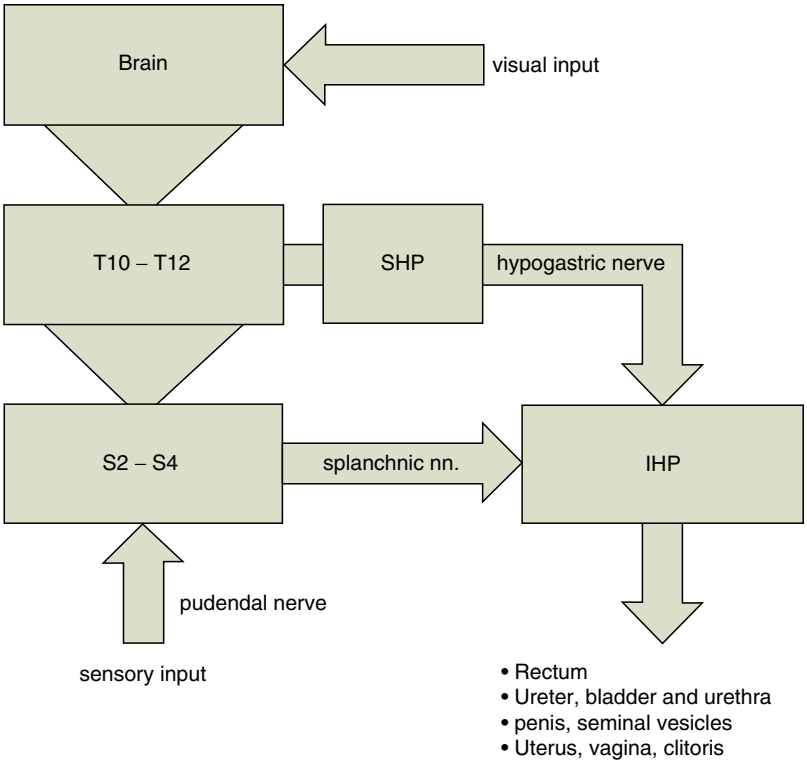

Fig. 35.1 Diagram of the pelvic autonomic nerves and their connections with the central nerve system. T10–T12, thoracic spinal cord level 10–12; S2–S4, lumbar spinal cord level 2–4; SHP, superior hypogastric plexus; splanchnic nn, splanchnic nerves; IHP, inferior hypogastric plexus. (From C.P. Maas. Nerve-sparing radical pelvic surgery. Thesis, Leiden 2003 with permission. (permission is granted by prof. C.J.H. van de Velde.)

apex and base of the prostate, where they are also closely related to the anterior wall of the rectum [40].

Very little and rather controversial is the information regarding the sexual function following laparoscopic TME [35, 41, 42]. Laparoscopic TME offers short-term advantages, like earlier return to normal diet, less postoperative pain, less narcotic use and shorter hospital stay [43, 44]. The magnified laparoscopic view enables excellent exposure of the pelvic cavity and facilitates sharp dissection of the lateral, anterior and presacral spaces, all being autonomic nerve locations. However, the technical demands of laparoscopic TME may just predispose to nerve injury [41]. One study describing sexual function after laparoscopic TME reported a higher rate of male sexual dysfunction than after open resection [32]. The sample size of this study was small; 15 patients underwent a laparoscopic resection and 22 patients had an open TME. Asoglu reported on sexual dysfunction after laparoscopic TME and found that open resection is associated with a higher rate of sexual dysfunction [35]. In a recent retrospective single center series by Jones et al. the authors reported a low incidence of sexual dysfunction after laparoscopic TME: only two patients of 101 had ED and 4 had EJD (37). The authors suggest that studies describing poorer functional outcome after laparoscopic rectal resection have probably included a significant number of patients on the surgeons "learning curve" [45]. However, this was not a randomized study and selection bias can have had impact on the results of this study. Sexual function appears to be more affected after abdominoperineal resection than after low anterior resection. Impairment of sexuality in patients after an abdominoperineal resection

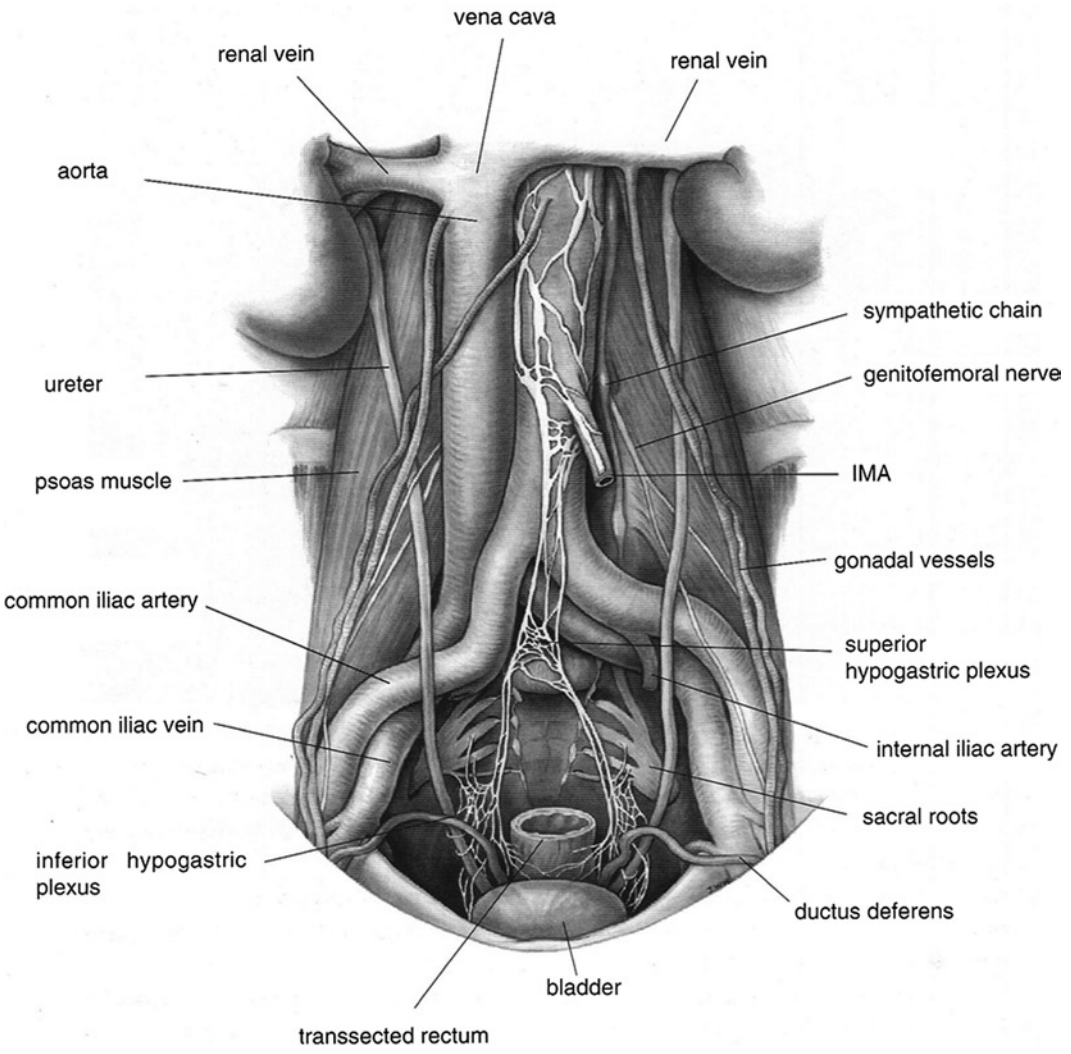

Fig. 35.2 Drawing of the abdominal and pelvic autonomic nervous system. From WH Steup. Colorectal cancer surgery with emphasis on lymphadenectomy. Thesis, Leiden 1995 with permission

may be caused by a combination of higher proportion of low tumors and/or to the extended dissection behind the prostate and the perineum causing damage to the pelvic autonomic nerves and pelvic floor [46–48].

The loss of sexual function in patients after rectal cancer surgery is initially sudden and in many cases total and definitive. This is in contrast with ED as occurs by nature (due to aging, atherosclerosis, etc.) in patients who experience a gradual reduction in rigidity over many years.

The Impact of Treatment of Rectal Cancer on Female Sexual Function

In the literature, male sexual dysfunction after rectal surgery is well established. However, studies reporting on sexual dysfunction in female patients after rectal cancer surgery are limited, perhaps reflecting the fact that it is not well understood and that until recently, validated scoring systems were not available [34, 48, 49]. Other explanations for

the lack of evidence include difficulties to measure changes in sexual function over time in female patients when compared to the obvious (erectile) dysfunction in male patients and reluctance of (male) doctors and (female) patients to discuss such a sensitive subject.

The incidence of sexual dysfunction in females reported in the literature varies between 8 and 58%. [50, 51] The large range in outcome may be due to the fact that most studies included only a small number or female patients were retrospective and used different methods of investigation [30, 52, 53]. Another reason may be that there are different definitions used for female sexual functioning: possibility of or satisfaction during intercourse or the possibility of having an orgasm? A recently published prospective study from the Cleveland Colorectal Cancer Clinic using nonvalidated questionnaires reported on the sexual function of 295 women undergoing rectal surgery for rectal cancer. They found that abdominoperineal resection, radiotherapy, intra-abdominal sepsis and age older than 65 years were predictors for poor sexual function after therapy [54].

Damage to the pelvic autonomic nerves is likely to explain the impaired sexual function in women after rectal surgery. In women the parasympathetic nerves are responsible for increased blood flow to the vagina and vulva, causing vaginal lubrication and swelling of the labia and clitoris [55]. The sympathetic nerves are responsible for emission and the rhythmic contractions of the genital ducts and organs during orgasm [56]. The addition of autonomic nerve preservation to TME resulted in preserved female sexual functioning [33]. Furthermore, it has been shown that experienced pelvic surgeons have more knowledge of the course of the pelvic autonomic nerves and are more able to preserve these nerves [57, 58].

In addition to nerve injury, postoperative scarring around the vagina may contribute to dissatisfaction during, or avoidance of, sexual intercourse. Low rectal dissection requires full mobilization through the rectovaginal septum. Several studies described that female patients who underwent pelvic surgery felt that their vagina was inelastic and too short during sexual intercourse [55, 59].

Radiotherapy may also compromise female sexual function. Several studies have shown the negative impact of radiotherapy on sexual function in cervical cancer [60, 61]. Following an acute reaction to radiotherapy, there is initially loss of the vaginal epithelium. This will resolve within 3–6 months in most patients. Reepithelialization occurs after treatment; however, this lining is histologically different from normal epithelium with more hyalinization and collagenization, fibrosis and obliteration of small vessels and disappearance of small glands leading to decreased blood flow and less lubrication and genital response. Furthermore, radiotherapy is associated with direct toxicity of the autonomic nerves. It has been suggested that the fibrosis occurring after radiotherapy causes nerve entrapment with secondary demyelization, with the fibrotic process causing vascular damage [62]. Up-to-date there are still no conclusive data on radiotherapy techniques, field sizes, energy used and their specific influence on sexual dysfunction in women.

In case the (posterior) vagina needs to be removed during surgery, the option of vaginal reconstruction should be discussed with the patient at least a few days before the operation. The option of a vaginal reconstruction should be offered to all women who have an indication for vaginectomy. In discussing the vaginal reconstruction preoperatively it is important to address the role sexual intercourse plays in a woman's life, her expectations of a vaginal reconstruction and her motivation to use pelotes postsurgery. In the literature the most common technique described is a myocutaneous rectus abdominis flap [63, 64]. In our own institution we use a pedicled omentoplasty with a split skin graft placed on a mold. All women after vaginal reconstruction need post surgical counseling and follow-up by a sexologist or a dedicatedgynaecologist, surgeon or nurse.

Sexual dysfunction is an entity in which multiple psychological and somatic factors are involved [65]. Breukink et al. evaluated the vaginal blood flow response during sexual

arousal in female patients undergoing rectal surgery for rectal cancer [66]. The results were compared with an age-matched group of healthy women. In this pilot study the changes of genital and subjective sexual arousal between patients and healthy controls were not different, though lower vaginal flow was found in the patient group compared to the healthy women (58). This indicates that the physiological reaction on erotic stimuli in these patients may be probably intact but may function at a lower level. The observed lower vaginal blood flow might be explained by autonomic nerve damage caused either by radiotherapy or rectal surgery.

Despite a lower vaginal blood flow patients felt an equally strong sexual arousal like healthy volunteers. Similar outcomes have been demonstrated by Pras et al. [67]. They compared changes in vaginal blood flow between patients treated with radiotherapy for gynaecological cancer and healthy women. This demonstrates that sexual satisfaction is modulated, not only by biomedical factors, but also by personal, societal and relationship factors, all of which need to be taken into account when sexual dysfunction is addressed [68].

Counseling and Treatment

The high incidence of sexual dysfunction warrants an increased effort to discuss these complications both initially at diagnosis and throughout treatment and follow-up. Hendren et al. reported that only 9% of female patients and 39% of male patients remembered discussing the effect of treatment on sexual function preoperatively [69]. Chorost showed a failure to document possible sexual effects of treatment in the informed consent process [70]. These findings stress the need for discussing and documenting sexual dysfunction as a complication after treatment for rectal cancer. A well-informed patient may have an advantage in coping with postoperative sequela, as symptoms may be better tolerated if they can be anticipated.

In the case of iatrogenic ED, patients should be offered a phosphodiesterase 5 inhibitor (PDE5i), preferably in the early postoperative phase in close cooperation with the sexual partner. Her (or his) sexual interest and function is an important aspect of sexual rehabilitation. In general there is a good response to a PDE5i (87%) [71] but the effect of such a drug is dependent on, at least partially, intact cavernous nerves to produce nitric oxide. Therefore, if the cavernous nerves have been totally ablated, PDE5i will be ineffective [72].

Research in gynaecological cancer has shown that the communication between healthcare professionals and the women with cancer is not adequate [73]. Reasons for not discussing sexual issues in this study included "it is not my responsibility," "embarrassment," "lack of knowledge and experience" and "lack of resources to provide support if needed." The previously mentioned study from the Cleveland Colorectal Cancer Clinic reporting on the sexual function of 295 women undergoing rectal surgery found that 81.4% of the women wished to have a conversation about sexual function preoperatively. According to the majority of the patients, the discussion should be initiated by the health professional rather than by themselves. There was no correlation between the interest in discussing sexual issues and age, menopausal status, marital status, BMI, ethnicity, number of children, previous hysterectomy, frequency of sexual activity and/or type of disease [24]. Platell et al. have demonstrated similar outcome. They reported that older patients are still concerned with limitations in their postoperative sexual function [59]. The results of this study demonstrated that there is a need from the women's perspective to improve communication about sexual issues (51).

In future, health-care professionals should become more aware of the sexual difficulties of female patients with rectal cancer and better communication with female patients about sexual dysfunction is necessary. Some of the difficulties experienced can be relieved by the use of lubricants for vaginal dryness and the use of vaginal dilators to prevent stenosis.

If a patient or a couple suffers from serious psychological problems due to sexual dysfunction, they might benefit from psychosexual counseling.

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Chapter 36
Stem Cell Transplant

Jean C. Yi and Karen L. Syrjala

Keywords Graft • Hematopoietic • Immunosuppression • Graft Versus Host Disease • Gvhd • Total Body Irradiation

Description of HSCT

Hematopoietic stem cell transplant (HSCT) began in humans in the late 1950s and since that time more than 800,000 people have been treated with this procedure. To date 150,000 patients are living 5 years or more post transplant, with this number expanding rapidly [1]. As advances have been made in refining HSCT and making it more accessible, a larger proportion of people are surviving and it becomes important to determine and address their long-term and late effects. One of the most prevalent long-term difficulties for both males and females is sexual dysfunction.

HSCT is a procedure designed primarily for hematologic malignancies such as leukemia and lymphoma, although some premalignancies and nonmalignant blood disorders such as aplastic anemia are also treated with this method. Prior to transplantation, to prepare the body to receive stem cells from either marrow or peripheral blood, the conditioning regimens always include chemotherapy, usually supralethal doses of an alkylating agent such as cyclophosphamide and/or busulfan, and often include total body irradiation (TBI) at a dose of 1200 cGy or higher. Newer methodologies use low dose chemotherapy with or without low dose TBI and use the infusion of donor marrow in a "graft versus leukemia" effect to eradicate the malignant cells from the body. In either case, conditioning treatment lowers immune defenses so that stem cells, donated from oneself (autologous) or from another related or unrelated person (allogeneic) can be infused as a way to "rescue" the patient from the immunotoxic effects of the conditioning regimen. If the transplant is allogeneic, survivors are at risk for graft versus host disease (GVHD), where the donor immune cells identify the body as foreign and attack it. Chronic GVHD can last for years and manifests anywhere in the body, most often involving the skin, liver, eyes, mouth, sinuses and gut, and for women, vaginal tissues [2]. Chronic GVHD is managed with the use of immunosuppressants that include high dose corticosteroids along with a calcineurin inhibitor such as cyclosporine or other newer agents that suppress immune recovery and bring a host of potential additional complications.

Sexual dysfunction is a common long-term outcome following HSCT [3, 4], in contrast to research demonstrating a return to pretransplant

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levels of overall physical function by 1-year post-transplant [5]. A few papers have described the extent and nature of sexual difficulties in this population [4, 6–8], and have also documented elevated problem rates relative to healthy controls [3, 4, 9, 10]. The goals of this chapter are to review current research about sexual function following HSCT, to examine problems related to sexual dysfunction after HSCT, and to address strategies for treating these long-term problems.

Challenges from the Start of HSCT

The population of HSCT survivors is usually well under the age of 50, and most often relatively healthy until their diagnosis, without major comorbidities, as required for eligibility for HSCT. However, diagnosis may occur years before HSCT and previous treatments may have already impacted sexual function. As a result of previous chemotherapy, at least half of the women may be prematurely and chemically postmenopausal. Similarly, as a result of previous treatment, male testosterone levels may be lower than an individual's usual level although within normal range. Alternatively, women may be premenopausal, have had little or no previous treatment and may report active sex lives until the start of cancer treatment. The dramatic changes brought by treatment can make sexual adjustments more challenging for women who become abruptly postmenopausal after HSCT as compared with those who are postmenopause prior to HSCT. Even in the absence of prior treatment that can lead to postmenopause, the upheavals and emotional adaptations of diagnosis and preparations for HSCT may disrupt family and intimate relationships. HSCT is not only a medical procedure that requires several intensive months with recovery lasting a year or longer, but the procedure often requires families to move from their home to be close to a transplant center in case of emergency needs while in ambulatory care. In addition, living arrangements are often reconstructed, with parents moving in with adult children to assist with caregiving to the transplant recipient or with childcare. This context begins to explain some of the issues facing HSCT survivors and the deficits seen even many years after treatment in these transplant recipients and their sexual partners.

Challenges After HSCT

Lower sexual activity and satisfaction after HSCT in comparison to the time before transplantation or relative to the general population is a consistent finding across time points after HSCT, and across ages at time of transplantation, in both prospective longitudinal and cohort comparison studies [6, 10–19]. Numerous cross-sectional studies have documented declines in sexual satisfaction and functioning of HSCT survivors [3, 6, 16]. Survivors of both genders report a loss of sexual desire [20]. Nonetheless reported rates of sexual satisfaction vary quite widely perhaps because of different measures used or adequacy of sampling. As few as 22% of participants have reported sexual dissatisfaction [16], while in most studies half to two-thirds of the participants report dissatisfaction [17, 21]. Few studies have continued to follow HCST survivors long-term to assess their sexual functioning after full recovery. However, decrements in sexual functioning have been found in long-term survivors past 5 years after treatment [4]. In general, women report more problems than men do [18, 22], and men report higher levels of sexual satisfaction than women [23]. However, both males and females generally note that their difficulties are not in their sexual relationships but rather with desire and specific sexual problems. Since differences in problem rates, problem types and satisfaction are marked between males and females, it is necessary to consider effects on these survivors separately.

Women

Before HSCT 42% of females compared with 17–35% of the general population of females report one or more sexual problems [6, 24]. By 3 years after HSCT, the prevalence of problems increases to 80%. In a 5-year prospective, women

continued to have lower rates of sexual activity than men across time, and at all times over 40% of female HSCT survivors were sexually inactive [4]. Due to the expected ovarian failure for nearly all women who receive high dose HSCT, it is common for women to experience menopausal symptoms. By 3 years posttransplant, a majority of women report difficulties with vaginal dryness and desire [6, 21, 25–27]. The lack of vaginal lubrication during arousal can make intercourse uncomfortable [6, 21, 28, 29]. Women also report pain during intercourse and, less often, bleeding after intercourse [29, 30]. Another problem for women that seems to increase with time is the ability to achieve an orgasm [6].

Men

Prior to HSCT, 14% of males report one or more sexual problems compared with 4–38% of the general population of males report one or more sexual problems [6, 24]. By 5 years posttransplant, 45% of men reported problems that interfered with sexual activity [4]. For men, the most prevalent problems include obtaining and maintaining erections and desire [6, 21, 25–27].

These findings to date with HSCT survivors highlight that, while physical and emotional functioning may return to normal with the passage of time for most survivors [3, 5], sexual functioning does not follow a similar trajectory [4, 27]. A finding that highlights the importance of assessing sexual functioning early after treatment is that, for women in particular, if sexual activity has not returned by 1 year, these problems can persist for 5 years and possibly indefinitely [6]. Our research highlights that if women are not taking HRT by 1 year, their sexual problems are more likely to continue [4, 6].

Treatment Factors Contributing to Sexual Dysfunction

Medical treatments that may impact sexual function include chemotherapy, TBI, medications for chronic GVHD, and the other treatments for symptoms or side effects that are commonly used in cancer patients, such as antidepressants. Alkylating agents are particularly toxic to gonadal function and consequently nearly all HSCT recipients are infertile following treatment. However, infertility is not guaranteed, leaving a level of uncertainty unless confirmed with fertility testing. TBI is also toxic to gonadal function [31] and can contribute to genital tissue sensitivity, atrophy or scarring. These treatments impair the production of testosterone at least for the first year for males, and induce permanent ovarian failure for most women [28, 32–37]. Even if ovarian function returns for some women, this premenopausal status is likely to be shorter in duration than for women who have not received chemotherapies for cancer. Thus women may only have a few years of fertility before becoming permanently postmenopausal [38].

Chemotherapy and TBI

The type and dose of chemotherapy are factors to consider when identifying potential effects of treatment [35, 39]. In a study of young adult survivors of childhood hematologic malignancies, more men developed hypogonadism who were treated with HSCT than another group who were treated with chemotherapy alone (83 versus 17%, respectively) and all women treated with HSCT and had an engraftment had ovarian failure [40]. In some studies comparing chemotherapy alone to HSCT, those patients who received only chemotherapy reported less sexual dysfunction in all phases of the sexual response cycle [18]. However, this differential effect has not been confirmed in other research [41].

Chemotherapy and TBI toxicities are not solely gonadal. Treatments are known to permanently damage function of the hypothalamic–pituitary–gonadal axis [42, 43]. Luteinizing hormone (LH) is elevated in most female survivors and normal in most males. Follicle stimulating hormone (FSH) is elevated in over 90% of females and most males. Most females have low endogenous estrogen levels, and vaginal tissue atrophy is a risk. Male sexual problems have been attributed to gonadal and cavernosal arterial

insufficiency with resulting libido and erectile dysfunction [44, 45]. TBI or chronic GHVD may contribute to scarring or adhesions in the blood vessels of the penis. Most males recover Leydig cell function by 1 year, returning testosterone levels within normal range [42, 43]. However, males with sexual problems may have testicular insufficiency and diminished libido or erectile dysfunction even when serum testosterone levels are within normal range [44–47]. Thus they may require dynamic testing of pituitary–gonadal function or empirical testing of testosterone supplementation if levels are low to normal. Ideally male testosterone levels would be tested before beginning treatment as a baseline indicator of an individual's "norm." This would then provide more guidance in addressing testosterone changes on an individual basis.

Graft Versus Host Disease and Sexuality

High dose corticosteroids are a common component of chronic GVHD treatment and can continue for years. This treatment not only suppresses endogenous hypothalamic and adrenal hormones, but also has major impacts on physical features and body image, along with potential for emotional lability and depression. Over time it creates cushingoid features with weight and fat gain along with loss of muscle. Major joint problems are not uncommon and include avascular necrosis that can require joint replacement. With all of these changes, it is not surprising that feelings of attractiveness and sexual responsiveness suffer, along with aches and pains disrupting sensate focus during sexual activity. For many survivors who experience this treatment and its effects, sexual activity is put on hold for years and can consequently be difficult to re-initiate without intervention. In this circumstance, a combination of medical and behavioral treatments may be needed [48].

Chronic GVHD can impact sexual functioning for women through a number of symptoms and physiological changes [6, 18, 23, 25]. Vaginal dryness, irritation, pain, and bleeding can be due to chronic GVHD as well as to ovarian failure [29, 49]. At times, as GVHD diminishes in other parts of the body, medication doses may be lowered but then GVHD in the vaginal area can develop *after* resolving in other organs [50]. In a medical chart review of 11 patients with vaginal chronic GVHD, women had been on a regimen of systemic cyclosporine and hormone therapy yet still developed chronic GVHD in the vulva and vagina [29]. Onset occurred on average 10 months posttransplant but some women developed GVHD of the vulva/vagina as much as 2 years after HSCT. The pattern of GVHD of the vulva/vagina was most similar to GVHD found in the skin, although the severity of GVHD of the vagina did not correlate with the severity of GVHD found elsewhere. The work to date in this area has focused on women. For males, evidence of chronic GVHD effects specific to male genital tissue or sexual functioning has been very limited, although, chronic GVHD can cause inflammation, rash, and sensitivity in the skin of the penis.

The Interaction of Physiological, Behavioral, Psychological, and Social Effects on Sexuality After HSCT

When addressing sexual dysfunction in research or clinical care, it is important to consider contributions from biological effects on psychosocial factors. For example, low levels of testosterone (in both males and females) and years of high dose corticosteroid treatments for chronic GVHD are associated with decreased sexual desire and depressed mood [6, 22]. Calcineurin inhibitors or interferon treatments can affect cognitive function and mood [51]. Fatigue related to cancer and its treatment is likely to impact sex drive if it has other functional impacts [18, 52]. Hypothyroidism, diabetes, cardiovascular health problems, and significant loss of muscle mass are all frequent after HSCT and can contribute to sexual performance problems and loss of libido. Depression and antidepressant use, along with insomnia are known risk factors for sexual dysfunction in the general population and occur widely in transplant recipients. Thus a full

medical exam is needed for HSCT survivors who report sexual dysfunction.

Other Issues Contributing to Sexual Function

Numerous relationship issues after HSCT can disrupt the psychological responsiveness of one or both partners. A partner's needs and responses are relevant in determining both participants' sexual satisfaction. Preoccupation with health-focused tasks or worry by a partner, or a change in relationship balance, will potentially influence the couple's intimacy and, in turn, their sexual interest and responsiveness to sexual signals or approaches. Two aspects of this balance that are predictable after HSCT include the issue of infertility and the changes in roles. Any couple or individual who does not yet have children at the time of transplantation can be expected to have concerns about how they will manage infertility [53]. Caregivers may need help in moving from their role as caregiver back to a sexual partner and also to see their partner in a sexual way again and not just as a patient [36, 54]. Our research has documented that these concerns do not usually resolve with time and take active discussion and problem solving by couples. In addition, survivors and spouses may engage in protective buffering [55] and not express sexual interests or concerns about infertility for fear of upsetting or burdening their partner.

For single individuals the issues can be somewhat different than for those who are in a stable couple relationship. It can be difficult to explain to a new partner, or to repeat for new partners, the effects of chemotherapy and/or chronic GVHD on genital tissues and sexual responsiveness. This is especially true for young women who may be prematurely postmenopausal or young men whose erections are not as firm as expected. Guidance in raising these issues with new dating situations can be helpful for young adults especially, who may avoid relationships out of fear of not meeting their partner's expectations for sexual behavior.

Psychological Factors Contributing to Sexual Dysfunction

As noted above, common symptoms after HSCT have both physiological and psychological components. Consequently, separation of these factors is somewhat artificial. Figure 36.1 contains a conceptual model of sexual dysfunction that includes physiological and psychological aspects. Fatigue, depression, insomnia, body changes, even pain or other physical discomforts may have biologic roots, but they also have cognitive and emotional consequences that can actively contribute to inhibiting sexual activity or responsiveness. If one barely has the energy to maintain mandatory daily activities to promote health, it can be hard to imagine saving time and energy for sex. For survivors of HSCT this is a common experience in the months after treatment. In addition, appearance changes in hair loss (including pubic hair), muscle loss, skin rashes, skin sensitivity or dryness, scars, and weight changes influence body image which in turn contributes to sexual self-consciousness [16, 22, 52]. Fear of pain or discomfort, along with fear of failing to become aroused can become barriers to trying again for both survivors and their partners. Another barrier to return to sexual activity is the expectation that responsiveness should return to prediagnosis levels. Lack of communication about what has changed, what feels good or not, and insecurities about appearance can inhibit couple's attempts at intercourse. These worries and lack of communicating concerns are often also reflected in reduced intimacy. Patterns set in the months after returning home can turn into habits that continue for many years. Discussing with patients the potential changes that could occur with their sexuality could help manage expectations such that people are not as disappointed or anxious about changes that occur after treatment [56].

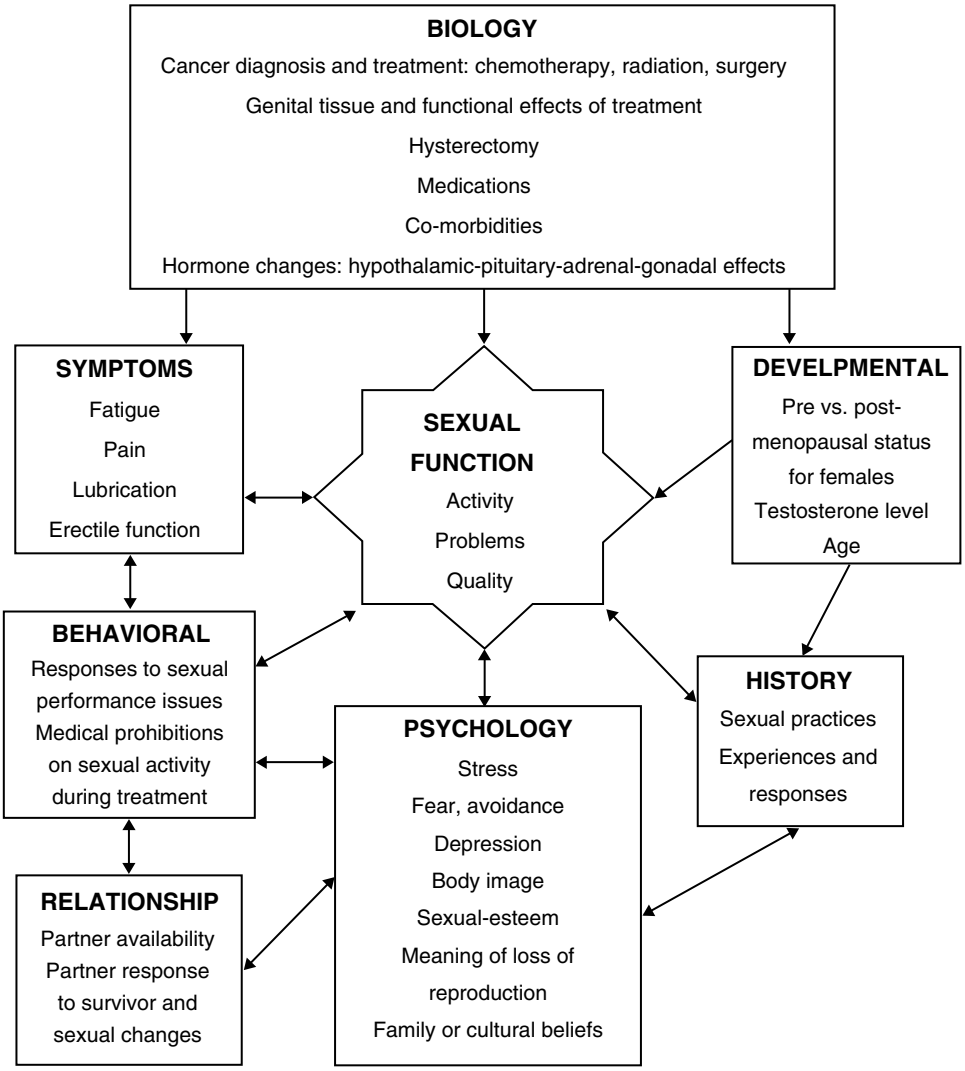

Fig. 36.1 Conceptual model of sexual dysfunction causes and effects in cancer survivors

Determining Who Is at Greater Risk for Sexual Dysfunction After HSCT

Other than gender, few clear risk factors for poorer sexual function after HSCT have been identified. In part, this is because these difficulties are so prevalent and most treatments have at least some impact on sexual problems. Men and women are at risk for enduring sexual problems, regardless of the type of transplant received [7]. Age is also a variable to consider, as younger women and those who are premenopausal before transplant report more problems with lubrication and other menopausal symptoms [6]. Other risk factors for women include not initiating hormone therapy until a year or more posttransplantation, being premenopausal before transplant, and chronic GVHD. Beginning hormone therapy as early as is medically safe for women who were premenopausal or on hormone therapy before

transplant seems to be protective of return to sexual activity and sexual satisfaction [6]. Evidence does not support any association between hormone therapy and chronic GVHD [46]. Unfortunately, prospective cohort studies indicate that hormone therapy with oral estrogen improves or prevents more serious decline in sexual function in women after HSCT, but does not eliminate problems [6, 23, 46]. For men risk factors include older age, chronic GVHD, and psychological function prior to HSCT [6, 9, 18].

Evaluating Sexual Functioning After HSCT

To be able to confidently measure a construct, it is important to have measures that are well validated within the population being tested. The timing of assessments also becomes critical as assessing sexual functioning *before* treatment allows evaluation of changes from an individual or couple's norms [52]. Since sexual function varies so greatly across the population even within the United States [57], individuals' norms constitute a better reference than population averages. After HSCT our data indicate that pretransplant sexual function predicts 19% of the variance in sexual function after 5 years, whereas 1-year sexual function predicts 36% of the variance after 5 years [4]. Thus baseline and 1-year function are strong indicators of how a survivor's function will be long term for both males and females. These results also provide evidence that intervention needs to be timed to intercede if possible within 1 year of transplant. In a 1-year longitudinal study of sexual functioning of HSCT patients who had received high dose chemotherapy as part of their conditioning regimen, just under half of the patients reported sexual dysfunction prior to treatment [58]. This finding has been supported in another study of male HSCT survivors [39].

To decrease potential hesitation to raise questions or discuss sexual problems, routine assessment of sexual function by designated health care providers needs to be provided to all patients [18, 32]. Reluctance to engage in these discussions is often as great or greater on the part of health care professionals as for patients, in part because providers do not see themselves as knowledgeable and able to treat the problems that patients raise [59–61]. However, the health care professional asking about sexual functioning also normalizes sexual issues and leaves the door open for the patient to disclose any concerns he or she may have now and in the future [62]. Having a standard assessment tool can decrease these barriers and give survivors and their health care providers a way to start a conversation about sexuality. This standardized measurement then becomes a reference language for explaining both problems and progress. Thus assessment not only provides a reference marker for change but also the terminology that facilitates clinical communications [63].

Recent reviews of sexuality after cancer [64] have indicated a need for further research into assessing sexual function [63]. A limited number of tools have been developed for or tested with cancer patients and survivors. Those that do exist have focused on gynecological cancer [65, 66] and erectile dysfunction after prostate cancer [67, 68]. Several broad quality of life measures contain sexual functioning subscales but may be limited to 1–3 questions and were not designed with long-term cancer survivors in mind. Thus, there has been a need to devise a measure targeted to HSCT survivors for their specific needs and to do rigorous psychometric testing of sexual function measures in this population.

To meet this need, we tested the Sexual Functioning Questionnaire (SFQ) in a sample of 400 cancer survivors and their matched noncancer controls who were of the same gender, ethnicity, and within 5 years of age of the cancer survivors [9]. The questions were based on the Brief Sexual Functioning for Women (BISF-W) [69]. The initial form of the SFQ was tested with 200 HSCT recipients before and after their treatment. The instrument was revised to delete items that did not load on any factor and to add items that participants had written in the open-ended questions. In its final form the SFQ is a gender-specific measure with 30 items. It has nine subscales and two overall scores (overall SFQ

score and SFQ Treatment Impact). The nine subscales correspond to the sexual response cycle plus specific sexual behaviors or difficulties: interest, desire, arousal, orgasm, satisfaction, masturbation, relationship, activity, and problems. A more brief version is in preparation.

The SFQ asks about sexual practices in the past month. The measure does not depend on the participant having a partner, the sexual orientation of the participant, or the medical condition of the respondent. However, a Treatment Impact Scale can be scored separately so that the impact of specific treatments on sexuality can be assessed. Principal component analyses were conducted separately for men and women. No item factor loading differences were found by gender, therefore the final factor analysis both combined males and females. Factor loadings for each item were above 0.5. Reliabilities were above 0.8 for each of the subscales and for the total score. There was also high test–retest reliability when comparing pre and posttransplant scores. The SFQ had very good psychometric properties as evidenced by the reliability and validity testing. Validation was confirmed with content, construct, and criterion validity. Discriminant validity was also established with the ability of the measure to distinguish between survivors and controls.

With the National Institutes of Health and the Patient-Reported Outcomes Measurement System (PROMIS) Network [70], there is a unique opportunity to have an item bank specifically for sexual functioning. Measures for fatigue, distress, pain, social function, physical function have already been developed through the PROMIS initiative. A sexual function item bank will be available in the near future for use [71]. The items were developed through focus groups and were further tested with a new group of cancer survivors [72]. Each item was tested with at least five participants for their ease of comprehension with at least two people who were low in literacy and a person from an ethnically diverse background. The authors noted that the process of interviewing specific items enabled them to further refine and clarify the items so that they could be more understandable to a broader audience. Further work needs to be done to be able to use computerized-adaptive testing (CAT) but that is the goal of the PROMIS group. An additional need in assessment is to validate a measure for same sex couples as the work to date has been primarily with heterosexual couples, although the SFQ is usable by heterosexual, and homosexual couples, or individuals without partners. The validity of using sexual functioning measures has not been tested with racially or ethnically diverse populations and also demonstrates a research and clinical need.

Medical Treatment Options

While treatments exist for sexual dysfunction, health care professionals are usually untrained to have the relevant discussions needed to appropriately prescribe effective care [60]. Training of these health care professionals is needed to improve outcomes in both sexual function and reproductive health after HSCT. A needs assessment conducted at the MD Anderson Cancer Center demonstrated that a third of the patients assessed, who had various types of cancer that included hematologic malignancies, would have liked a fertility consultation *prior* to the initiation of treatment [73].

Park and colleagues offer a model to assist health care providers in starting the conversation about sexuality and is called the “5 A’s” [74]. The first A stands for Ask – it is important for the health care team to ask about a patient’s sexual functioning as it gives permission for the patient to disclose any concerns now and in the future. The patient should be asked periodically over the course of treatment and survivorship as sexual functioning can change over time. The second A stands for Advise. It indicates a need to convey to patients that sexual functioning could be affected due to their cancer and treatment and to report changes that could occur. The third A is for Assess. The measures discussed in the earlier section on the assessment of sexual functioning could be useful so that changes can be monitored over time. The fourth A stands for Assist. Patients can be directed to various resources, over the internet or to a referral to see a specialist in sexual functioning if that is

deemed appropriate based on the needs of the patient. The last A is for Arrange Follow-up. At subsequent visits, the health care team can check to see if the patient has followed up with the referral or has any additional concerns or questions after looking at print or internet materials. As evident in Table 36.1, treatment options will vary based on the gender of the patient.

Women

If a woman is premenopausal or has been on hormone therapy before HSCT, discussion of hormone therapy options is needed so that, if appropriate, these can begin as soon after transplant as medically safe. The risks and benefits of hormone therapy need to be reviewed, along with a plan for when hormone therapy would be discontinued and under what conditions. In a nonrandomized study of younger women who did versus did not take hormone therapy, taking hormones did not affect chronic GVHD in allogeneic survivors [46]. Nonetheless hormone therapy would not be an option for women with elevated risks for hormone-sensitive tumors or those who have chronic GVHD of the liver [6, 34]. Hormone therapy will sometimes restore ovarian function [75] in addition to alleviating symptoms. Studies that have assessed the relationship between hormones and sexual functioning have found that women still experience sexual dissatisfaction while taking estrogen therapy [23, 46]. It has been proposed that is due to the reduced effectiveness of hormones absorbed through the intestinal tract [34]. Testosterone therapy has been thought to increase sexual libido for women, but was not found to do so in a group of female cancer survivors who also were not on estrogen therapy [76]. Randomized

Table 36.1 Treatment recommendations for sexual dysfunction

	Type of problem	Treatment options
Women	Vaginal dryness	Lubricants, vaginal moisturizers, hormone therapy, topical estrogen
	Vaginal atrophy, dyspareunia	Estrogen creams or rings, lubricants, dilators
	Ovarian failure	Hormone therapy if risk-benefit considerations support use
	Graft versus host disease in genital area	Topical cyclosporine
	Vaginal stenosis	Dilators, estrogen creams or rings, surgery
	Lack of desire/arousal	Retraining of sexual responsiveness through genital massage and use of vibrators
		Sensate focus training
	Vaginal dryness	Lubricants, vaginal moisturizers, hormone therapy, topical estrogen
Men	Erectile dysfunction	Erectogenic medications
	Low testosterone	Testosterone therapy
	Performance anxiety	Communication with partner about sexual satisfaction versus erectile function
		Scheduling intimacy dates without sexual intercourse
		Sensate focus training
Couples	Lack of intimacy or sexual activity	Communication intervention
		Scheduling intimacy "dates" to gradually reintroduce sexual activity
		Scheduling sensate focus, initially proscribing intercourse
	Lack of desire/arousal	Scheduling intimacy dates without sexual intercourse
		Sensate focus foreplay with gradual progression toward sexual intercourse
		Teaching in partnered use of lubricants, dilators, vibrators, and sensate focus to assist with relearning sexual comfort and satisfaction with partner responses

These treatment options have not been tested with HSCT patients in clinical trials

controlled trials have yet to be conducted on the efficacy of hormones for sexual dysfunction in women after HSCT. Thus more research is needed on the risk–benefit ratio of hormone therapy to be able to recommend this option with appropriate safety and efficacy qualifications. Still the abnormal and premature cessation of endogenous hormones for young adult females is equally untested for consequences, safety and efficacy. In short, a balance of empirical testing of hormones and thoughtful weighing of risks and benefits for the individual is the best recommendation possible at this point.

Women may find topical estrogen to be helpful in the treatment of vaginal dryness or constriction, and for women who have vaginal or vulva chronic GVHD, topical cyclosporine may be another treatment to consider [29]. Some women use vaginal dilators or vibrators to reduce constriction and sensitivity to penile penetration. In more extreme cases, women with vaginal stenosis may need surgery [29, 50]. However, the use of estrogen creams, dilators, or vibrators may obviate the need for surgery to correct stenosis. One study has described the use of topical estrogen as helpful in relieving chronic GVHD symptoms [29], and another found it ineffective [50]. Again, the research in this area is very limited, has small sample sizes, and data are conflicting or nonexistent.

Men

Male sexual problems center on lack of libido and erectile dysfunction [26]. Results from a small case series of eight patients 6 months after HSCT suggested that testosterone injections and sildenafil one to two times per week improved sexual performance for men with erectile dysfunction, low libido, and ejaculatory disorders [26]. However, other data indicate that most males recover testosterone levels and sexual function between 6 months and 1 year after transplantation [77]. Thus without controlled clinical trials, it is unclear whether sexual function in the treated men would have recovered without treatment so caution is needed when interpreting the results and in applying them in clinical practice. If medications do not work, men can consider external vacuum devices or penile implants, but very few elect mechanical solutions to erectile problems [78, 79].

A drug that has shown promise in treating erectile dysfunction in men and lack of arousal in women is a class of drugs called melanocortins [80]. Bremelanotide, a type of drug in this class, has been used in healthy men and was found to be effective in treating erectile dysfunction. This drug may have a safer profile than that of the PDE5 inhibitors because melanocortins can be used in conjunction with nitrates, which is not the case for PDE5 inhibitors. In women, bremelanotide has been associated with increases in self-reported arousal. However, more research needs to be done with melanocortins with regard to efficacy and risk–benefit ratio, and to also test the drug in HSCT survivors as the samples to date have used healthy people. Although untested in HSCT survivors, men may benefit as much as women from nonmedical interventions that emphasize intimacy and adaptation to sexual responsiveness changes after treatment.

As noted earlier, sexuality involves both biologic and psychological responses. While medical factors and medications may inhibit sexual response, the cognitive and psychological responses to these biologic factors will have a major impact on sexual satisfaction. As a major component of this psychological reaction, relationship quality and the response of a partner to the physiologic changes after transplant can positively or negatively affect sexual functioning [18, 20].

Behavioral Treatment Options

A majority of sexual changes after HSCT are managed with behavioral strategies and, for women, topical agents or devices rather than medical treatment. A combination of approaches is likely to be most effective for both men and women utilizing education, hormone evaluation, hormone or other medication therapy where indicated, topical or behavioral strategies, and couples intervention. However, no study has

tested this combination of therapies to address sexual dysfunction after HSCT.

While traditional sex therapy such as sensate focus treatment [81] and medications are available to treat sexual dysfunction, there are other important issues to consider. We find in our clinical practice that a communication and intimacy-based approach is remarkably effective for many couples in facilitating return to satisfying sexual activity after cancer and HSCT. In addition to addressing fears and overcoming avoidance, we encourage gradual re-introduction of sexual activity beginning with scheduling of time for "dating" and intimacy without intercourse. Even one or two couples counseling sessions focused on communication around appearance, fears, barriers, and changes in sensation can facilitate readiness to engage in intimacy and return to sexual practice. Since vaginal dryness is so common, we recommend lubricants for all women after HSCT until experience informs them whether continued use of lubricants is needed. When avoidance, fear or negative experiences have added to sexual problems, we urge women alone or couples to try vibrators and dilators until they are comfortable with their physical responses. Helping couples to decide on hand signals or other brief communication cues can facilitate their feeling safe to try sexual activity after a long period of abstinence and numerous psychological and physical adjustments.

Few sexual function biobehavioral treatments have been tested with other HSCT or other cancer populations. Robinson and colleagues [82] used a group intervention for women who were diagnosed with gynecological cancer and were treated with radiation therapy. Women were randomized to one of the two groups: an intervention that included education about how to use lubricants and vaginal dilators or a control group. The intervention group consisted of two 1.5-h group sessions. Women were informed about sexuality and cancer, encouraged to talk about their fears, and educated about the use of dilators and lubricants. Women in the control condition met with a counselor and were given a book on sexuality. Women of all ages reported a decrease in the fear of sexual activity and women under the age of 50 in the experimental group were more adherent to the recommendations regarding the use of lubricants and dilators than were older women. This trial is a promising start in testing strategies to teach women how return to sexuality after treatment but also demonstrated that compliance is an issue with behavioral treatment recommendations. Behavioral treatments after breast cancer have also demonstrated improvements in sexual functioning. Scott and colleagues [83] tested a couple-based intervention for patients diagnosed with either early stage breast or gynecological cancers. The intervention consisted of communication training, sexual counseling, and to explore as a couple the cancer experience. The couple-based intervention was more effective at improving sexual adjustment at 1-year outcome than an individually based intervention. Rowland and colleagues tested a 6-week psycho-educational group intervention in a randomized controlled trial with breast cancer survivors (without their partners) who had been identified as having problems with their sexuality [84]. The intervention focused on educating survivors, improving communication skills, and reducing anxiety in sexual situations. Those randomized to the group intervention reported increased relationship adjustment, communication and satisfaction with sex compared to the control group at 4-month outcomes. Although these findings are promising, interventions need to be tested with HSCT survivors.

Depression or fear, fatigue, loss of muscle mass, antidepressant use or other medications that impact libido and arousal, as well as relationship conflict are just a few factors that need to be assessed when considering behavioral approaches to sexual dysfunction [20]. When deciding on treatment strategies, it is important to consider the multiple pathways to sexual dysfunction along with the many ways that people can increase their sexual satisfaction beyond traditional intercourse. For most people this involves a gradual return to intercourse with a partner, but not infrequently, full erections, orgasm or sexual responsiveness are not achieved at the same level as before diagnosis. Nonetheless many survivors find satisfaction from renewed intimacy and sexual function that is rewarding if not a full return to the level they had before diagnosis. Table 36.1 summarizes treatment options for women, men, and couples.

Research Needs in the HSCT Population

While we know from survey and longitudinal research that sexuality is a major concern for many HSCT survivors, there are gaps in the research that need to be filled. Much of the research has been conducted with white, heterosexual, middle or upper economic class couples. Little is known about the sexual functioning, needs or concerns of people who are not in committed relationships, who have cultural or other differences from the usual research samples, or who are in same-sex relationships. In addition, little is known about HSCT survivors who are sexually inactive for many years after treatment. We do not yet know much about the sexual outcomes of survivors who received reduced intensity chemotherapies followed by HSCT. While descriptive studies have been recently published, mechanism and treatment studies are severely lacking. The impact on partners also needs more research as sexual problems in the patients more than likely also affect the partners. The need for studies of treatment in this area cannot be overstated given the prevalence of problems, the conflicting or uncertain data from those outcomes that are published, and the questions of safety for some of the hormonal treatments frequently prescribed.

Recent efforts to reduce the toxicities of HSCT have utilized very low dose chemotherapies and TBI in attempts to optimize a "graft versus leukemia" effect. This increasingly widely used methodology for treating hematologic malignancies seems to spare gonadal function along with other organ systems, but risks for chronic GVHD remain. Prospective, longitudinal studies need to be conducted to assess the sexual function of patients who undergo these reduced intensity regimens.

Conclusions

As more people survive cancer and its associated treatments, it becomes imperative to monitor survivors for long term and late effects. These generally young adult survivors have typically undergone high dose treatments to cure their malignancies, and sexual dysfunction is one of the most prevalent long-term complications of treatment. Survivors and their partners should be assessed for their sexual functioning prior to treatment so that any changes may be monitored over time and the appropriate treatment recommendations can be made. Although medical and behavioral treatments can be used that are similar to those used in other populations who experience dramatic changes in sexual response, the safety and efficacy of these treatments in the long-term HSCT survivor population remains to be tested and documented.

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Chapter 37
Sexual Health in the Terminally Ill

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Keywords Muscle Relaxing Effects of Sex • Oncosexology • Pain Reducing Effects of Sex • Pain Threshold • Pair-Bonding Effects of Sex • Palliative • Palliative Phase • Sex In Hospice Setting • Sexual Expression • Sexual Function • Sexual Identity • Sexual Motives • Sexual Rehabilitation • Terminal • Terminal Phase

Introduction

Despite the integral role sexuality and intimacy play throughout a person's lifetime at physical, emotional and social levels, the topic of sexuality is rarely raised by health professionals in advanced cancer or palliative care setting. The objective of this chapter is to raise awareness, increase knowledge and provide professionals with practical strategies on communication and patient support regarding sexuality and intimacy during the palliative–terminal phase of cancer. Drawing on numerous case studies and qualitative examples from a predominantly older age group, the information presented in this chapter does not pretend to have any quantitative value. The intent is to share our experiences and information on a topic that is nearly never discussed in the sexological literature, and rarely in the oncology literature. Thus, our aim is to bring sexuality and intimacy out from under the wraps of palliative–terminal care, naming one of the great taboos at end of life.

Sexuality and Intimacy in Cancer and Palliative Care

People neither have a "standard sexual pattern" nor "standard sexual relationship." Throughout sexual relationship changes occur, irrespective of health status, so that after the first falling-in-love stage couples develop very different patterns of sexuality and the meaning of sexuality tends to vary between individuals. Accordingly, when cancer strikes, the influence will differ from one person to the other and from one couple to the other.

Experiencing a Cancer Diagnosis

When a person is newly diagnosed with cancer much energy will be spent on coming to terms with an event that frequently transforms the way they view themselves, their partners and their sexual and intimate world. The diagnosis can mean an unexpected shock or may come after a protracted period of feeling unwell. Just hearing the words "you have cancer" raises fear of disability and death for many people, where sexuality and intimacy usually pales into the background of active treatment regimes and survival. Some people will

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deliberately choose a cancer treatment that has less physical impact on sexual function [32]. Other people are far more concerned by the emotional reactions to cancer [33]. As a result of the physical and emotional impact of cancer, many couples have an extended period of nongenital sensual contact, providing a powerful way of connecting.

Effects of Cancer Treatment on Sexuality and Intimacy

Most cancer treatment regimes have negative sexual consequences. For example, sexual desire can be diminished by fatigue, weight loss or gain, disfigurement due to stoma, surgery scars, lymphoedema and loss of hair. Similarly, lubrication and erection can be disturbed by surgical or radiation neural damage and by antidepressant medication [22, 26, 36]. Ejaculation will reduce or disappear after prostate treatment and can become retrograde after surgery for testicular or rectal cancer; orgasm can disappear due to medication or neural damage [18]. Intercourse can become impossible after extensive surgery for cancer of penis, vulva or bladder [5, 21, 25]. Besides there can be emotional damage to desire, relationship or identity by fear, depression, guilt, changed partner roles and the communication confusion due to female–male differences.

Treatment Ends: Now What?

At the completion of active cancer treatment, most people are longing for a return to the important things in their lives including those that result in intimate or sexual pleasure. Many patients and couples now enter a stage of sexual rehabilitation which is the process of restoration of sexual function, intimate competence and sense of identity so as to regain as much as possible within the physical capacities of "the new self" and the emotional capacities of "the new relationship." One can expect that the recovery process will be more complete when the quality and the quantity of the sexual relationship were better before the diagnosis and when better sexual information and counseling were given during diagnosis and in the treatment phase. The rehabilitation process is more challenging when disease and treatment have destroyed the anatomy and physiology needed for sexual functioning or when the relationship with the partner has come to an end.

Depending on the physical damage of the medical interventions, their flexibility and their core values, couples return to different levels of sexual satisfaction. Most resettle either at their precancer or prediagnosis levels of sexual functioning or at a lower level. Some even reach better levels. Reflecting upon priorities in behavior and relationship, they no longer want to be guided by unrealistic expectations and decide to only have "good sex."

Sexuality in the Palliative or Terminal Settings

For some patients, cancer will be cured completely by treatment. However, this paper deals with sexuality in the group of patients for whom treatment no longer aims to cure the cancer but controls the physical burden of the disease. The term *palliative care* means that quality of life is the primary goal of living with, and dying from an eventually fatal condition. [28]. For some people, palliative care comes after a long trajectory of cancer treatment or lengthy periods of remission. For others who are diagnosed with advanced cancer or aggressive disease, the palliative approach to quality of life, management of disease or treatment side effects and the psychological support and care of the person and their family to live as actively as possible until death is the central focus [28]. With *terminal* we mean the final stage before death. Said differently, terminal care is when a progressive condition has no cure and is reasonably expected to cause the death of a person within a foreseeable future. The definition includes both malignant and nonmalignant [28].

Slowly or acutely the health professionals, the patient and the partner realize that the patient now has reached the palliative–terminal phase where cure is no more possible, and care has

become the major goal. In this phase of care sexuality can become a very important aspect.

The need for pleasure, grief, love, relaxation, distraction, painkilling, affirmation or anger results across people and within couples in a wide variety of love-making.

Some couples quit sex completely and some are satisfied with only petting. But other couples get into active, desperate and sometimes even violent sexual encounters. Then pain, tiredness, changed physical sensations and disturbed hormone levels can interfere with these sexual needs. In these palliative–terminal phases of cancer, sexuality can be accompanied by a rollercoaster of emotional reactions with depression, anxiety and confrontation with mortality [33]. Thus, it is not surprising that sexuality means different things to different people at different stages of their lives [14]. The variety of sexual reactions clearly shows that sex has many more meanings than only recreation, relation and procreation. Maybe the most impressive message is that sex is not only for the young, the healthy and the beautiful and that people remain sexual beings until they die [16]. In this phase, when quality of life becomes very important, patients and their partners deserve optimal sexological care and attention. Since most contraindications towards treatment strategies now have disappeared, different treatment strategies and interventions can improve the quality of life in general and the quality of sexual life in particular.

Discussing Patient Sexuality in Palliative and Terminal Care

Although listening to sexual or intimate concerns in the palliative–terminal phase of cancer can highlight important lessons for the treating team, it is painfully clear that the majority of health professionals are very reluctant to raise the topic. Among the reasons are fear of causing the patient embarrassment, fear of litigation, not knowing where to begin, not having the skills to deal with emerging problems, as well as concern about what colleagues would think of them in a culture where patients are not perceived as sexual beings [14, 15]. As a result health professionals rarely provide the opportunity for patients to express their more intimate sexual concerns, particularly in terminal situations. For some patients that is no problem, but for others the failure of health professionals to acknowledge their changing sexual and intimate needs can be devastating and result in additional loss and grief – as a substantial range of couples have a compelling need for sexuality and eroticism in the face of life limiting illness [16, 20, 29]. Sexuality in this sense encompasses a wide area of sexual identity (including feeling beautiful and feeling manly or womanly), sexual expression (including sexual function, masturbation, sexual release, eroticism and sensuality) and sexual relationships. Health professionals need to be aware that despite the sexual openness in the western world, patients and partners are frequently reluctant to raise such topics for fear of jeopardizing their care, feeling they should be grateful to be alive and their assumption that “if it were important, the health professional would have raised it with me” [15].

Sexologists do not usually meet couples in the terminal stage of a disease. We draw upon the clinical experience gathered by of one of the authors (W.L. Gianotten) when meeting widowed people with sexual problems after starting a new relationship. A common example is the man with an erectile problem that developed after his wife died of breast cancer or bowel cancer. Taking the sexual histories of such men, it has been surprising to hear the great variety in sexual and intimate behavior after the cancer was diagnosed; especially in the last stages of the disease. Some told that they lost all erections (included the early morning erections) when the partner got very ill and for some men the erection did not return until many months after the woman’s death. However, other men have shared that they continued to masturbate, more or less independent of the partner’s process, through several or all phases of their partner’s disease and after death. In other scenarios there was increased mutual sexual contact until the very last days. The topic was raised as a regular part

of health assessment in every person who had experienced the process of disease and death of a former partner. Amazingly nearly all widowers and widows were relieved and very glad to share that information both with the health professional and with the new partner. Despite ageist assumptions about people lacking interest in sexuality after the age of 60 [33] many of the surviving partners were from the higher age ranges defying an implicit myth that only the young are sexually active.

The Why of Sex

Human beings have sex for various reasons. In the common belief people do so out of love, to reproduce, to experience pleasure, or to release sexual tension. However, there are many more reasons as Meston and Buss [23] highlighted. In a group of >400 relatively young people (17–52 years) they identified 237 expressed reasons for engaging in sexual intercourse. Ranging from physical reasons (aiming for instance at stress reduction or pleasure) to goal attainment reasons (aiming for instance at resources) and from emotional reasons (guided by love and commitment) to insecurity reasons (aiming for instance at self-esteem boost, out of duty/pressure or because of mate guarding).

For the population with serious diseases, other reasons for sexual expression and intimacy come to the fore ranging from very physical (aiming at pain relief, sleep, muscle relaxation and "recharge the batteries") to psychosocial (giving or receiving comfort or as a way "to deal with heavy emotions").

After dropping our taboos on *cancer and sexuality* and our taboos on *dying and sexuality* we become aware that this palliative–terminal phase goes with different motives for sexuality that subsequently will lead to different sexual expression. These motivations vary according to age, culture, stage of the relationship, personal character and emotions of the moment. There are not only huge differences between individuals, but also in one person between the various moments of the day, the week or the phases in the palliative–dying phases. Some people, for instance, need sex to charge the batteries of their sexual identity, whereas others need it to charge the batteries of their relationship.

The Direct Physical Benefits of Sexual Expression

In spite of the fact that many psycho-oncology professionals still struggle to address sexuality in their patients, one could argue that "talking sex" belongs to their discipline, since the benefits of sexuality and intimacy especially will cover the emotional aspects of quality of life.

A new approach in sexual health deals with the physical benefits of sexual expression. [10, 35]. Some of those benefits are long term and related to disease risk reduction and even longevity. In the context of palliative care, the direct benefits are far more relevant, so here we will pay attention to those elements.

- *Pain reducing effects*. Good sex, like other pleasurable things in life, can distract from pain. For women there is an additional payoff. Genital (especially vagino-cervical) stimulation and orgasm actively elevate the pain threshold [19].
- *Muscle relaxing effects*. Both sexual stimulation (especially genital vibration) and orgasm decrease muscular tension for several hours [1, 6, 12].
- *Sleep enhancing effects*. Having had good sex (with or without orgasm) is for many people an introduction to healthy sleep. Probably caused by a mixture of being tired, relaxed muscles, relaxed mind and maybe neuroendocrine changes.
- *Immediate pair-bonding effects*. During sexual excitement and at orgasm oxytocin is released [7, 8, 27]. Oxytocin is also released during massage and for many people stroking is one of the forms of good sex. Oxytocin acts

on many levels [34]. It increases the amount of trust [9] and diminishes the autistiform ("autism resembling") aspects of behavior [13]. The increased oxytocin level after sex is probably one of the reasons why men talk after orgasm.

- *Mood-enhancing and antidepressant effects*. Oxytocin is also negatively correlated with anxiety and depressive symptoms [31].

The How of Sex in the Palliative Stage?

Healthy people, including health professionals, apparently assume that people facing life limiting disease or palliative–terminal illness have no sexual desire and are not interested in sexual expression. They probably believe that the energy for such feelings is lacking or that the disease status is at odds with sexual commitment and sexual pleasure. However, many patients (and partners) do not fit into that assumption. Whilst we do not have the literature to support numbers for the palliative situation, we can make comparisons with figures for depression. Swiss research in young people and American research in men showed that when getting depressed 35% of females and 26–47% of males indeed had less sexual desire. [2–4]. However, 56% of females and 37–51% of males had no diminished sexual interest, whereas 9% of the women and 9–23% of the men were more interested in sexual expression.

We suppose that comparable processes happen in cancer patients and in the palliative–terminal stage. Besides, sexuality is not just a patient topic. For most people it is a joint venture where the partner can not only be in tune with the patient, but also have very opposite needs. Apparently the change into a caretaker–patient relationship can kill sexuality for some couples, while for others it can enhance intimacy to a level never experienced before.

Various Reactions and Topics in the Palliative–Terminal Phase

Some people quit sex completely. Usually it is the patient who stops everything because of physical problems, absence of motivation for physical contact or otherwise. However, the partner can also be the one who stops or both members of a dyad. In other couples sexual contact consists of sensual contact without genital involvement, which can imply less than what they had before, but it can also mean an improvement in the quality of contact. A small number of couples apparently seem to continue sex as usual, as if nothing has happened. Once in a while this appears to be caused by obsessive–compulsive elements in the sexual relationship. For others, however, continuing sex seems to be a routine which gives them energy or whatever else sexual expression can offer people in terms of physical relaxation, pain-relief, emotional relaxation, easy sleep, togetherness, consolation, comfort, self-esteem or coping with heavy emotions. In some couples their sexual contact is intensified and increased. Here are some quotes to support our assertion:

> We made love every day, because it could be the last time! (69-year-old widow of a man who died of stomach cancer).
>
> Those last months we had sex very frequently. In spite of the cancer he was my hero. We both enjoyed that so very much! (74-year-old widow of a man who died of liver cancer).
>
> We had sex and cried and had sex. That was nearly the last thing I could do for her. She was so happy to share that with me! (48-year-old widower of a woman who died of breast cancer).

The argument of coping with heavy emotions was important in the few couples who had very intense and sometimes even aggressive sex. Mentioned were anger and confusion, but also desperate clinging to each other (as a way to say farewell?). One explanation for intensified contact is that sexual arousal can happen more easily in the context of strong emotions (as many couples have experienced after an intense quarrel).

Some couples have variations in between with, for instance, the female patient having only sensual contact and the male partner experiencing the full range of sexual response on his own. Some partners apparently follow a different track. They have sex outside their relationship and we only can guess at the underlying motives. It could for instance be a reaction to the stress of the situation. For men who are not able to masturbate it could be a way to deal with their sexual tension without disturbing the diseased partner. According to Meston and Buss [24] such behavior could also be a way to boost the sexual ego or to prepare for moving on.

In the face of death there frequently is an intensification of emotions towards each other. Memories from the past can pop up. Some couples are confronted with "unfinished business" like missed sexual opportunities, or jealousy regarding real or supposed extramarital relations. In some couples this is the final moment of acceptance, in others it seems as if this is the last opportunity to let the other pay the bill of guilt and pain. Some couples speak of the sexual future or the relationship of the surviving partner. The "third one" can become part of the couple discussions (even during sex itself). Some patients advise or "allow" the surviving partner to restart after dying an extramarital affair of the past, and this will bring some couples closer. However, the supposition that after the surviving partner can restart an old affair can also be threatening and severely disturb the so badly needed intimate contact. The reactions indeed seem to cover a wide range between manipulation based on nagging jealousy and warm, caring love.

The Role of the Medical and Helping Professionals

In the last stages of living with cancer the quantity and quality of sex are determined by a multitude of factors [30]. On one hand, there are the personal and relationship factors (single or coupled, the kind of relationship, flexibility, coping capacities and value system).

On the other hand, there are the disturbances due to the cancer itself and the treatment interventions (anatomical damage, pain, fatigue, hormonal deficits, medication side effects, disfigurement, etc). And finally there is the quality of care. Here the medical and helping professionals have important responsibilities towards the patient's quality of life (as many of the sexual disturbances are caused by anti-cancer interventions). In this situation there are at least three important aspects: attention, optimal information and proper interventions.

Attention for the sexual topic is nearly always forgotten in the palliative stage. Since we know that sexual expression remains important for many of these patients and since we know that most of them feel embarrassed to ask questions or discuss sexual problems, it is our responsibility to pro-actively raise the sexuality topic in our consultation and care [17].

Optimal information on sexual functioning and its various disease and treatment-related changes is, on one hand, a way to facilitate discussing sexuality and, on the other hand, an important way to improve the mutual understanding in the couple. An example is explanation on the side effects of antidepressants or anti-emetics (see opening lines below).

Proper interventions in this stage can be very different from the interventions in the curative stage. Knowing that just little time is left, one need not to worry about the cancer-enhancing capacity of some hormones or the risk of dependency on painkillers or sleep medication.

Various Organizational Problems and Solutions

Introducing Discussions About Patient Sexuality and Intimacy

Many health professionals have shared with us that especially in palliative–terminal care, they "just don't know where to begin" in raising the topic of sexuality or intimacy. Previous chapters

in this book have addressed strategies to validate the topic and make it okay for patients to discuss sexual or intimate issues.

When the patient is not going to survive, apparently the taboo on discussing sexuality and intimacy increases. There is, however, no reason to abstain from such discussion. Usually even then good contact can be achieved by asking open-ended questions such as;

> You have been through so much lately. How has this affected the more intimate parts of your relationship?
>
> How do you feel about your sexual relationship since your cancer has progressed?
>
> Many patients who have been through similar experiences have shared that the side effects of this drug really get in the way of their intimate or sensual relationship. How has it been for you?
>
> How has all of this affected the way you feel about yourself as a man/woman?

Creating one's own opening lines and practicing them with a colleague or friend enhances the comfort in raising this important issue with patients in our care.

Creating Space/Room for Undisturbed Intimacy

Many patients in the palliative–terminal phases of cancer report that one of the greatest deterrents to achieving intimacy or sexuality is lack of privacy and fear of being disturbed, whether at home or in a hospice setting. Placing patient sexuality on the agenda requires a cultural shift in viewing the patient as a sexual being until the moment they die. That should include asking them how the environment could be better adapted to promote intimacy and sensuality.

For some patients in a hospice setting, it is as simple as placing a "do not disturb" sign on their door or curtain and providing adequate analgesics to ensure comfort. Enabling mattresses to be tied together or providing double hospital beds, ensuring there are extra pillows for comfort and to support aching limbs, towels or incontinence pads for hygiene, encouraging the couple to take a shower or bath together to relieve muscle aches or fear of incontinence, are some of the practical strategies health professionals can engage in to change the culture of palliative–terminal care. Some hospice and palliative care settings in Australia have set up private, sensuality rooms with a comfortable double bed, massage oils, CD player and fun sexual aids to experiment with behind the privacy of a closed door.

People being cared for at home also speak of multiple interruptions, lack of intimate time and space to explore sensual changes that have occurred throughout the palliative–terminal phase. Placing intimacy and sexuality on the agenda at home is about setting aside a time of the day or night when the sick person is likely to have energy and comfort to "have a date" with themselves or their partner. We say to people that they do not have to answer the door bell, or phone and that if they have set aside an intimate moment alone or with a partner, it is more likely to happen. Knowing the time and date gives people time to plan and prepare. Home nursing care should sometimes be arranged in the evening since it is for many people difficult to change from the nurse and patient roles to the roles of lover and beloved. The couple may wish to dress up, set the scene with candles or sensual oils, play favorite music and anticipate pleasure and fun. For some, just being held will provide enough intimate connection. Others will explore new ways to touch their changed body and enjoy a wider range of sensual experiences.

Various Physical Problems and Solutions

There are many nonphysical reasons for disturbed sexuality and intimacy (Table 37.1). Examples are shame due to a changed body, performance fear and recurring memories of past sexual or physical abuse, and also relationship changes such as the complexity of simultaneously being caretaker and lover and regression into traditional gender roles. Here we will concentrate on solutions for the more physical aspects. Some of these solutions may seem superfluous since patients

Table 37.1 Problems and solutions

Problem	Possible solution(s)
The vagina is dry and atrophic	There is no more reason not to allow local or general estrogens
The vagina is dry during intercourse, for instance due to radiotherapy	Liberal amounts of proper lubricants should be advised. Application by the gentle fingers of the partner will increase intimacy in some relationships, but can, in others be felt as too "medical" and forestall intimacy
The vagina is too narrow for vaginal intercourse	Alternative ways for sexual contact and satisfaction are one part of the discussion. When both partners are very keen on penetration a strong local anesthetic cream can be used in the vagina. One can also recommend considering anal intercourse (usually not a solution if the vaginal stenosis is due to radiotherapy). For satisfying anal intercourse at least proper muscular relaxation and a liberal amount of petroleum jelly or silicone lubricant is needed
The vagina is too shallow	Deep dyspareunia partly depends on the length of the penis in erection. In some couples a different coital technique can prevent pain. The woman can elongate the coital barrel by firmly closing her legs and the man can try not to go too deep (but then usually loses his erection). Another solution is to put a soft foam donut around the base of the penis (available at a hardware store), by which the penetrating part of the penis is shortened
Desire is lost due to too low androgen levels	This situation needs testosterone/androgen replacement. In woman in the palliative phase most reasons for not administering it have disappeared. Next to improving sexual energy, androgens also improve vitality, general well-being and mood. This effect can already be produced with very low doses of testosterone. An additional benefit of androgen supplementation is being less tired
Desire and/or excitement are disturbed by pain	Adequate and liberal painkillers should be prescribed and proper timing explained. Now, there is no reason to be afraid of dependency. In some countries cannabis can be prescribed ("medical marijuana") to control both pain and nausea. The prosexual side-effects can give additional benefit
Sexual contact is impeded by a painful body or belly	The peak of maximum effect of a strong painkiller should be combined with advice on a change in position (especially the use of several soft pillows). In women, genital stimulation and orgasm release endorphins and as such can elevate the pain threshold [19]

The erection of patient or partner fails	Fear of hurting the partner can be, on one hand, an important cause, but no erection can be, on the other, disappointing for both partners. Explicit information on the various possibilities should be part of care, including proper use of a good lubricant and a constriction ring. Usually there is no reason not to consider erection-enhancing medication
Orgasm is important, but difficult to reach	To "reach orgasm" and get the accompanying physical release a given amount of stimulation has to be transferred to centers in the spinal cord. This process can be disturbed due to neural damage. In such cases a vibrator can help (for males and females) because of producing more intense stimuli than the penis, fingers or tongues can do
The ability to "reach orgasm" is disturbed due to a change in the neurotransmitter environment	This easily happens with selective serotonin reuptake inhibitor-antidepressants. Among the various solutions are antiserotonergic or dopaminergic "antidotes" and sometimes phosphodiesterase-5 inhibitors. Another approach is the search for new erogenic zones
A stoma causes sexual disturbance	After a stoma many patients have learned to make love again in the nude with a sexy sash or a romantic scarf over the stoma. Fear for stoma-incontinence during lovemaking should be discussed. Timing for "safe lovemaking" can be planned since food-intake usually can be organized in a way that emptying of the bowels occurs at a fixed time of the day. In some patients the stoma can be temporarily taped or stoma plugs can be used
In case of fatigue	Consider advice on proper timing, for instance after a nap or in the morning
When (young) couples really miss sexual excitement	Instead of choosing between dyspareunia when having intercourse or refraining from sex, some of these couples can learn to have (again) exciting and adventurous sex without pain. Some couples just need the advice to forestall penetration but go experimenting with everything else which is acceptable for them

and partners are supposed to have considered such solutions themselves. However, for various reasons, many men and women do not do so (sometimes because of not daring to discuss out of shame or "respect" for the partner). Then, simply by mentioning this dilemma, the helping professional can provide support.

These interventions belong to the realm of (medical) care. Sexology is responsible to teach these aspects to the professionals in oncological care. Basically this is the new area of oncosexology, a subdiscipline of medical sexology [11].

Conclusions

Sexual and intimacy issues after cancer treatment have a wide range of physical, psychological and relationship causes and can influence the quality of life of the palliative and terminal phase in a negative way. Even in the last phase of the disease couples may need and deserve an acceptable erotic and/or sexual contact. Sexuality requires our attention. Since shame makes most patients reluctant to bring up sexuality, the helping professional should have a pro-active role.

The experience from this last phase of life teaches sexology some important lessons on the complexity of sexual motivation by highlighting the various functions of sex, "development" of new meanings of sex and the impressive message about the power of human sexuality. It becomes very clear to us that sex is not only for the healthy, the young and the beautiful.

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Part V
Treatment Strategies

Chapter 38
Survivorship: An Overview

Mary S. McCabe and Joanne Kelvin

Keywords Survivorship • Advocacy • IOM • Late effects • Long term follow up clinics (LTFC)

Introduction

This chapter provides an overview of adult cancer survivorship focusing on a unique patient population whose quality of life and future well being requires that we, as health professionals, pay greater heed to their comprehensive needs, including their sexual functioning and intimacy [1]. This new focus in oncology is possible primarily because advances in cancer screening and treatment have resulted in a dramatic increase in the number of cancer survivors nationally and world-wide. As of 2009, the National Cancer Institute has estimated that there are over 12 million cancer survivors in the United States alone [2]. For many individuals diagnosed with cancer, long-term survival is now a reality [3–10]. However, along with this important progress, we also know there are numerous challenges that survivors face in the long term. Thus, it is increasingly important to formally incorporate the post-treatment survivorship period into the continuum of care. Once cancer treatment ends, the need for cancer surveillance, assessment of long-term and late onset problems, and the use of targeted interventions to treat them remain important. Survivorship care needs to include comprehensive services based on scientific evidence in just the same way as we approach care during the diagnostic and treatment periods.

Definition of Survivorship

Before focusing on the complex and diverse needs of cancer survivors, it is important to first understand who is considered a cancer survivor and what cancer survivorship means. As defined by a number of organizations and national reports, the time at which a person becomes a cancer survivor varies greatly. Both the National Coalition for Cancer Survivorship and the National Cancer Institute's Office of Cancer Survivorship have put forward the widely embraced definition that a person is a survivor from the moment of diagnosis [11]. "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted by the survivorship experience and are therefore included in this definition."

When considering the sexual health needs of the person diagnosed with cancer, this broad definition of survivorship – spanning the continuum of care – is appropriate since individuals continue to be sexual human beings whether or not they are cured of disease, are in active treatment for their cancer or are terminally ill because of the progression of their cancer. However, since the posttreatment period has so often been neglected by the oncology community in the planning and

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implementation of care, this chapter will focus, as did a report by the Institute of Medicine (IOM), on the survivorship experience following first diagnosis and treatment, and prior to the development of a recurrence of the initial cancer [11].

Current Focus on Survivorship

Until recently, there has been limited attention to the medical and psychosocial needs of cancer survivors, in part, due to the fact that the greatest attention by the medical community has been on developing better diagnostic techniques and curative therapies [12]. With the growing number of individuals living many years after their diagnosis and treatment for cancer, there has been an alignment of priorities. Patients have increased expectations for a high quality of life after treatment and health care providers increasingly include quality of life assessments as part of the care of these individuals.

But who are these cancer survivors? The largest numbers of adult cancer survivors are those individuals who have been diagnosed with the most common cancers. Breast cancer survivors account for 22%, prostate cancer survivors 19%, and colorectal cancers 9% of the total number of cancer survivors [56]. As for age distribution of survivors, cancer is a disease of the elderly with approximately 60% of individuals being 65 years of age or older [13]. But in thinking of survivors with serious need, childhood cancer survivors should not be overlooked just because the numbers are smaller. There are currently 300,000 survivors of pediatric cancer in the United States as of 2009. Of these, 200,000 will have at least one long-term medical effect related to their cancer requiring specialized follow-up [14].

A National Survivorship Agenda

Key in gaining the needed national attention to the issue of cancer survivorship has been the publication of major national reports on this topic. These include the joint report published in 2004 by the Centers for Disease Control and Prevention (CDC) and the Lance Armstrong Foundation entitled, *A National Action Plan for Cancer Survivorship: to Advance Public Health Strategies* [15]. Although this report focused on broad national strategies and recommendations relevant for the nation, it offered an important perspective on how institutions and individual programs could contribute to a much larger strategy. In the same time frame, the President's Cancer Panel released two publications, *Living Beyond Cancer: Finding a New Balance* in 2004 and *Assessing Progress: Advancing Change* in 2006, that provided first-hand testimony and data about the needs and preferences of survivors [16, 17]. Most influential among all the publications is the seminal work published in 2005 by the IOM entitled, *Cancer Patient to Cancer Survivor: Lost in Transition* [11]. This extensively referenced, comprehensive report serves as the guiding reference for all survivorship programs nationally. It gives extensive attention to the domains of concern for the survivor; highlights the status of research on late effects, identifying where the gaps remain; describes the education and training needed to train health professionals to properly care for survivors; and discusses optimal survivorship care and the barriers to achieving it. This report has been largely responsible for the increasing focus by the public, patients, and health professionals on survivorship care.

Challenges of Survivorship

Along with the important progress that has been made in cancer treatment (providing many patients with long-term survival after cancer) is a set of challenges that patients face after the therapy has successfully been completed [3–10]. These include long-term and late effects. Long-term effects are those that develop during treatment and continue for a time after treatment ends. These effects may resolve over time, such as neurotoxicity and cancer-related fatigue; they may be amenable to interventions; or they may become chronic [5–18]. Examples of long-term, persistent effects of treatment include permanent amenorrhea associated with chemotherapy and

sexual dysfunction due to prostate cancer surgery or radiation therapy.

Among the most serious effects of treatment are those that occur after treatment ends. As defined by Aziz, late effects generally are toxicities that are clinically absent at the end of therapy but "manifest later with the unmasking of hitherto unseen injury to immature organs by developmental processes or as a result of failure of compensatory mechanisms because of the passage of time or organ senescence" [3]. These late effects appear months or even years after treatment ends and may include serious organ dysfunction, such as cardiac or pulmonary disease [6, 7].

Second cancers are among the most frequent life-threatening of these problems, and may arise as a result of the cancer treatment (e.g., breast cancer as a result of chest radiation in women treated for Hodgkin's disease), genetic susceptibility or an interaction between the treatment and an inherent susceptibility [10, 19]. Other significant problems may arise as well, varying greatly in type and severity. The specific organ system or tissue affected depends on the treatment intervention (chemotherapy, radiation, and surgery), the intensity of the treatment (dosage of chemotherapy or radiation), as well as the age and the health status of the person undergoing treatment. Relevant examples include premature menopause, infertility, and osteoporosis.

The domains of concern affecting cancer survivors are not limited to medical problems. They also include the psychological, social, spiritual, and economic problems [20]. Increasingly, we understand that the diagnosis and treatment of cancer can impact many areas of life. In particular, the psychological effects can be of particular concern. These problems include fear of recurrence, anxiety and depression. We now know that major depression and depressive symptoms occur much more frequently than was originally appreciated by health care professionals. According to a review of the literature by the Agency for Healthcare Research and Quality (AHRQ), cancer survivors have a prevalence rate for major depressive disorders at least four times the general population [21]. Studies have shown that, within 2 years of initial diagnosis, patients treated for cancer have the highest risk of significant depressive symptoms relative to other diagnosed diseases [22]. Marcus and Shelby have both documented that little assistance is provided to assist survivors during this adjustment period, despite the existence of clinically significant problems [23, 24]. In women treated for breast cancer (the most studied group of cancer survivors), psychological distress has been shown to occur at specific transition periods in the care continuum. Those at highest risk include younger women, those with serious comorbid conditions and women with inadequate social support [25, 26]. An important example of the interplay between physical functioning and psychological well being is the patient recovering from prostate cancer surgery or radiotherapy. He is adjusting to changes in urinary, sexual and bowel function, all of which may contribute to significant psychological distress. Awareness of these and other key stressors is important so health care providers can intervene early and reduce distress that can interfere with functioning and quality of life.

Economic concerns may become a serious problem for the cancer survivor and family. Even with insurance coverage, there may be significant uncovered costs associated with the treatment that leave the family with a significant financial burden. For example, copayments and co-insurance costs can be significant when the therapy is expensive, and often little attention is paid to out-of-pocket expenses that can quickly mount up for things like prescription drugs, medical equipment and supplies, along with family-oriented items, such as day care. For those individuals who are underinsured or who lack insurance, needless to say, the costs of treatment can lead to financial catastrophe, leaving the survivor with tremendous financial burdens that become the indirect effects of treatment.

In addition to the concerns about the direct costs of having been treated for cancer, there are also concerns about future employment and education. Retaining one's employment status is important for a variety of reasons in addition to the obvious financial one of having a paycheck; it is often necessary for keeping health insurance coverage. In addition, it relates to self-esteem and can be a source of social support during the survivorship period [27]. Fortunately, federal and state laws passed in the 1990s, most importantly the Americans with Disabilities Act (ADA), the

Health Insurance Portability and Accountability Act (HIPAA), and the Consolidated Omnibus Budget Reconciliation Act (COBRA), have greatly reduced the problem of employment discrimination [28]. But there can be more subtle work place issues for the survivor. Can the individual still perform the physical tasks of the job? Are cognitive tasks more difficult? Does the employer think someone who has been treated for cancer should not be promoted?

Models of Survivorship Care

As survivorship takes its place as a distinct period of cancer care, one of the greatest challenges is the lack of models for how cancer survivors should be followed and by whom. Although cancer survivors in the United States are routinely followed by their oncologist, the duration of this follow-up is variable and the guidelines upon which to base this follow-up care are limited. Recently the National Comprehensive Cancer Network has developed consensus-based guidelines for posttreatment care and the American Society of Clinical Oncology (ASCO) has undertaken an evidence-based effort to define the follow-up care of adult survivors [29, 30]. Yet, the follow-up visit is commonly focused entirely on surveillance for recurrence, and the other critical elements of the visit are missing. Ideally, comprehensive follow-up should also include monitoring for long-term and late effects with referral to specialized services to address them, such as physical rehabilitation, psychiatry and assisted reproduction specialists, recommendations for cancer screening using national guidelines, and recommendations for healthy living strategies such as diet, exercise, and smoking cessation [31].

In addition, we also know that communication between the patient's oncologist and the primary care physician is frequently very limited (despite both sharing in the care of the survivor), and a formal transition of care from the oncologist to the primary care physician is rare [32]. This lack of coordination is the standard despite information that primary care physicians are already engaged in cancer care in their practices and want communication with the oncologist about how best to do this [33].

Until recently, the contribution of the primary care physician to the care of these cancer survivors has been given little attention, and even less attention has been focused on how these two groups interact and who was responsible for which components of care. Although oncologists frequently think they are the only ones providing follow-up care to survivors, one recent study of breast cancer survivors found that only 27% of women continued to see their oncologist annually for 3 years following chemotherapy treatment [34]. In addition, other surveys have shown that survivors often have significantly fewer health care interactions with their oncologists than with their primary care physicians [35–37]. The National Ambulatory Medical Care Survey conducted in 2002 found that primary care physicians are actively providing cancer-related care. In fact, of all the cancer-related visits, nearly one-third (32%) were to primary care physicians and only 18% to oncologists [38].

As the focus of care moves from treatment of disease to an emphasis on rehabilitation and health promotion, a renewed partnership with the primary care physician is needed to assure that a coordinated approach for long-term care is established [39, 40]. Fortunately, models for this collaboration already exist for other chronic diseases and studies from the United Kingdom and Canada seem to demonstrate that these models are applicable to oncology [41, 42]. In support of this shared-care model, the IOM report makes important recommendations for how this relationship should work – an ongoing knowledge exchange between providers with clear delineation of who is responsible for what services [11, 43].

Current and Evolving Clinic Models

The first survivorship clinics were initiated in the 1980s when pediatric oncologists recognized the unique and important follow-up needs of pediatric

cancer patients and developed multispecialty long-term follow-up clinics (LTFC) at academic institutions where most children in the US are treated. These clinics are not disease focused, but rather include survivors of pediatric cancers of all types. The program staff usually includes a pediatric oncologist and nurse practitioner with approximately half of these clinics also having a social worker and psychologist. The current challenge for these clinics is how to transition these survivors as they age to adult providers who are prepared to handle the late effects of pediatric cancer treatment.

More recently, there have been a number of models initiated for survivors treated for adult onset cancers. Academic medical/cancer centers have taken the lead in their development, but components of these models are applicable to hospitals and community practices as well. The two main types of models are:

- Disease-Specific Survivorship Programs
  - Most often developed for groups, such as breast cancer survivors
  - Multidisciplinary approach to posttreatment problems
- Comprehensive Survivorship Programs
  - Multidisciplinary clinic

    Follows pediatric model
    Ongoing care of survivors
  - Consultative clinic

    Multidisciplinary one-time visit
    Sole nurse practitioner physician visit
  - Ongoing care clinic

    Nurse practitioner led
    Patient transitioned from oncologist to NP
    Communication reestablished with primary care
    Eventual transition to primary care provider

Each of these models has been initiated in response to a need to figure out how to care for the large number of posttreatment patients and has been designed with sustainability and cost-effectiveness in mind. The disease-specific clinics have usually arisen because there is an institutional champion who is interested in coordinating a broad set of services for a particular group, such as breast cancer survivors. They may or may not be part of an institutional survivorship plan. The comprehensive model usually is part of an institution-wide plan and includes three distinct types of clinics [11, 31]. The *multidisciplinary clinic* is modeled on the pediatric LTFU clinic and can be an ideal way of providing comprehensive care; it is resource intense and complex to maintain for a large number of cancer survivors. The *consultative visit* provides the survivor with the opportunity to remain with the oncologist, but have one-time comprehensive visit focused on a systematic plan for surveillance for late effects, attention to psychosocial needs and healthy living recommendations. This model can utilize either the multidisciplinary team or a nurse practitioner trained in survivorship care. It allows for more individuals to receive survivorship services with only limited impact on institutional resources. More and more, institutions are piloting *nurse practitioner-led clinics* as the model for providing survivorship care [11]. Such a model allows for ongoing care and can be in a separate clinic or the nurse practitioner/physician assistant can be embedded within the treatment team.

Going forward, evaluation of these models is essential so we can assure we are providing quality care that contributes to the health and quality of life of our survivors in a cost-effective way.

Providing a Care Plan for Survivorship

An essential component of all survivorship programs/models is the education of the survivor about the plan of care going forward and the establishment of informative, ongoing communication between the oncologist team and the primary care physician [44]. To accomplish this, the IOM report includes a recommendation that all cancer survivors receive a Treatment Summary and Care Plan. "…patients completing primary

treatment should be provided with a comprehensive treatment summary and follow-up care plan that is clearly and effectively explained" [11]. This document is intended to be a source of information for patients, families, and health care providers and serve as the tool for bidirectional communication and knowledge acquisition.

The first component of the plan consists of a summary of all the treatments received, including important disease characteristics. This information can be used by clinicians to interpret patient symptoms that may be the chronic toxicities from a specific treatment or a late effect occurring many years after cancer therapy has been completed. The second component of the plan outlines the follow-up schedule for visits with the oncologist and surveillance testing where appropriate. This section of the plan should be survivor-specific and also include information about the late effects that the individual may be at risk of. This information will serve to inform the survivor about problems that should be brought to the attention of the oncologist and/or primary care physician, and for the primary care physician, it serves as a guide for monitoring the patient so that problems needing attention can be promptly evaluated. In addition to the treatment-specific information, the care plan should include recommendations about health maintenance with specific information about diet, exercise, and smoking cessation, as well as appropriate cancer screening recommendations.

Along with the medical aspects of follow-up care, an assessment of the psychosocial concerns of the survivor needs to be included in the plan. Too often survivors are reluctant to raise these issues, and they go unaddressed. Providers are also reluctant to ask the survivor about psychological issues despite evidence that important unmet needs persist after the completion of primary medical treatment. The "don't ask, don't tell" approach to the management of psychosocial concerns can be effectively eliminated by a follow-up care plan that includes both the physical and psychological domains as areas for assessment and intervention [45]. Also included in the plan, or provided as part of the visit, should be information about referral to ancillary services, such as counseling and support groups.

Finally, the care plan should also serve as a tool delineating who is responsible for each aspect of care [46–48]. This role delineation is important for survivors as well as providers since in a recent study, one-third of cancer survivors were not sure which physician was in charge of their cancer follow-up [49]. The plan should identify who will take the lead for ongoing cancer surveillance, the nononcology-related medical problems, and the psychosocial issues. This explicit identification of roles is key to shared-care and is critical in establishing a seamless coordination of services in order to prevent redundancy and to assure that needed services don't fall through the cracks.

Despite the obvious advantages of and support for the survivorship care plan, important barriers exist limiting their broad adaptation. The first major challenge is the lack of evidence-based guidelines to guide follow-up recommendations, requiring this information to be based on consensus. In addition, there are two important barriers at the practice level – time and resources – both very scarce items in any busy clinic setting. To try and address these challenges, a number of groups are developing standardized survivorship care plans. ASCO has both disease-specific and a generic survivorship plan templates available on their web site at www.asco.org. The Lance Armstrong Foundation has partnered with Penn Medicine's *OncoLink* to launch a web based product, LIVESTRONG Care Plan (www.livestrongplan.org). This care plan is a free and publically accessible tool that is focused on having survivors create their own plan of care. Another collaboration (between the National Coalition for Cancer Survivorship, UCLA Cancer Survivorship Center, WellPoint, and Genentech) has produced a care plan tool called, *Journey Forward*. This web-based tool currently has disease-specific versions for breast and colon cancer survivors based on the ASCO templates, and there are plans for the development of additional plans in the future.

Cancer and Sexuality: Where Does Survivorship Fit In

As mentioned previously, national recognition of the need to better address the issues patients face in their transition to survivorship after cancer treatment includes those issues that impact on quality of life. This includes sexual health, which can be approached as an exemplar in how individual clinicians, cancer centers, and national organizations can better provide care to cancer survivors.

Sexuality is a multidimensional phenomenon with physical, psychological, and social domains. The *physical* domain incorporates the structures and functions involved in the sexual response cycle: libido or desire for sexual activity; arousal or excitement; and orgasm, associated with intense pleasure, rhythmic muscle contractions, and release of sexual tension. The *psychological* domain incorporates the individual's perception of him or herself as a man or woman and as a sexual being, influenced by one's body image and self-esteem. The *social* domain incorporates the emotional intimacy and connection established with another person through sexual activity [50].

Most of the research on sexual dysfunction in patients with cancer has focused on women with breast or gynecologic cancer and men with prostate cancer. However, it is estimated that 40–100% of patients diagnosed with all types of cancer experience some degree of sexual dysfunction [51]. Many factors can impact on the sexual health of cancer survivors. Emotional distress, anxiety, depression, fear, or uncertainty about the future may arise following the diagnosis of cancer, during treatment, and following completion treatment. Side effects of treatment with surgery, radiation therapy, and chemotherapy include pain, fatigue, weight change, hair loss, nausea and vomiting, and diarrhea or constipation. Treatment may also result in permanent loss of body parts or in alterations in body structures or functions. Examples of permanent physical changes that may impact on sexual function are listed in Table 38.1. Clearly throughout the cancer continuum, many factors may affect desire for or ability to engage in sexual activity: body image, self-esteem, and the emotional intimacy patients are able to maintain with their partners.

Table 38.1 Physical changes that may affect sexual health

Potential changes in body structure and function
Scarring and disfigurement
Loss of a body part (e.g., breast, limb)
Ostomy
Urinary incontinence
Loss of libido
Change in sensations during orgasm
Infertility
Women
Vaginal atrophy and stenosis
Dyspareunia
Premature menopause
Men
Erectile dysfunction
Retrograde ejaculation

Kattlove and Winn [57], Hewitt et al. [11], Galbraith and Crighton [58], Hughes [59], Ofman et al. [53], Tierney [50], Fobair and Spiegel [55], Foster et al. [60], NCI [13]

Oncology Clinician Practice Related to Sexual Health

Oncology physicians and nurses report that addressing sexuality is important, but in fact rarely discuss sexual issues with their patients [52]. Barriers to discussing sexual health include: inadequate knowledge and training, feeling uncomfortable or embarrassed, underestimating the prevalence of sexual dysfunction, believing that someone else should address this issue, concerns about the appropriateness of discussing this with certain groups of patients (e.g., elderly, adolescent, unmarried, gay, different ethnicity), not having enough time, and inadequate resources to make patient referrals [52–54]. There is clearly a significant opportunity to improve the quality of care provided to cancer survivors related to sexual health.

Sexual Health as an Exemplar for Survivorship Care

Specific physiologic changes, components of clinical assessment, and strategies to treat sexual dysfunction and maximize adjustment in patients with cancer are outlined in detail throughout this text. The challenge is in how to ensure the application of this knowledge in clinical practice to achieve significant improvements in the sexual health of cancer survivors. This can be approached on multiple levels: improving the practice of the individual clinician, developing institutional programs within cancer centers, and supporting advocacy on a national level.

Improving Clinical Practice

Patients are often reluctant to bring up issues of sexuality during their follow-up visits. They may be hesitant to discuss such intimate topics or feel "they are a cost of surviving their cancer" [16]. Individual clinicians have the responsibility to initiate the conversation about sexuality with their patients, introducing this in a matter of fact way that normalizes sexual concerns. Beginning these conversations early in the cancer continuum can help patients better understand what long-term changes they may expect. A number of models have been proposed to guide clinicians in having these discussions. These are listed and described in Table 38.2. Regardless of the model used, the clinician must start the dialog to create an opening for the patient to address any concerns they have. Patients can be asked directly if they have any concerns or problems related to sex, or a simple open-ended question to start can be used. Examples are: "How are things going sexually?" What changes have you noticed sexually?" "Many women undergoing this treatment have questions or concerns about sexuality. What questions or concerns do you have?" [53, 55]. It is important to keep in mind the unique needs of patients of different ages. Patients treated as children or adolescents may have growth impairment with body image changes, and as with young adults may experience loss of fertility. Any of these can impact on their ability to form intimate relationships. Adults in longstanding relationships can have difficulty reestablishing physical intimacy with their partners. Body image issues and need for intimacy are equally important in older adults [16].

When providing information, clinicians must "accommodate cultural, spiritual, educational, and language differences that may affect the patient's and family's acceptance and absorption of this crucial information." [16] Providing written material and reliable internet sites for additional information is helpful. The American Cancer Society publishes two books, "Sexuality for the Woman with Cancer" and "Sexuality for the Man with Cancer" which clinicians can stock in their office or which patients can get for free by calling 1-800-ACS-2345 or online at www.cancer.org. And finally, clinicians should become aware of specialists in their community to which they can refer patients as needed for medical treatment or counseling.

Institutional Program Development

To support oncology clinicians in these efforts, institutions can put in place a number of supportive structures. *Education of clinicians* is essential to ensure that they understand the prevalence of sexual dysfunction in their patients, learn the skills for discussing sexuality, and are knowledgeable about the current options available to help patients improve their sexual health. These can be presented by specialists in the community and scheduled during service conferences with content tailored to the group's patient population. *Resources for patients* that can be developed include: written materials, lists of reliable internet sites to obtain additional information, educational programs with speakers specializing in a variety of sexual issues, and support groups. *Resources for clinicians* that can be developed include: standardized electronic orders to generate prescriptions for medications or products that are helpful in addressing different aspects of sexual dysfunction, easy accessibility to educational

Table 38.2 Models to enhance sexual health communication

PLISSIT	P	Giving permission to discuss the topic
	LI	Providing limited information
	SS	Providing specific suggestions
	IT	Referring for intensive therapy
ALARM	A	Activity (frequency of sexual activity)
	L	Libido/Desire
	A	Arousal and orgasm
	R	Resolution (feelings of release of sexual tension and satisfaction)
	M	Medical history relevant to sexuality
BETTER	B	Bringing up the topic
	E	Explaining that sexuality is part of quality of life
	T	Telling the patient about resources
	T	Timing the discussion to the patient's preference
	E	Educating the patient about side effects that may impact on sexuality
	R	Recording in the medical record that the topic has been discussed
5 A's	Ask	Bring the topic up
	Advise	Normalize symptoms, acknowledge he problems
	Assess	Using a variety of resources to provide standardized assessments
	Assist	Provide information, refer as needed
	Arrange follow-up	Check at subsequent visits how patient are doing

Hordern [61], Park et al. [52]

materials to provide patients in the clinical area, and even the creation of an institutional intranet web page with content about the types of problems sexual patients may experience, treatments available, and lists of specialists and centers to refer patients to based on their problems or concerns. And finally, creating a network of *specialists* to which clinicians can refer patients based on the specific physiologic and emotional aspects of sexuality they are having difficulty with.

National Advocacy

There is also an opportunity to put in place a variety of programs at the national level to ensure we better meet the needs of our survivors in relation to sexual health. *A National Action Plan for Cancer Survivorship: Advancing Public Health Strategies* outlined strategies based on four components of public health. *Applied research* is needed to better quantify the prevalence of sexual dysfunction; identify who is most at risk; and determine what programs and services are most effective at preventing and addressing these problems. *Communication, education, and training* are needed both for clinicians and patients. *Programs and policies* are needed that identify best practices and ensure the availability of evidence-based practice guidelines to be used by clinicians and which may improve insurance coverage for sexual health care. And finally, ensuring *access to quality care and services* is needed. This can be provided by fostering multidisciplinary teams of clinicians collaborating in the provision of sexual health care [17].

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Chapter 39
Nutriceuticals in Sexual Health

Mark A. Moyad

What works and what is worthless or even dangerous

Keywords Nutriceuticals • Supplements • Dietary • Nutrition • BMI • Waist circumference • Fitness • Fatty acids • Anti-oxidants • Fiber • Lycopene • Selenium • Zinc • Lifestyle modifications

Introduction (Part 1): Heart Health = Sexual Health (Ageless Education)

There are certain comments derived from observational clinical research and television commercials that are almost beginning to sound cliché in the urologic world and this is remarkable if one looks back just a few years on the educational progress that has occurred in the area of sexual health. For example, the relationship between erectile dysfunction (ED) and the potential for a first cardiovascular disease (CVD) event is now well known that I do not even need to really provide a medical reference after stating this fairly obvious relationship pick a study-Prostate Cancer Prevention Trial (PCPT) 1… [1]. However, these correlative findings seem to promote more intervention compared to education and prevention in my opinion. Health care professionals need to sell the concept of lifestyle changes and dietary supplement additions and deletions to promote sexual health first as much as pharmacologic intervention in my opinion. I often tell patients that it has become an adage that they can reiterate over and over to say that "when diet and exercise do not work there is …!" However, this should be true of every aspect of preventive medicine and not just heart disease. For example, when diet and exercise does not work there is … . This is the simple goal of this chapter. It is not to convince the reader that there are enough diet and exercise studies in the area of sexual health because the literature is now replete with reviews from this and other authors, but to point out the vital studies that provide a sound basis and hopefully enthusiasm to convince the reader to tell patients that "When diet and exercise along with certain dietary supplements do not work there is … !" And, even if the patient has to go on any conventional intervention such as a PDE-5 inhibitor, the good news is that the diet and supplement additions or knowledge should only improve the impact of the conventional medication and (ready for this) assist the patient in the living a longer and better life! This is what is most exciting about some of the recommendations proffered in this chapter.

Additionally, when referring to prevention recommendations there needs to be evidence that is derived and utilized not just for and from the young but middle aged and older men. The first large-scale in person (face-to-face) comprehensive

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study of sexuality among older Americans found that many individuals continue to be sexually active well past the age of 80 years [2]. The national survey of more than 3,000 U.S. adults ages 57–85 essentially found that more than half to three-fourths of those inquired said they remained sexually active, with a significant number still frequently involved in sexual behavior. The study found a close correlation between health and sex, with healthier individuals reporting the highest rates of sexual activity. Older individuals seemed grateful to be involved in this study because the response rate was unusually and dramatically high (75%). Many of the participants mentioned that they had never had the opportunity to discuss these issues with their spouse or even their doctor. In fact, only 38% of men and 22% of women reported having talked about sex with a doctor since the age of 50 years. Approximately 75% of the participants with partners reported being sexually active, and this is the same rate reported in the past for very young couples. Although, the percentage of people having sex decreased with age, so by age 75–85 it was 39% of men and 17% of women. Similar to the younger men, older men reported more sexual activity compared to women, but the researchers mentioned that this was mostly due to the fact that women live longer compared to men, which allows men more opportunities to have sexual relations compared to women. In other words, it is time to promote preventive health in young, middle age, and older persons. Men and women remained sexually active or interested in sex to a degree similar to many younger individuals. Sexual health and mental and overall physical health were directly related in this study, so this is another reason to stay fit or mentally and physically healthy as one gets older. It is critical from this study that doctors need to inquire about sexual health regardless of the age of the patient because a number of the sexual side effects reported by individuals in this study could easily be corrected with some lifestyle or medical intervention. Finally, I now also understand why men are lucky for numerous reasons if they live to an older age.

Introduction (Part 2): Heart Health = Sexual Health and Promoting Probability

Simplistic and practical observations from critical studies need mentioning to place lifestyle recommendations in perspective. CVD is the number one overall cause of death in the United States and in other industrialized countries [3]. CVD is currently the primary cause of death worldwide, and is the number one cause of death in every region of the world with the exception of sub-Saharan Africa, and it is predicted that this disease will become the number one cause of death in that specific region within the next decade [4]. However, cancer is expected to potentially mirror the number of deaths from CVD in the next several years in various regions of the world. Regardless, the bottom line is that CVD is and has been the number one cause of death in the United States every single year since 1900, with the exception of 1918, which was the year of the great influenza pandemic [3]. And, the majority of what is known for lifestyle and dietary change for CVD prevention applies to cancer prevention. For example, it is should be of enormous interest to health care professionals and patients that one of the most dramatic reductions in mortality rates in U.S. history for CVD and cancer was through a common behavioral change (smoking cessation) that had such a profound simultaneous impact on the rates of both diseases. In other words, heart healthy changes are tantamount to primarily overall healthy changes regardless of the part of the human anatomy that is receiving attention, including the penis. Why not sell heart healthy changes to patients concerned about ED? This is triaging preventive medicine or providing probability-based advice via evidence-based medicine.

Several of the largest U.S. and worldwide cancer prevention trials in urology and cancer screening studies exemplify the immediate need for a more proper perspective. For example, results of the PCPT seem to have generated a lot of interest and controversy regarding the use of finasteride daily versus placebo to reduce the risk of prostate cancer [5–8]. Finasteride was

responsible for a significant 25% reduction in the number of prostate cancer cases during 7 years of study, but adverse effects were not minimal. The debate over the advantages and disadvantages of finasteride will continue, but one important observation from this important trial has not received adequate exposure in the medical literature. Over 18,000 men were included in this randomized trial, and five men died from prostate cancer in the finasteride arm and five men died of prostate cancer in the placebo arm, but 1,123 men totally died during this primary prevention trial. Thus, prostate cancer was responsible for approximately less than 1% of the deaths in this trial, while the majority of the overall deaths were due to CVD and other causes. Therefore, the results of the first large-scale prostate cancer prevention trial demonstrated that another disease is indeed the primary cause of death in men, and randomized trials tend to mirror day-to-day morbidity and mortality in this regard. This finding does not reduce the seriousness or impact of prostate cancer prevention utilizing a prostate-specific chemoprevention agent, but again it places the overall risk of morbidity and mortality in its proper perspective. Men inquiring about the benefits and detriments of finasteride for prostate cancer prevention need to be reminded that the number one risk to them in general is CVD and then the potential prostate cancer risk-specific consult should occur after this first more relevant point is discussed and emphasized.

The well-known selenium and vitamin E supplementation randomized trial (SELECT) that was terminated approximately 7 years early because of a lack of impact or a potential negative impact with these high-dose supplements again represented a pertinent teaching moment that again was missed in my opinion because of the focus on the tree over the forest [9]. Keep in mind that SELECT was the largest randomized primary prevention trial of men only in urologic and medical history, and once again CVD represented the number one cause of mortality overall in this study with over 500 deaths occurring compared to the one death from prostate cancer in just 5 years follow-up. This observation mirrored similar smaller past randomized trials utilizing some of these agents in the past [10]. Heart healthy programs simply need to receive more emphasis in urology.

Again, it is important to reiterate these findings, but not to belittle the seriousness of prostate cancer or another urologic condition, but to place the average risk of mortality for a man in its proper perspective. Dietary or lifestyle changes to reduce the risk of CVD just make sense when examining the larger overall mortality picture. A so-called "forest over the tree" approach seems most appropriate when discussing options with men. Heart healthy seems tantamount to overall health, and this should be constantly and consistently reiterated and emphasized to the individual concerned about sexual health or any other urologic condition. The basic and easy to implement lifestyle recommendations proffered in this chapter serve to impact sexual health and CVD simultaneously. Individuals may now be offered lifestyle changes that can potentially impact all-cause morbidity and mortality rather than the seemingly more common and myopic focus on just disease-specific morbidity and mortality.

Recommendation #1: Patients need probability-based education, which means they should know their fasting lipid profile, blood pressure values and other cardiovascular markers as well as they any other health numerical values.

What has been truly educational and surprising in my opinion is not that patients know so much about their health or nutrition facts with the advent of Google health searches, but the lack of general health knowledge despite an impressive and obsessive need-to-know position concerning prostate, ED, or other health issues. The lack of comprehensive health knowledge is not only prevalent in some urologic populations, but surveys of the general population indicate that a majority of individuals do not know their cholesterol values or have little understanding of what they actually represent in terms of potential health outcomes, and this finding is consistent regardless of age, race, and even gender [11, 12]. In my experience when the dual concern of CVD and ED risk is emphasized and

consistently promoted, men tend to become familiar with all of their clinical values, numbers, and overall risks. For example, it would seem more appropriate to conduct a cholesterol/blood pressure screening and ED screening on the same day at any institution. Second, men should be educated regularly on the normal values of a cholesterol panel and blood pressure test, because these values have recently been updated two different times by the expert panel from the National Cholesterol Education Program (NCEP) [13, 14]. An individual who attends an isolated free PSA screening, for example, may be leaving medical institutions and centers with an isolated and myopic health and disease perspective. For example, at our institution we have attempted to change our previous paradigm by currently abandoning PSA screening day and conducting at the very least an annual general health lecture for our urologic patients, or by also providing lipid, glucose, and blood pressure screening at an off-campus community site instead of just a traditional PSA and DRE-only annual screening event. Obviously, this takes more extensive coordination with other medical departments, but this also results in an increase in diverse resources and sources that were not available before at the PSA-only screening event. Men simply need a review of the basic optimal lipid and general health values [13, 14]. Table 39.1 is a simple modified review for patients and urologic health professionals.

Table 39.1 The partial summary of goals for total cholesterol, LDL, HDL, and triglyceride with some added modifications that can be used to discuss goals simply with patients concerned about ED [13, 14]

Serum parameter	Opinion of the measurement
Total cholesterol (mg/dL)	*A lower number is better*
<160	Optimal
<200	Desirable
200–239	Borderline high
≥240	High
LDL = "bad cholesterol" (mg/dL)	*A lower number is better*
Less than 70	Optimal for some high-risk individuals[a]
Less than 100	Optimal
100–129	Near optimal
130–159	Borderline high
160–189	High
Equal to or greater than 190	Very high
HDL = "good cholesterol" (mg/dL)	*A higher number is better*
Less than 40	Low
40–59	Normal
Equal to or greater 60	High (optimal)
Triglyceride (mg/dL)	*A lower number is better*
Less than 150	Normal
150–199	Borderline high
200–499	High
Equal to or greater than 500	High

[a]High-risk individuals (existing CVD disease or a previous CVD event) may be required to reduce their LDL below 70 mg/dL based on new information provided to the Expert Panel

During the time of this chapter's submission one of the most profound potential findings from the PCPT was published [15]. Men with low cholesterol had in the placebo arm of the study a 59% lower risk of being diagnosed with aggressive prostate cancer (Gleason 8–10)! This is nothing less than remarkable if accurate, but this finding is similar and consistent to what has been found in previous large prospective epidemiologic studies [16].

It is of interest that the NCEP suggests a first cholesterol screen at an age of 20 [13], but few if any men in my experience have had such a test at this early age. Perhaps, clinicians can help patients to adhere to this early screening age. For example, when men with a family history of prostate cancer or ED or an early diagnosis of most diseases inquire about what their children should do first to prevent this condition, a common suggestion to just have an initial cholesterol screen seems most appropriate. In my experience, this tends to pleasantly surprise patients because most did not previously consider this thought or option for their children.

Clinicians should also discuss other potential risks for CVD. It is well accepted that CVD risk is also affected by lifestyle risk factors such as obesity, physical inactivity, and a high-caloric and overall unhealthy diet. Other emerging risk factors or risk markers should ideally be discussed because despite the cholesterol test

being a good test for predicting future cardiovascular problems, it is not a perfect test. This should be similar to the clinician's approach to a PSA test. PSA is a good test for potential risk or recurrence following definitive therapy, but it is not a perfect test. Other newer cardiovascular markers such as high-sensitivity C-reactive protein (hs-CRP), impaired fasting glucose or hemoglobin A1c, and evidence of subclinical atherosclerotic disease should also be discussed for example with the patient [17–20], or a referral to a cardiologist or perhaps a note to the primary care physician may be appropriate in other cases because some of these markers may also be related to overall mortality as well as CVD risk and some urologic conditions.

Additional advantages may occur for the patient and clinician that continue to follow these overall cardiovascular markers. For example, cholesterol levels are an outstanding indicator of how well a patient may be adopting lifestyle changes or even medication compliance following a PSA test, ED diagnosis, or after some definitive therapy. If these numbers improve it may be more likely that the patient is adhering to a sexual and CVD healthy lifestyle program. High-density lipoprotein (HDL) is a good indicator of the commitment to exercise by the patient. The HDL tends to increase, and at times substantially with a greater amount of aerobic physical activity [21], and a higher HDL may be correlated with a lower risk of abnormal prostate conditions that could impact ED [22]. Triglycerides are an excellent indicator of changes in belly fat because this compound is generally stored in this anatomic location with increasing blood levels. On the other hand, in a minority of patients that follow a healthy lifestyle, a less than optimal change in cholesterol may occur, but these patients can then be referred to a specialist for potential drug intervention and more aggressive lifestyle therapy.

Blood pressure values should also be emphasized as much as the cholesterol values. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure altered the criteria for what constitutes a healthy blood pressure [23]. Patients should be informed that normal blood pressure is less than 120/80 mmHg and individuals with a systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg are actually considered to be "prehypertensive" and lifestyle changes should be advocated in these individuals (see Table 39.2).

Table 39.2 A partial summary of the new blood pressure guidelines according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [23]

Blood pressure (systolic/diastolic)	What does this mean to patients?
Less than 120/80 mmHg	Normal = low-risk
120–139/80–89 mmHg	Prehypertensive (moderately high or prehigh blood pressure) = moderate-risk
140/90 mmHg or greater	Hypertensive (high blood pressure) = high-risk

Blood pressure tends to decrease with a healthier lifestyle [24], and again is a good indicator of lifestyle compliance, and a healthy blood pressure may also lower the risk of ED [25]. A minority of patients may not reduce their blood pressure with lifestyle changes, but these men can be referred to a specialist. Men that adopt healthy lifestyle changes that do not result in ED improvements should still be given encouragement to continue these changes because of the other potential profound impacts these behaviors may have on overall health. In my opinion, patients seem more motivated to continue a healthy lifestyle when there is some tangible healthy outcome with the behavioral change, and this becomes more probable when all numbers including cholesterol and blood pressure for example are followed compared to just other (PSA …) values.

Recommendation #2: The body mass index (BMI), but more importantly the waist-to-hip ratio (WHR) or especially waist circumference (WC) measurement should become a standard part of the patient clinical record.

The negative impact of being overweight or obese on overall health and longevity is well known. BMI is a moderately reliable but rapid method to determine who may be overweight or

obese [26]. BMI is defined as the weight (in kilograms) divided by the square of the height in meters (kilograms per square meter). Another method to calculate the BMI is to take weight in pounds and divide it by the height in inches squared and to multiply this number by 704 ($lb/in.^2 \times 704$). A BMI<25 is considered normal by the World Health Organization (WHO), whereas 25–29 is overweight, and ≥30 is defined as obese, and 35 or more is considered morbidly obese. Several large recent randomized trials have demonstrated that most individuals in these studies are indeed overweight at baseline [27], and this includes dietary trials to prevent urologic abnormalities [15, 28]. In other words, it has become so common to be overweight or obese that only a minority of men in past clinical trials has a BMI in the healthy range.

WHR may be another rapid and simple measurement to determine obesity [26]. Individuals must stand during the entire measurement of WHR. WHR more precisely measures abdominal adipose circumference or tissue and fat distribution. The waist is defined as the abdominal circumference midway between the costal margin and the iliac crest. The hip is defined as the largest circumference just below the iliac crest. For men, a WHR >0.90, respectively, is a fairly accurate indicator of an increased risk for obesity-related conditions independent of BMI.

WC is perhaps the easiest and fastest method to currently access obesity, and is my personal preference in men because "belly fat" seems to have one of the best predictive value of CVD and potential all-cause mortality risk among all the other weight measurements from the largest prospective studies in the world [29]. WC is also one of the best predictors of a future cardiovascular event, regardless of the ethnic group studied [30]. WC is also one of the five specific criteria of metabolic syndrome. WC has an important advantage over BMI, which can be appreciated after individual commits to resistance exercise or weight training. An increase in muscle mass from resistance exercise can actually cause an increase in BMI, which is frustrating to the patient and clinician. However, this does not occur when utilizing the WHR or WC measurement. In the meantime, again WC and WHR works well, and a summary of the meaning of the BMI and WC values are listed in Table 39.3.

Table 39.3 A summary of the body mass index (BMI), and waist circumference (WC) values for patient discussions [26]

BMI number	What does this mean to the patient?
Less than 25	Normal weight
25–29	Overweight
30 or more	Obese
WC number	*What does this mean to the patient?*
Less than 35 in. (or 89 cm) in men	Normal
35–39 in. (or 89–100 cm) in men	Overweight
40 or more inches (101 or more centimeters) in men	Obese
Less than 32.5 in. (or 83 cm) in women	Normal
32.5–36 in. (or 83–93 cm) in women	Overweight
37 or more inches (94 or more centimeters) in women	Obese

Clinicians need to keep in mind that ultimately the meaning of these numbers compared to the rest of the population is not what is vital, because the individual should only be competing with herself or himself. In other words, a patient with a BMI of 35 and a WC of 40 in. is not what I personally find concerning, but a lack of aerobic fitness and not being able to reduce their value slightly over time is more of an issue. Obesity is also associated with lower testosterone levels, higher estrogen levels (partial androgen suppression), and higher risk of CVD, which could partially explain the preliminary finding that obese men have a higher risk of ED [31–33]. Even kidney stones and renal cell carcinoma (RCC) may have a strong relationship with obesity [34, 35]. Health care professionals working in the field of urology should constantly emphasize the negative overall impact of obesity because there is plenty of evidence to allow this critical teaching moment. Clinicians need to let patients know that maintaining a healthy weight and waist should be one of the primary goals.

For example, placing a BMI or WC chart in the clinic office and always making BMI or WHR or WC a part of the individual clinical record should be a goal for every patient, regardless of his or her concern of a specific disease risk because early mortality from all-causes is associated with increasing WC and BMI [29]. Clinicians should also refer patients on a consistent basis to nutritionists, therapists, a variety of professional weight-loss programs, and to become familiar with local weight-loss resources. Clinicians should be able to provide the name and number of the recommended individuals and organizations to the patient at the time of the urologic appointment in order to improve compliance, convey enthusiasm, and the immediacy or importance of this lifestyle change. Clinicians need to begin to carry and utilize tape measures that can rapidly assess WC, and I often argue that this is as important as the stethoscope to the individual working in the field of urologic disease.

Recommendation #3: Emphasize fitness primarily and overall health by encouraging patients to get approximately 30–60 min of physical activity a day or more depending on individual need, and to lift weights or perform resistance exercises several times/week. Aerobic and resistance exercise should be emphasized equally; one is not more vital than the other.

Higher levels of physical activity defined as at least 3 h of vigorous exercise weekly were associated with an approximate 70% lower risk of an aggressive prostate cancer, advanced disease, and a potential for improved survival in the Health Professionals Follow-up Study [36]. Over 47,000 men were included in this study with a mean follow-up period of 14 years. The investigators from this study appropriately concluded their publication by recommending 30 min a day of physical activity to all individuals due to the overall health benefits of this intervention.

CVD morbidity and mortality is impacted by exercise, and the data are profound, and weight lifting also seems to provide additional benefits. Additional data from the Health Professionals' Follow-up Study prospectively followed over 44,000 men for 12 years [37]. Men that ran for 1 h or more per week had a 42% reduction (RR = 0.58; $P < 0.001$ for trend) in the risk of CHD, and those that just walked for 30 min or more per day or who were involved in other physical activities also had a risk reduction in CHD versus those that did not engage in these activities. Men who trained with weights (resistance exercise) for just 30 min or more per week experienced a 23% risk reduction (RR=0.77; $P = 0.03$ for trend) in CHD. This was a unique finding because previous prospective studies have not addressed this subject. Weight training can increase fat free mass, lean body weight, increase resting metabolic rate, and potentially reduce the risk of abdominal fat deposition [38, 39]. Weight training or resistance training also seems to improve glucose control or increase insulin sensitivity, may slightly improve lipid levels, and reduce hypertension [39, 40], which are all potential risk factors for ED. Physical activity may also dramatically reduce the impact of sympathetic overload and BPH [41]. These studies emphasize the need to engage in aerobic and resistance activity because synergism seems to exist between these interventions.

Positive mental health improvements with increased physical activity seem to be as profound as the physical health benefits [42, 43]. A trial of 156 adult volunteers with major depressive disorder (MDD) randomly assigned a 4-month course of aerobic exercise (30 min 3 times/week), sertraline therapy, or a combination of exercise and sertraline [44, 45]. After 4 months patients in all three groups demonstrated significant mental health improvements; however, after 10 months, individuals in the exercise group had significantly lower recurrence rates than individuals in the medication arm of the study. Exercising during the follow-up period was correlated with a 51% reduction in the risk of a diagnosis of depression at the end of the investigation. Men need to be instructed that regular physical activity and resistance training have sufficient physical and mental health benefits that not performing these activities certainly reduces the potential for improved overall health. In my opinion, it is important to tell patients that if the overall results from exercise studies were viewed similar to a specific

pharmacologic intervention than it would have already garnered attention worthy of a Nobel prize in medicine many years ago.

Recommendation #4: Patients should reduce unhealthy dietary fat intake and be encouraged to increase the consumption of healthy fats. In other words, saturated, trans-fatty acids, and even dietary cholesterol should be reduced and replaced by more healthy types of monounsaturated or polyunsaturated fat (omega-3 fatty acids).

Saturated fat (SF) is also simply known as "hydrogenated fat" on food labels. SF reduces LDL receptor expression and increases LDL serum levels [13]. LDL increases by 2% for every 1% increase in total calories from SF. The NCEP (Adult Treatment Panel III or ATP III) recommends that SF be reduced to less than 7% of total calories to reduce the risk of CVD. The average U.S. adult intake of SF is approximately 11% of total calories. Some nonlean meats, high-fat dairy products (whole milk, butter, cheese, ice cream, and cream), tropical oils (palm oil, coconut oil, and palm kernel oil), baked products and mixed dishes with dairy fats, and shortenings are some of the larger sources of SF. Many foods that contain high levels of SF also contain the highest levels of trans fat ("partially hydrogenated fat"), cholesterol, and especially total calories in many cases. For example, there are almost twice as many calories in 8 oz of whole milk (5 g of saturated fat) compared to skim, or even soymilk (0 g of saturated fat) [46].

Reducing all saturated fat in an individual's diet is not necessarily a practical and healthy dietary lifestyle change. The current cardiovascular goal of obtaining less than 7% of calories from saturated fat seems almost ideal from past studies, because getting minimal to no calories from saturated fat not only seems too excessive; it actually reduces levels of HDL from past CVD and urologic clinical trials [47, 48]. Reducing all saturated fat consumption also implies that this type of fat in and of itself is heart unhealthy, which is not accurate from the largest recent meta-analysis of prospective studies [49]. Again, a potential impact of reducing saturated fat, in my opinion, is that it may reduce overall caloric intake and reduce weight and waist gains. And, another benefit of reducing saturated fat is that it allows for the opportunity to increase the consumption of other monounsaturated and polyunsaturated fats that have shown a greater reduction in CVD from past clinical trials [50]. Finally, a summary of the different types of dietary fat, food sources, and impacts on cholesterol are found in Table 39.4 [13, 46].

Recommendation #5: Encourage patients to consume a diversity of low-cost fruits and vegetables and not high-caloric, expensive, and high-antioxidant exotic juices. Dietary supplements

Table 39.4 A partial review of the types of dietary fat available to patients, some of the primary sources of these fats, and their impact on lipid levels and heart health [13, 46]

Specific type of dietary fat	Where it is commonly found?	Good or bad fat, and impact on cholesterol versus carbohydrates (sugars)
Monounsaturated fat	Health cooking oils (canola, olive, safflower, etc.), nuts, etc.	Good Lowers LDL Increases HDL
Polyunsaturated fat (includes omega-3 fatty acids)	Healthy cooking oils (canola, soybean, etc.), flaxseed, fish, nuts, soybeans, etc.	Good Lowers LDL Increases HDL
Saturated fat (also known as hydrogenated fat)	Nonlean meat, high-fat dairy, some fast food	Mostly bad (only because it is associated with high caloric intake) Increases LDL Increases HDL
Trans fat (also known as partially hydrogenated fat)	Some margarines, fast food, snack foods, deep fried foods, etc.	BAD Increases LDL Lowers HDL

that claim to substitute for fruit and vegetable consumption should not be recommended.

The compound known as "lycopene" seemed to be synonymous with urologic health in a variety of media and commercial sources. Few topics in urologic disease prevention in my opinion enjoyed as much attention as lycopene, tomato products, and their potential benefits. For example, a past regularly referenced analysis of over 80 epidemiologic studies was completed on tomatoes and health [51]. Half of the studies analyzed supported the consumption of tomato products at least once a day to reduce the risk of a variety of cancers including prostate cancer, but a large number of studies in this same analysis failed to detect a correlation. The overall recommendation of the author of the meta-analysis was to increase the consumption of a diversity of fruits and vegetables and not just tomato products, which in my opinion was the most critical finding of the analysis that never seemed to garner any commercial attention.

Perception is not tantamount to reality in this area of nutritional medicine in my opinion because of aggressive advertising versus science. For example, tomatoes were never the only or necessarily the primary source of lycopene. A variety of other healthy foods contain this compound such as: apricots, guava, and pink grapefruit [52]. Watermelon is also an adequate source of lycopene, and is in fact the largest source per gram compared to any other source, including tomato products [53]. This may come as a surprise to other clinicians and patients, but it highlights the problem of perception versus reality in advertising.

Fruits, and especially vegetables in general, have been associated with a reduced risk of urologic conditions [54]. For example, the Brassica vegetable group is diverse and includes: broccoli, brussels sprouts, cabbage, cauliflower, kale, watercress, and others and may reduce the risk of urologic disease [55]. The Allium vegetables have also been associated with a reduced risk, and this group includes: chives, garlic, leeks, onions, scallions, etc. [56]. Fruits and vegetables have combined unique and shared anticancer and antiheart disease compounds that may contribute to improved overall health [54]. The sum of the epidemiologic data continues to support the increased consumption of a diversity of fruits and vegetables to potentially impact urologic disease, but the overall data currently supports a greater potential reduction in CVD risk and mortality [57].

Attention gathering shifts from one fruit or vegetable to another with each passing day and news story seems more likely than ever before. Clinicians need to explain to patients that this does not necessarily represent any major breakthrough, but rather supports the ongoing and past research that consuming a diversity of low-cost fruits and vegetables is the most practical and logical approach currently and in the future. One of many potential recent examples of this controversy is the recent research concerning pomegranate juice [58, 59]. The first attention gathering study did not include a placebo group or another group of men that consumed another type of healthy juice product [58].

The second study demonstrated no significant impact on ED [59]. It is also important to keep in mind that larger intakes of healthy juices can contain a significant amount of calories. Many brands of pomegranate and other novel juices contain at least 140 calories per 8 oz serving, which translates into more calories than most commercial regular soft drinks and alcoholic drinks (about 100 calories). Many of these juices are also costly and it is concerning that our low-income patients cannot afford them, and finally drug and juice interactions are still being researched, which is important since grapefruit juice studies have provided a paradigm of medication interactions, but novel juices such as pomegranate may also cause such concerns with medications metabolized by CYP3A4 [60, 61].

The competitive nature of the food and beverage industry, like any commercial business, translates into millions of dollars spent yearly on advertising, that in my opinion usually impacts how patients eat and drink. Again, clinicians need to be the objective voice in this area, which means being advocates for general evidence-based advice instead of encouraging hype on a specific compound or product. Another personal clinical observation needs to provoke some thought when promoting fruit and vegetable consumption. In my experience, when a patient begins to depend

on a pill instead on a lifestyle change, the potential for seeking other nonlifestyle changes to be substituted for pills increases [46]. In other words, when a patient begins to exercise there is an increased potential to seek other healthy behavioral changes such as eating better or quitting smoking or consuming less alcohol. However, this momentum effect also works in a negative direction, so the patient that takes fruit- and vegetable-based pills will reduce overall fruit and vegetable consumption and look for other pills (cholesterol, blood pressure, weight loss, etc.) to substitute for healthy behavioral changes.

Recommendation #6: Encourage patients to consume more total (soluble and insoluble) dietary fiber (20–30 g/day) from food for overall health advantages, especially soluble and insoluble fiber. One-third of a cup of bran cereal with flaxseed and some fruit provides approximately 20 g of fiber!

General health benefits from consuming dietary fiber have been well documented in the past medical literature and include a reduction in coronary heart disease (CHD) risk [62, 63]. A pooled analysis of past cohort studies of dietary fiber for the reduction of CHD included research from ten studies from the United States and Europe [64]. Over a period of 6–10 years of follow-up, a total of 5,249 total coronary cases and 2,011 coronary deaths were documented among over 91,000 men and 245,000 women. Multivariate adjustment for demographics, BMI, and behavioral changes, revealed that each 10 g/day increase of calorie-adjusted total dietary fiber was correlated with a 14% (relative risk or RR = 0.86) reduction in the risk of total coronary events and a 27% (RR = 0.73) decrease in risk of coronary death. Cereal, fruit, and vegetable fiber consumption demonstrated a relative risk reduction of 0.90, 0.84, and 1.00 for total coronary events, and 0.75, 0.70, and 1.00 for coronary deaths with each 10 g/day increase of calorie-adjusted total dietary fiber from these sources. Findings were similar for both genders. Researchers completing this analysis also attempted to determine whether the reduction in risk of CHD was from soluble (also known as "viscous") and/or insoluble fiber. In this pooled analysis, inverse associations occurred for both soluble ("viscous") and insoluble fiber. Past studies have not found a consistent benefit with one class of fiber over the other [65, 66].

Simplistic additions of fiber to the diet can even have an impact on reducing medication dosages. The incorporation of 15 g of psyllium husk supplementation daily with a 10 mg statin (simvastatin) was demonstrated to be as effective as 20 mg of statin alone in reducing cholesterol in a preliminary placebo-controlled study of 68 patients over 12-weeks [67]. A meta-analysis of 24 randomized placebo-controlled trials of fiber supplementation found a consistent impact on blood pressure [68]. Supplementation with small amounts of fiber (mean dose, 11.5 g/day) reduced systolic blood pressure by −1.13 mmHg and diastolic pressure by −1.26 mmHg. The reductions were larger in individuals over the age of 40 years and in hypertensive individuals compared to younger and normotensive patients. Daily intakes of fiber in the United States and many other Western countries is approximately 10–15 g/day, which is approximately only half of the total amount consistently recommended by the American Heart Association (AHA) and American Dietetic Association (ADA) (25–30 g/day) for adequate overall health [69].

The bottom line is that dietary fiber from food is easily achieved by low-cost sources of soluble and insoluble fiber. For example, I often tell patients to have just a third of a cup of a bran cereal in the morning with flaxseed and some fruit, and before they leave the door in the morning approximately 20 g of fiber will have already been consumed! Low-cost fiber sources such as flaxseed can provide potentially numerous heart healthy and urologic healthy outcomes [70–74]. Flaxseed is also one of the highest plant sources of heart healthy omega-3 fatty acids.

However, fiber seems to have become too commercialized and in my experience patients are turning toward powders and pills only to solve their problem, and this is not only costly, but it also provides primarily small amounts of soluble fiber that would never allow a patient to reach their fiber goal utilizing only these sources. Often I ask student and residents how many fiber capsules/pills need to be consumed daily to

obtain just 20 g of fiber and the answer always seems to provide adequate shock value (note the answer is 30–40 pills a day depending on the commercial source) [46]!

Recommendation #7: Encourage patients to incorporate more moderate (approximately two servings or more) weekly intakes of a variety of canned, broiled, baked, and even raw/smoked fish in their diet, but fried and high mercury fish should be generally discouraged. Other healthy sources of omega-3 fatty acids (e.g., nuts and healthy plant cooking oils) should also be encouraged.

Ground flaxseed and soy are good sources of omega-3 fatty acids, but numerous types of oily fatty fish also contain high concentrations of omega-3 fatty acids (EPA and DHA) and they are also the best natural food source of vitamin D3 (cholecalciferol), and they contain high concentrations of high-quality protein and minerals [46]. Omega-3 fatty acids have demonstrated numerous benefits in terms of reducing the risk of a variety of prevalent chronic diseases [75], especially CVD [76, 77]. Potential positive mechanisms of action for fish and fish oil include a reduction in: triglycerides [78], blood pressure [79], platelet aggregation [80], and arrhythmias [81]. However, their primary benefit has been their potential ability to reduce the risk of sudden cardiac death (SCD) [82–84].

Again, numerous types of fish contain high levels of omega-3 fatty acids, vitamin D, and protein including salmon, tuna, sardines, and a variety of other baked, broiled, raw, but fried fish are not potentially beneficial [46]. Variety should be encouraged to increase compliance and exposure. The benefit of fish consumption to reduce the risk of certain urologic diseases is preliminary [85, 86], but its role in reducing a cardiovascular event or impacting all-cause mortality is a more definitive conclusion from clinical trials encouraging fish or fish oil consumption in patients with and potentially without a history of heart disease [87–90].

Mercury concentrations in specific fish have been reported by the Food and Drug Administration (FDA) and in the overall medical literature, but the preliminary data remain controversial and it is not known at this time what kind of clinical impact these mercury levels may have on the individual [91, 92]. Four types of larger predatory fish have been most concerning (king mackerel, shark, swordfish, and tilefish) because they have the ability to retain greater larger amounts of methyl-mercury. However, moderate consumption (2–3 times/week) of most fish should have minimal impact on overall human mercury serum levels. A large investigation of moderate mercury serum levels in older individuals found little to no negative long-term impacts on neurobehavioral parameters [93]. A randomized trial of mercury exposure from dental amalgam in children also found no significant issues [94]. This preliminary data will not provide enough comfort to patients concerned about mercury in seafood. Regardless, the positive impact of consuming fish always seems to outweigh the negative impact in the majority of individuals with the exception of women considering pregnancy or who are pregnant. I find it pertinent that low-cost fish such as anchovies and sardines are low in mercury, and have some of the highest concentrations of omega-3 oils that are used primarily more than any other fish in omega-3 fatty acid randomized trials utilizing supplements for heart disease and cancer. It should also be kept in mind that the AHA recommends about two servings of fish per week (equivalent to one fish oil supplement a day) [95], which I try to reiterate often to urologic patients.

Tree nuts share some similar clinical positive impacts to omega-3 oils found in fish. A consistent decrease in the risk of CHD and/or SCD has been associated with an increased consumption of a variety of nuts in prospective studies, and they can also reduce inflammatory markers that impact a variety of organ systems [96–103]. Nuts contain a variety of potential beneficial compounds such as: ALA (an omega-3 fatty acid), other polyunsaturated fats, mono-unsaturated fats, vitamin E, magnesium, potassium, fiber, flavonoids, and selenium [96]. However, the limitation of tree nuts is their high caloric content when going beyond several servings a day.

Healthy plant cooking oils such as soybean, canola, olive oil, safflower, etc., also contain a

high concentration of omega-3 fatty acids, monounsaturated fat, and numerous other vitamins and minerals such as natural vitamin E [46]. Most cooking oils contain 120 calories per tablespoon; therefore, moderation again is the cornerstone to good health and nutrition. An extensive review of healthy omega-3 fatty acids can be found in the literature [104, 105]. These publications emphasize the general health benefits of certain diets and supplements without a myopic focus only on one disease or condition. However, again these publications continue to emphasize that heart healthy products appear to be tantamount to male sexual health.

Recommendation #8: Please constantly and consistently emphasize and encourage heart healthy lifestyle recommendations (#1–7) because now the emerging clinical trial evidence is that these recommendations precisely mirror the most effective ED prevention and potential treatment advice that health care professionals can now offer to their patients. Remember it is the sum of what patients can do in moderation that has the highest probability of impacting male sexual and overall health compared to just one or several lifestyle changes in extreme.

Perhaps it would sound overly dramatic to say that I have waited for a comprehensive ED heart healthy lifestyle clinical trial my entire career, but at least I am being honest. A truly ground breaking and unique 2-year randomized trial from Italy of vigorous exercise and diet to improve ED should receive more clinical attention [106, 107]. This was a very unique and interesting trial from Italy that should change the way health care professionals treat men with ED. A total of 110 obese men (average BMI of 36–37 = morbidly obese), average WHR of 1.01–1.02, average age 43 years, average ED score 13–14 out of 25 (IIEF), and without diabetes, high cholesterol, or hypertension with ED were included in this trial. A total of 55 men were included in an aggressive intervention group that reduced calories and increased physical activity via personalized dietary counseling, exercise advice (Mediterranean-style diet), and regular appointments with a nutritionist and personal trainer. Another group of 55 men were in the control group and were given general information about exercise and healthy food choices. After 2 years, the BMI significantly decreased on average from 36.9 to 31.2 in the intervention group, and serum levels of interleukin-6 and C-reactive protein (CRP) (higher levels may indicate more inflammation) also decreased significantly. The average physical activity level increased significantly from 48 min per week to 195 min per week in the intervention group, and the mean erectile function score increased significantly from 13.9 to 17. A total of 17 men in the intervention group actually reported an erectile score of 22 or higher (normal function). When considering all other factors several changes were independently and significantly associated with a higher rate of improved erections including a lower BMI or BMI reduction, increased physical activity, and a lower CRP levels. The bottom is that approximately 33% of the men in this study with ED regained normal erectile function after 2 years of following healthy behaviors mostly from exercise, weight reduction, caloric control and healthy dietary changes. This study had one major limitation, which was the lack of looking at psychological factors, because it is also plausible that these lifestyle changes improved mood, self-esteem, and reduced depression and this could have also been a reason for improved erectile function. Regardless, if one is to look at some of the healthy changes in the intervention group that occurred after 2 years the results were nothing less than remarkable! Lets look at how many healthy changes actually took place over the 2-year trial:

- Total calories were reduced by 390 calories/day (2340–1950)
- Complex carbohydrates increased and simple sugars decreased
- Fiber intake increased by 10 g/day (15–25)
- Protein consumption increased
- The overall percentage of fat in the diet did not change (30% of calories), but there was a reduction in saturated fat (14–9%) and an increased intake in monounsaturated fat (9–14%)
- The ratio of omega-6 to omega-3 fatty acids in the diet was reduced by half (12–6)
- Cholesterol in the diet was reduced by 84 mg/day (360–276)

- Exercise time (mainly walking) increased from about 7 min/day to almost 30 min/day
- Average weight loss was 33 lb (226.6–193.6)
- Average BMI decreased by almost 6 points (36.9–31.2)
- WHR decreased by 0.09 (1.02–0.93)
- Erectile function scores increased by 3 points (13.9–17 points)
- Systolic (127–124 mmHg) and diastolic (86–82 mmHg) blood pressure decreased by 3–4 points
- Total cholesterol decreased by 11 mg/dL (213–202), but HDL (good cholesterol) increased by 9 points (39–48 mg/dL)
- Triglycerides decreased by 19 mg/dL (169–150) and glucose decreased by 8 mg/dL (103–95) and insulin level also decreased by 7 points (21–14 μU/mL)
- CRP was reduced by 1.4 mg/L (3.3–1.9)
- Interleukin 6 (IL-6, an inflammatory marker) was reduced by 1.4 pg/mL (4.5–3.1)
- Interleukin-8 (IL-8, an inflammatory marker) was reduced by 1.2 pg/mL (5.3–4.1)

Again, one-third of the obese men reporting ED regained normal function in this trial, but the majority of men experienced at least some improvement in sexual function and a simultaneous reduction in the risk of common CVD markers [106, 107]. For example, hs-CRP levels were significantly reduced in these men, and it is interesting that greater reductions in this inflammatory marker were associated with some of the largest improvements in ED. Again, heart health is tantamount to urologic and erectile health [106–109]. What this first of a kind randomized trial demonstrated was that recommendations #1–7 found in this chapter are the mirror reflections of what has the greatest potential of being effective in terms of lifestyle changes in men concerned about ED.

Lifestyle modifications, including smoking cessation, need to be discussed by clinicians to reduce all-cause mortality including cancer [110–114], and potentially to reduce the risk of ED [109]. Moderate alcohol consumption also seems to reduce cardiovascular events [115], and is part of the Mediterranean diet. In my experience, minimal time is needed to suggest changes that can impact all-cause mortality. These recommendations may seem simplistic, but past general studies of men have demonstrated that few (<5%) have reported adhering to numerous moderate healthy behaviors at one time [116]. Following one dramatic healthy change in excess, rather than multiple changes in moderation seems to be a more disturbing current trend and concern that needs to be reversed. This may be the result of past studies focusing on one lifestyle change to produce an overall impact on disease risk, poor compliance overall, or just a lack of attention, time, or understanding to this detail, or a lack of enthusiasm or motivation on the part of the health professional and the patient. There are multiple potential etiologies for minimal adherence or behavioral compliance, but the studies of combined moderate lifestyle changes continue to demonstrate that it is more the sum of what you do, rather than one or two specific behavioral changes that can impact cardiovascular markers, CVD, cancer, and all-cause mortality [117].

I often use two checklists derived and modified from the notable Mediterranean diet U.S. study [118], and the 52-countries study and other combined male lifestyle studies to ensure motivation and compliance in patients [119–123]. These studies found that regardless of race, age, genetics and geographic location around the world, the ability to essentially maintain nine consistent features of lifestyle and/or diet was associated with a 85–95% reduced risk of a cardiovascular event, and these similar features in other recent studies demonstrated an improved ability to live far beyond average life expectancy with minimal mental or physical morbidity. It is interesting that the characteristics in these individuals included behavioral changes with no commentary or benefit or detriment in taking a dietary supplement. If any preventive pill (supplement or prescription) were ever associated with a reduction in the risk of a cardiovascular event by approximately 90%, the designer of that pill would probably be an immediate candidate for a Nobel prize in medicine, and this is what I try to reiterate to patients. Tables 39.5 and 39.6 is a modified handout or checklist that

Table 39.5 U.S. Mediterranean diet study – individuals with scores of 6 or more on the checklist had a lower risk of early mortality compared to those with scores of 4 or less. Just review the checklist, and add up the points [46, 119]

Beverage or food	Answer yes or no (1 point for each question answered "yes" and 0 points for a "no")
Alcohol – two drinks a day or less for men and one drink or less for women	
Fat intake focused on healthy fats, mostly monounsaturated and polyunsaturated (canola, olive, safflower oil, etc.)	
Fish – at least two or more servings per week	
Fruit – four or more servings a day	
Legumes/beans – two or more servings a week	
Meat – one or less servings a day	
Nuts and seeds – two or more servings a week	
Vegetables (other than potatoes) – four or more servings a day	
Whole grains (e.g., whole/multi- grain and whole wheat foods with high amount of fiber and protein) – two or more servings a day	
Total score	

Note: Traditional Mediterranean diets also allow moderate intakes of dairy, such as cheese, milk, and yogurt

Table 39.6 A partial Dr. Moyad summary of the moderate lifestyle changes that in combination may have reduced the risk of a first cardiovascular event by approximately 85–95% from a combination of other lifestyle studies. Note that each healthy change was associated with an approximately 5–10% reduction in a clinical event [47, 120–124]

Lifestyle changes	Yes	No
Do you smoke?		
Do you consume alcohol in moderation (at least once a week but not more than 1–2 servings per day)?		
Do you have low cholesterol?		
Do you have normal blood pressure?		
Do you have abdominal obesity?		
Do you have depression or stress issues?		
Do you have diabetes?		
Do you consume fruit and vegetables daily?		
Do you engage in at least 30–45 min a day minimum of physical activity (4 or more hours a week) and lift weights several times a week?		

I provide to patients [46]. How many of your patients or even colleagues have all of these features or need to work on these changes? How many urologic conditions could be prevented or improved with these heart healthy changes? Clinicians should feel free to use these checklists in their office.

Recommendation #9: Quality controlled *Panax ginseng* should be considered a viable dietary supplement option for men to improve erectile function and libido. In the near future, other supplements as well may have a positive impact on ED.

Panax ginseng is a plant, and is also known as "Korean Red ginseng" (KRG), and it is usually harvested when it is 6 years old and nonskinned before it is steamed and dried [124]. A systematic review of the impact of KRG on erectile function taken from 20 electronic databases without language restrictions was recently published [125]. Only randomized clinical trials were considered for inclusion, and the quality of each trial was determined using a Jadad score from 1 to 5, with 5 being of the highest methodology [126]. A total of seven randomized clinical trials met all the inclusion criteria, and the quality of the studies was low to high on the Jadad scale. A total of 363 men aged 24–70 years old with a duration of ED from 1 to 30 years were included in the meta-analysis. The duration of treatment ranged from 4 to 12 weeks. The doses of ginseng ranged from 1,800 to 3,000 mg per day and included psychogenic, vasculogenic and mixed ED participants. The meta-analysis demonstrated a significant ($P<0.00001$) benefit with KRG and a subgroup analysis also demonstrated a significant benefit for psychogenic ED ($P=0.001$). At the time of this chapter's submission another randomized and positive clinical trial of KRG was published [127]. Keep in mind

that the benefits of KRG were observed with validated scoring symptoms in these clinical trials (published over the last 15 years), including the IIEF, and benefits were noted in multiple areas/parameters in several trials including erectile function, maintenance, overall satisfaction and libido. I know of few clinicians that are aware of the data on KRG.

A variety of mechanisms of action have been proposed but one of the leading theories is that compounds in KRG may induce corpus cavernosum smooth muscle relaxation via the nitric oxide pathway [128–130]. Ginsenosides are the active ingredients in KRG and a variety of them are being identified may cause a dose-dependent increased release of nitric oxide [128, 131–133]. However, in working with KRG and having a good command of the background literature that are numerous other pathways both centrally and peripherally that could potentially explain some of the benefits [134]. In fact, another route not yet proposed, but observed from other variants of ginseng in the clinical literature include an energy or antifatigue impact [135], which theoretically could improve a variety of ED types, including psychogenic. Regardless, the most impressive findings from KRG clinical studies in my opinion are not concerning sexual dysfunction improvement, but rather the overall heart healthy safety and potential diverse clinical applications in men and women [136, 137], Alzheimer's disease [138], CVD and long-term intake and overall early mortality prevention [139–141], and because of a minimal or lack of warfarin and other prescribed medication negative interactions [142–146]. Still, questions still always need to be answered on long-term efficacy and safety with other or novel prescribed medications (PDE-5 inhibitors, etc.), most effective doses, and ginsenoside concentrations and types that have the most clinical efficacy. Thus, to say quality control may be an issue with this type of ginseng seems to be an understatement [147]. Still, and in my opinion, PDE-5 inhibitors combined with KRG could represent a novel, diverse and impactful medication option for men and women because of the libido enhancement, [125, 127] and compliance [148], that the PDE-5s were not able to achieve could potentially be found in this unique combination approach. And, the dramatic impact on ED itself from the PDE-5 inhibitors could assist with the overall impact of KRG while at the same time utilizing a potential novel lower dose of the PDE-5s may also be plausible to reduce acute safety issues with this drug class [149]. Additionally, a lifestyle change study in addition to the consumption of KRG would represent a wonderful insight into the synergistic potential of the ginsenosides for men with sexual dysfunction. The bottom line is that no other dietary supplement compounds compared to those found in KRG has received more human safety, diverse clinical data, and overall data in the area of ED compared to it in my opinion and from the sheer number of overall publications, which is also why it needed to receive such a large amount of attention for the reader.

Lepidium meyenii or "Maca" is an Andean plant that is a part of the Brassica family and has been used for centuries in the Andes to enhance fertility in humans and animals [150]. Maca may also improve sexual function from a series of recent and past preliminary clinical trials in men [151, 152]. One such trial was published at the time of the chapter's submission [152]. Thus, past clinical reviews of this compound should be located and reviewed by the clinician if there is any current interest [150, 153]. The data points toward good preliminary safety and a potential enhancement in fertility that should receive attention in the future as much as its potential impact on ED. We are currently conducting the first large-scale review and analysis of this compound that should be published in 2011. Regardless, clinicians should follow the ongoing data on the compounds found in MACA because it may represent a near future viable alternative for men with sexual dysfunction.

Recommendation #10: Try to avoid or caution patients about the numerous dietary supplements that have not proven themselves to be heart or overall healthy regardless of the data in ED with

this agents. If there is a safer, viable, cost-effective prescription option it should be utilized over a minimally researched supplement.

As of 20 January 2005 it became illegal to sell androstendione supplements in the United States [154, 155]. Androstenedione was considered a "prohormone" supplement that some men used to attempt to build muscle. Remember, the year (1998) that Mark McGwire from the St. Louis Cardinals achieved the homerun record for major league baseball? He was also taking this supplement during that season and it created a lot controversy! It was a potentially dangerous supplement because it had been associated with a reduction in "good cholesterol" or HDL and it had potentially other health consequences. Therefore, there were so many concerns with this supplement that eventually the FDA and the U.S. government decided to remove it from the market. Now, here comes the catch … it turns out that other so-called "prohormone" supplements like DHEA will not be banned but are still being allowed to be sold. Now, if DHEA is similar to androstenedione in that it has similar effects, then why is this supplement still allowed to be for sale over the counter? This is part of the strange circumstances surrounding some dietary supplements and the inconsistency in the policies that are applied. Regardless, if some store is selling over the counter androstenedione in your neighborhood then they are doing this illegally. However, if they are selling DHEA supplements, which has a similar effect to androstenedione, then this is perfectly legal.

DHEA supplements enjoy a unique exemption under federal law, because of a bill quietly approved by Congress in late 2004. How did this occur among all the issues of sports, athletes, and steroid use? How did DHEA survive, where the other supplements did not? Sports officials were in favor of an overall ban on steroids and related products, including DHEA. DHEA is banned by the Olympics, the World Anti-Doping Agency, the National Collegiate Athletics Association, the National Football League, the National Basketball Association, and baseball minor leagues. The 2005 law that impacts prohormone supplements, passed without objection, also gave the Drug Enforcement Administration more authority to ban new or novel steroids, with one exemption, DHEA. The term "anabolic steroid" is defined now as any drug or hormonal substance, chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids, and dehydroepiandrosterone). Now, with this pertinent history what about any new data to support DHEA for men's health or sexual health?

In one of the longest duration clinical trials in the history of DHEA [156], the supplement was given for 2 years at a dose of 75 mg/day in men and 50 mg/day in women, and these researchers decided to look at the impact of this hormone on the body, physical performance, insulin and other factors compared to a placebo. There were a total of 87 men (29 received DHEA, 27 received testosterone, and 31 received placebo) in this study and 57 women (27 received DHEA and 30 received placebo), and the average age of the participants ranged from 66 to 70 years. Men and women in this study were just slightly overweight with a BMI of 26–27 (a BMI of 25–29 is considered overweight and 30 or more is obese). Women that had low levels of DHEA (median value of 0.4 μg/mL or 1.1 mmol/L), and men with low levels of DHEA (median value of 0.7 μg/mL or 1.9 mmol/L) had their levels increased by approximately 3.5 μg/mL or 9.5 mmol/L after taking DHEA. This is a 500% increase in blood levels of this hormone in some of the patients! This current study showed that quality of life did not change on DHEA, but perhaps a larger study would have provided more clarity in this area. There were no changes in oxygen intake (a measure of metabolism change), muscle strength, or insulin. I was concerned that the DHEA group experienced an unhealthy drop in HDL or "good" cholesterol, which was a significant 5-point reduction in women, and an almost significant 3-point reduction in men during the study. No such HDL drop occurred in the testosterone-receiving group of men during the study. Men receiving testosterone had a slight reduction in fat tissue, and bone mineral density increased at the hip area in men on DHEA and testosterone.

In women, DHEA increased bone mineral density only in the area of the wrist, but not at other sites. So, again this study leaves open the possibility of testing higher doses of DHEA and testosterone but safety will ultimately also be an issue. DHEA and other prohormone supplements in women and men have had a history of causing HDL cholesterol changes that have been concerning overall. Higher doses of DHEA need to be studied, but in the meantime, reversing the signs of aging with hormones has little to no evidence and may have harm. Why not just give testosterone replacement therapy (TRT) to the men that truly require or qualify for testosterone? This seems to make more sense as opposed to playing a guessing game with a dietary supplement for general antiaging purposes that also seems to possess safety and quality control issues [154, 155, 157].

I am often asked by urological associates why I am not more excited about endorsing high doses of L-arginine as an individual supplement for ED due to the obvious relationship with this compound and nitric oxide, and because there is some preliminary positive data using higher doses of this compound in men with low urine or blood levels [158]. The answer does not so much rely on an efficacy or dosing issue or selective qualification issues (these are more minor issues), but a heart healthy and safety issue that I have a difficult time to ignore that also seemed to receive little to no attention. This was a recent clinical trial to determine whether L-arginine dietary supplements given in addition to standard postinfarction therapy improves outcomes [159]. It was a single-center, randomized, double-blind, placebo-controlled trial for 6 months. A total of 153 patients following a first ST-segment elevation myocardial infarction were enrolled, and 77 patients were 60 years or older (68% were men). Ejection fraction changes, noninvasive measures of vascular stiffness, and clinical events were recorded over 6 months. Patients were randomly assigned to receive L-arginine supplements with a goal dose of 3 g three times a day or matching placebo for 6 months. No significant change from baseline to 6 months in left ventricular ejection fraction or vascular stiffness measurements were found in either group, including those patients age 60 years or older. However, 8.6% of the participants (six individuals) died during the 6-month study in the L-arginine group compared to none in the placebo group ($P = 0.01$). Due to safety issues, the safety monitoring committee closed enrollment. Thus, L-arginine supplements when included as part of standard postmyocardial infarction therapy did not improve ejection fraction or vascular stiffness measurements, and may even be associated with a higher rate of postinfarction death. The researchers warned that L-arginine should not be taken following acute myocardial infarction or perhaps in others with potential CVD concerns. Based on this single well-done trial (as rigorous as any previous trial of the supplement), L-arginine supplements, especially in high doses should be discouraged in any high-risk cardiovascular patients in my opinion, and perhaps anyone else until more safety and efficacy issues are resolved. It could have been acting as a pro-oxidant in this clinical trial because most men had normal levels of L-arginine at baseline. Regardless of the reason, it seems better to be safe in these circumstances, especially since obtaining large amounts of L-arginine from dietary sources is not difficult, but even the health impact with this approach, it seems, is minimal [160].

High doses of zinc for sexual health are a serious problem because of numerous potential heart unhealthy concerns such as a lowering of HDL cholesterol and immune suppressive abnormalities [161, 162]. Keep in mind that the recommended doses of zinc per day are between 10 and 15 mg [46]. So, how did the clinical research reach this point of concern? The largest randomized trial ($n = 3{,}640$, four groups) of a combination daily dietary supplement (500 mg vitamin C + 400 IU vitamin E + 15 mg beta-carotene + 80 mg zinc + 2 mg copper) versus the combination without zinc, just 80 mg zinc, or placebo for age-related macular degeneration (AMD) found a significant reduction in the risk of disease progression over the 6-year study in the combination supplement that included zinc in it [163]. However, the only individuals that benefited

were those with intermediate to advanced stages of already diagnosed macular degeneration. Individuals at risk or with early stage macular degeneration did not benefit from taking this supplement over the study period. In addition, the supplement did not have any effect on cataract development or risk. This study was a landmark study for eye health, because it made a combination dietary supplement standard medicine for those with the dry form of macular degeneration. However, there may have been in increased risk of urologic problems. There were some possible side effects reported with this supplement in the original study. Therefore, a research group from the University of Wisconsin did a remarkable follow-up study. In a further analysis from the original eye health study in 2001, they published the potential urologic side effects with this supplement [164]. There was a significant increase in hospitalizations for urologic causes such as BPH, kidney stones, urinary tract infection, and kidney failure in patients on the high-dose zinc versus the nonzinc supplement from this study ($P=0.0003$), and this risk was greater in male compared to female patients. Patients in this study were an average age of 69 years old and were followed for a little more than 6 years.

Researchers have also examined the relationship between supplemental zinc intake and prostate cancer risk among 46,974 U.S. men in the Health Professionals Follow-up Study [165]. During 14 years of follow-up from 1986 through 2000, a total of 2901 new cases of prostate cancer were documented and 434 of these cases were classified as advanced prostate cancer. Supplemental zinc intake at doses of up to 100 mg/day was not associated with the risk of prostate cancer. However, compared with nonusers, men that took more than 100 mg/day of zinc supplements had a relative risk of 2.29 (P trend $=0.003$), and men that consumed zinc supplements for 10 or more years had a relative risk of 2.37 (P trend <0.001). In this study, a large 131-item food frequency questionnaire was used to increase reporting accuracy. In addition, supplemental zinc provided 32% of the total zinc intake (the largest source), and beef (11%) and breakfast cereals (5%) represented other large sources of zinc.

Most men should not be ingesting high-dose zinc supplements because they have not been diagnosed with advanced macular degeneration or any other condition that requires such a large intake of supplemental zinc. However, if it is a matter of preserving your eyesight there should be some allowance of zinc in an eye health product, but keep in mind that the average multivitamin carries approximately 10–20 mg and this has been found to be generally safe, but getting larger amounts from male enhancement products or individual zinc supplements for immune health makes no sense in my opinion with all of these diverse safety issues.

Conclusion

Recommending a pill is simplistic, but not the usual solution because few supplements for ED, or even for urologic prevention or total mortality reduction can be recommended at this time. Compliance is also a major issue over a long period of time with any agent. No supplement or even drug therapy has ever matched the reduction in CVD or all-cause mortality observed in clinical studies or other investigations of lifestyle changes [46].

The time seems more than ripe to redirect our attention in regards to lifestyle changes and sexual health. Heart healthy seems tantamount to overall urologic and erectile health, and this is the best potential practical and realistic recommendation that has worked in my consulting practice for over 15 years. It seems that large and diverse (American Cancer Society, AHA, and the American Diabetes Association) health care preventive organizations are beginning to apply this same concept [166], because the truly life changing lifestyle recommendations for patients are not mutually exclusive. They impact a variety of potential outcomes and have the highest overall probability of impacting all-cause mortality. This is critical in my opinion, because again the forest has to take precedence over the

tree in order to improve the overall state of urologic and sexual health.

The recommendations in this chapter may be simplistic changes with a folksy tone, but they are powerful and they need your attention in your clinical practice. The more clinicians demonstrate to patients that they are serious about these changes, the more, I believe, patients will respond to the advice, and perhaps it is initially simple by just speaking the vernacular and applying it for brief moments in the clinic. On the other hand, the less a clinician wants to focus on these issues, the less I also believe patients will respond to them, and even worse the more likely in my opinion your patients will begin to listen to less credible sources for guidance. This latter choice is simply not acceptable, but unfortunately this abnormal situation has become so common today in other nonurologic areas that it is almost considered normal for some patients to take lifestyle, supplement, and general preventive advice from the person at the counter of the local health food store over their primary practitioner [167]. This simply cannot be allowed to happen in urology I know it already has-trying to be profound here, and perhaps this chapter is a simple small step in the appropriate direction. Heart healthy = male sexual health-can it be any easier than that!

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Chapter 40
Medical Treatments for Sexual Problems in Women

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Keywords Menopause • Fertility • Pain • Hormone therapy • Estrogen • Progestin • Testosterone • SSRI • Cancer • Iatrogenic menopause • Sexual dysfunction (and/or dyspareunia)

Introduction

Cancer today is more of a chronic than a fatal disease: the improving survival rates increase the likelihood of long survival after the diagnosis. Unfortunately, cancer treatment is the most frequent cause of premature iatrogenic menopause and psychosexual dysfunction. Therefore, an increasing number of cancer survivors have to cope with both the consequences of cancer treatment per se, the complex physical and psychological changes secondary to a premature iatrogenic menopause, and the burden of sexual dysfunctions, more difficult to accept in the youngest patients. Female sexual identity may be variably affected by a cancer diagnosis and treatment depending on the age at diagnosis (and the age at the time of any recurrences). Age is the first biological factor that may modify the outcome of cancer diagnosis and treatment, when sexuality is considered as an independent variable in the quality of life (QOL) evaluation. The impact of cancer is increasingly worse in younger patients, especially if radical surgery, adjuvant systemic chemotherapy, and/or local radiotherapy further reduce the biological chances of a fulfilling sexual and procreative life.

Iatrogenic Menopause

Iatrogenic menopause defines the appearance of menopause as a consequence of medical treatment, for benign or malignant conditions. In cancer patients, it may be the consequence of surgery (bilateral ovariectomy), chemotherapy, and/or radiotherapy.

Irreversible iatrogenic ovarian damage may be:

- Prepubertal (rare). In this case, puberty will be induced through exogenous hormonal therapy.
- Postmenarche. Even after a few physiologic periods, definite amenorrhea associated with elevated FSH defines a premature menopause.

Loss of estrogens deprives the woman of the lymph that nourishes the female body. Recent data on the widespread tissue distribution of alpha and beta estrogens receptors explain why estrogen loss affects all organs and functions [1], differences being accounted for by the complexity of genetic differences, receptor plasticity, and interplay among the various hormones and receptors themselves.

Bilateral ovariectomy reduces testosterone production by on average 50%, leading to the so-called "Androgen Insufficiency Syndrome" [2, 3] characterized by loss of libido, loss of vital energy, loss of assertiveness, loss of pubic hair, and changes in body shape, possibly contributing to the "fatigue"

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so often complained of by cancer survivors [4, 5]. Symptoms may be rooted both in biological and psychodynamic factors. Chemotherapy and radiotherapy may not only destroy ovarian follicles, thus causing the estrogen loss, but also may affect the Leydig cells, present in the inner part of the ovary and responsible for androgen production.

All these changes may wound physically and symbolically the *sensuality* and *sexiness*, leading to a self-perception of being defective, broken, or damaged, amplified if radiotherapy has caused a narrowing and shortening of the vagina, impairing or preventing intercourse and coital pleasure. Sexuality may be acutely affected also after chemotherapy, usually combined with surgery for ovarian cancers, for its general impact on well-being (fatigue, hair loss, weight changes, nausea and diarrhea, lack of sexual arousal, and vaginal lubrication). More so, after radiotherapy, when *sexual dysfunction* is reported on average in 50–82% of patients, even worse after combined surgery and radiotherapy [6–8].

Fertility Preservation

Motherhood is a critical part of women's sexual identity. Loss of fertility, secondary to surgery, chemo-, and/or radiotherapy (pelvic or total body), is a major cause of impaired sense of femininity and loss of sexual interest ("why have sex if I cannot get pregnant anymore?"). Unfortunately, when treated for cancer, women of reproductive age are still being inadequately counseled with regard to the negative impact of treatment on their fertility and on their options for fertility preservation. Appropriate information on fertility protection *before* oncologic treatment is essential. Healthcare providers should therefore know about current possibilities and inform women about fertility protection before cancer treatment begins. This would give patients an extremely powerful message of hope ("if they preserve my fertility, this means that I can be cured and have a child after all…") and maintain a fragment of clear blue sky even in the darkest moments. Moreover, pregnancy after cancer treatment does not seem to worsen the prognosis [9].

Embryo Cryopreservation

Currently, it is the most effective approach. The human embryo is very resistant to damage caused by cryopreservation. The postthaw survival rate of embryos is in the range of 35–90%, while implantation rates are between 8 and 30%. If multiple embryos are available for cryopreservation, cumulative pregnancy rates can reach greater than 60% [10]. Delivery rates per embryo transfer using cryopreserved embryos are reported to be in the range of 18–20% [10]. However, this approach requires in vitro fertilization and a participating male partner. This option may not be acceptable to prepubertal or adolescent girls [11].

Cryopreservation of Mature Oocytes

Oocyte banking is more problematic than cryopreservation of sperms or embryos. The first obstacle is the sensitivity of oocytes to chilling. Cooling and exposure to cryoprotecting agents (CPAs) affect the cytoskeleton and may aggravate the already high incidence of aneuploidy in human oocytes [12]. Exposure to CPAs also causes hardening of the zona pellucida, so that all oocyte cryopreservation protocols involve intracytoplasmic sperm injection (ICSI) as a precaution. Fertilization has to be carried out about 3–5 h after thawing while the oocyte remains fertile. Further disadvantages of this method are that cancer patients may not have more than one opportunity for oocyte harvesting before undergoing potentially sterilizing treatment, since a cycle of controlled stimulation requires several weeks, and there is normally a delay of a few months before treatment cycles. The success of the method is also dependent on the total number of eggs harvested (<10 oocytes is associated with a very low chance of pregnancy). However, with the introduction of ICSI and the publication of reassuring data [13], efforts to cryopreserve oocytes have resumed in recent years, with conventional slow cooling–rapid thawing protocols and later with vitrification. The overall live birth rate per cryopreserved oocyte is about 2%, which

is much lower than that with IVF using fresh oocytes [14].

Cryopreservation of Immature Oocytes After In Vitro Maturation (Without Gonadotropin Stimulation)

Oocytes are recovered for In Vitro Maturation (IVM) from fresh tissue or follicular aspirates before the dominant follicle emerges during the midfollicular phase of the menstrual cycle (normally 8–10 mm in diameter). Cryopreservation difficulties include the different optimal times of equilibration for the oocyte and its smaller cumulus cells. At present, the reported success of IVM in young women with polycystic ovaries is a pregnancy rate of approximately 25–30% per cycle, with a high miscarriage rate [15].

Gonadotropin-Releasing Hormone Analogue Treatment

Keeping the ovarian follicular development quiescent by suppression of gonadotropins has been proposed to protect women from damage by cytotoxic therapy. This research has suggested that receipt of gonadotropin-releasing hormone analogue (GnRH-a) throughout treatment may increase a woman's likelihood of remaining premenopausal after chemotherapy, although there has been an intensive debate concerning the existence of FSH (follicle-stimulating hormone) receptors in primordial follicles and GnRH-a receptors in the human ovary [16, 17].

Cryopreservation of Ovarian Tissue

Currently, it appears to be a very promising way of providing the cancer patient with a realistic chance of fertility preservation – a prospect that is also extremely important for psychological reasons [18]. The cryopreservation of ovarian cortical strips has emerged in recent years as an easy, fast, and inexpensive technique and has already yielded the first live births [19, 20]. The idea of cryopreserving ovarian tissue is based on the finding that the ovarian cortex harbors primordial follicles that are more resistant to cryoinjury than mature oocytes, because the oocytes they contain have a relatively inactive metabolism and lack a metaphase spindle, zona pellucida, and cortical granules [21]. Advantages include fewer logistical restrictions and no need for hormonal stimulation, a plus when time is short and a far larger number of oocytes preserved, with a greater fertility potential. Ovarian tissue cryopreservation may also be the only acceptable method for any prepubertal or premenarchal female patients receiving chemotherapy or pelvic radiotherapy [22, 23].

Medical Therapies of Sexual Disorders in Cancer Survivors

Female sexual disorders have been addressed in previous chapters. Table 40.1 summarizes sexual issues in women cancer survivors to reset the scenario where medical therapies are indicated, to ease the reader's comprehensive approach.

Medical therapies of FSD include different interventions that should be integrated with an appropriate rehabilitative and psychosexual approach (Table 40.2). The adequate diagnosis of different contributors of the current FSD is mandatory. Physicians should assess if the current complaint preceded cancer treatment, is concomitant to it, or is caused/worsened by the diagnosis/treatment of cancer per se, i.e., assessing if the disorder is lifelong or acquired. He/she should always evaluate if the etiology is prominently biological, psychosexual, or mixed, and if the disorder is generalized or limited to a partner and/or a specific situation [24].

A specific contributor of FSD after cancer treatment is the premature iatrogenic menopause, either due to premature ovarian failure (POF), secondary to chemo- and/or radiotherapy, or

Table 40.1 Factors contributing to sexual dysfunction after cancer in women

Sexual desire may be affected by:
Sexual identity-related issues: body image impairment, disfiguring cosmetic outcomes, negative sexual self-schema, premature ovarian failure, sterility, missed accomplishment of life cycle goals
Loss of sexual hormones and Androgen Insufficiency Syndrome
Cancer treatment's long-lasting side effects: severe fatigue, cognitive impairment, conditioned nausea, mouth sores, cough, hair loss, and headache, especially in postbone marrow transplant (BMT) patients; worse QOL; posttraumatic stress disorder (considering cancer a major traumatic experience)
Secondarily, because of concomitant sexual arousal disorders, orgasmic difficulties, and/or sexual pain disorders; negative relational factors (distant/indifferent or abusive partner; partners' emotional and/or sexual problem, cancer-related or independent)
Sexual arousal may be affected by:
Inadequate central arousal, due to the deprivation of sexual hormones – specifically androgens – mostly in women suffering from AIS, and the overlapping effect of factors inhibiting sexual drive
Genital arousal impairment, due to loss of sexual hormones and iatrogenic anatomic, vascular, and nervous damage, particularly after genital cancers
Nongenital-peripheral arousal, because of the reduced sexual repertoire and loss of sexual hormones
Couple problems, more significant in younger couples, affecting motivation, self-confidence, intimacy, and attachment dynamics
Sexual pain-related disorders may be determined by:
Vaginal dryness, secondary to arousal disorders of mixed origin; vaginal anatomical shortening and functional impairment, in consequence of pelvic surgery and/or radiotherapy
Defensive contraction of the pelvic floor muscles, leading to myalgia with tender and trigger points, contributing to introital pain at penetration
Orgasm and pleasure may be affected by the impairment of:
Sex drive and arousal disorders of mixed biological and psychosexual origin; specific effect of AIS on clitoral responsiveness
Reduced "orgasmic platform" for the loss of estrogens and vaginal anatomical damages (more frequent in cervical cancer survivors)
Sexual satisfaction may be physically and emotionally affected
Physical satisfaction is more vulnerable in younger women, when low desire, inadequate central and genital arousal, orgasmic difficulties, and/or dyspareunia are complained of
Emotional satisfaction may be maintained, when closeness and quality of intimacy are strengthened by the cancer experience. It can be worsened when cancer triggers a further physical and emotional distance and loss of communication and support between partners
The highest vulnerability is described in younger, single, and of low socioeconomic status, or women living in a couple with conflicts

Table 40.2 Integrative approach when addressing sexual disorders in women cancer survivors

Medical:
Appropriate and timely HT, local and systemic, except for hormone-dependent cancers, in all young cancer survivors affected by iatrogenic menopause
In patients treated for gynecologic and/or other pelvic cancers: treatment of inflammatory and/or atrophic conditions
Specific treatments of medical basis of FSD (antidepressant, analgesic)
Rehabilitative:
Moulds or dilators and lubricants to improve vaginal shortening and reduced elasticity
Local vaginal stretching and self-massage with medicated oil, to improve elasticity and restore positive attention to this part of the body
Physiotherapic rehabilitation of the pelvic floor, after pelvic surgery/radiotherapy
Psychosexual:
Individual and couple psychosexual support open to body image, intimacy, and attachment issues, and to relational contributors of FSD
Good doctor–patient relationship, open to listening to sexual concerns (up to 80% of physician never raise the sexual issues in oncologic consultations)

to surgical removal of both ovaries (surgical menopause). Symptoms and signs may include infertility, mood disorders (depression, loss of self-esteem, relational difficulties), disorders secondary to the estrogenic loss (hot flashes, insomnia, memory difficulties, vaginal dryness, joint pain, osteopenia/osteoporosis), and disorders secondary to the androgenic loss [loss of sexual interest up to hypoactive sexual desire disorder (HSDD), orgasmic difficulties, fatigue, loss of assertiveness]. Different factors may interact contributing to loss of desire (both in the biologic and motivational component), arousal difficulties (mental and genital), orgasmic difficulties, and physical and emotional dissatisfaction. Introital and deep dyspareunia may be comorbid with vaginal dryness and with specific anatomical impairments, specifically after surgery/radiotherapy for cervical cancer.

The most relevant medical therapies will be briefly addressed, with a short paragraph on new potential treatments.

Hormone Therapy

Systemic

Hormonal therapy (HT) is necessary to prevent short- and long-term systemic and sexual consequences of estrogen and androgen loss [1, 25–27], particularly in young cancer survivors affected by iatrogenic menopause. Estrogens, and progestins if the uterus is conserved, should be prescribed when oncologically appropriate (i.e., with the exception of hormone-dependent cancers) in doses adequate for the patient age, to induce regular periods with good cycle control and to maintain optimal stimulation of different tissue estrogen receptors. The goal is to restore at best the woman's well-being, which guarantees the best compliance. Androgens should be considered when women have undergone bilateral ovariectomy, systemic chemotherapy, pelvic or total-body radiotherapy, and/or when symptoms and plasmatic levels are suggestive of *Androgen Insufficiency Syndrome* [28].

The loss of sexual hormones has a widespread effect on all systems and organs, as virtually all cells of the female body have receptors for sexual hormones [1]. This loss accelerates the negative multisystemic effects of aging, with a further detrimental effect, which affects sexuality in a complex way. Current key predictors of HT use are: *age at menopause* (the younger the woman, the higher the probability she will require and be prescribed HT); *type of menopause* (surgical menopause is three times more likely to be hormonally treated); and *education and socioeconomic level* (women better educated and with higher socioeconomic background are more likely to use HT). In cancer survivors, those factors are maintained, with the exclusion of hormone-dependent cancers.

HT is the cornerstone of a well-designed treatment to maintain an optimal sexual function after the menopause, more so when it is premature. The sooner the treatment is initiated, the better. The complex positive impact of HT on the brain and its multiple systems (neurovegetative, affective, cognitive, and motor), on the peripheral nervous system, and on the vessels is a prerequisite to maintain an optimal biological component of desire, arousal (central, peripheral nongenital and genital), and orgasm. The potential of different hormonal treatment needs to be further documented in prospective studies.

Hormone therapy encompasses treatment with estrogens, estrogens and progestins, combined estrogen and testosterone, testosterone alone, tibolone, and dehydroepiandrosterone sulfate (DHEA-S). Sex hormones increase the sensitivity of an individual towards sexual stimuli [26, 28]. Estrogens, androgens, and progestins modify the "motivational" state towards or against sexual activity. The distinct effects of estrogens and androgens on desire are still not completely understood and the interplay between these hormones appears to be important. The role of testosterone is relatively well understood; it seems to play a crucial role in sexual desire, arousal, and receptivity towards sexual stimuli.

Progesterone has a mild sedative effect on sexuality. Progestins' action on sexuality varies and depends on a number of factors, mainly related to their androgenicity, which is the result of: (a) being 19-nor-testosterone derivatives, such as noretisterone; (b) having agonistic affinity with the androgenic receptors; (c) having competitive binding affinity (vs. testosterone) to sex hormone-binding globulin (SHBG); (d) inhibiting the 5-alpha-reductase type 1, which activates testosterone degradation to dihydrotestosterone. However, to these authors' knowledge, no specific study on progestins alone has been carried out in cancer survivors with a specific focus on sexual symptoms.

A few more notes will be specified for each class of hormones to help healthcare providers to have a clear scenario of key advantages hormones can offer to cancer survivors, when oncologically appropriate. A gynecologist skilled in medical treatments of the menopause and of comorbid sexual disorders can then tailor treatment(s) to the woman's individual needs with the best outcome in terms of personal and couple' sexual satisfaction, while minimizing the cancer treatment-related side effects.

Estrogens

Estrogens used in HT include different hormones (estradiol, estriol, and conjugated estrogens). They are important for the maintenance and function of neurotrophism and neuroplasticity, on one side, of the vaginal epithelium, vascular cells, smooth muscles, and nerve trophism on the other. Genital sexual symptoms are more frequent in women with estradiol levels <50 pg/ml [29]. Estrogens have vasodilatory effects and increase vaginal, clitoral, and urethral blood flow via nitric oxide synthase (NOS) and vasoactive intestinal polypeptide (VIP) pathways, leading to genital congestion and vaginal lubrication when sexual stimuli occur. Estrogens also modulate sensory thresholds to erotic stimuli.

Several randomized controlled trials have shown a positive effect of systemic estrogen on sexual function in naturally menopausal women [30–34]. Sherwin and coworkers pioneered the research in this field showing that systemic estrogens significantly increase sexual desire and arousal [30, 31]. Wiklund et al. and Nathorst-Boos et al. further support this finding [32–34]. Specifically, satisfaction with frequency of sexual activity, sexual fantasies, degree of enjoyment, vaginal lubrication, and pain during intercourse were positively influenced in the group who received estradiol compared to the placebo group. However, the frequency of orgasm and sexual arousal was not enhanced by estradiol treatment. [32–34].

In practice: *Systemic* estrogens alone (either oral or transdermal) are indicated in cancer survivors complaining of menopausal symptoms and comorbid sexual disorders related to the estrogen loss, who have been hysterectomized. Contraindication to systemic estrogens includes hormone-dependent cancers such as breast and advanced endometrial cancer.

Estrogen and Progestins

Progestins must be added to estrogens when the uterus is preserved. Progestins can better contribute to maintain a good sexual response when they have an androgenic profile, such as noretisterone, as mentioned above.

Estrogen/Androgen Combination Therapy

Androgens play an important role in sexual desire, arousal, orgasm, and satisfaction by interacting with receptors in the hypothalamus, with dopaminergic, serotoninergic, and opiatergic pathways, and with genitals receptors. Combining androgens and estrogens appears to enhance female sexual function, evidence of which was obtained from studies in estrogen-replete patients, when testosterone was added [35].

Sherwin et al. showed that women receiving combined estrogen/testosterone therapy experienced greater improvement in sexual desire compared to those receiving estrogen alone [31, 36]. Sarrel et al. showed that estrogen alone is not sufficient for addressing all aspects of sexual

function [36]. Adding methyltestosterone to estrogen resulted in significant improvements in sensation, desire, and frequency of sexual activity. Somboonporn and coworkers further reviewed the available literature on this subject and assessed 23 trials involving 1957 patients. A pooled estimate from the studies suggests that the addition of testosterone to hormone treatment (HT) regimens improves sexual function scores for postmenopausal women. The authors of this review concluded that there are benefits of combining androgens with estrogen in terms of sexual function. However, studies reviewed in the meta-analysis used different testosterone regimens, making it difficult to estimate the effect of testosterone on sexual function in association with any individual HT regimen [37].

Numerous studies have also investigated the effect of testosterone treatment on psychological variables in estrogen-replete surgically or naturally postmenopausal women. Some of these studies have assessed the effectiveness of testosterone treatment by using parameters such as mood, well-being, vitality and positive well-being Improvements in these parameters have been reported in several studies following the use of testosterone [38, 39].

In practice: The estrogen/androgen combination is of special appeal in cancer survivors with comorbidity between sexual and somatopsychic symptoms, after total hysterectomy and bilateral oophorectomy. Androgen may reduce sexual symptoms specifically related to the ovarian androgen loss.

Transdermal Testosterone Specifically for Women

It is worth stressing that testosterone has a powerful trophic impact on the whole woman's body. Meanwhile, it has a powerful neuroplastic and antiaging effect on the woman' brain. Clinical data indicate that the rebirth of sexual desire is associated with a better global physical and emotional response: physical and psychological excitement and the ability to reach orgasm are significantly improved. Furthermore, anxiety and concern are reduced, while the sense of femininity is improved [38].

In practice: Testosterone replacement may promote a "co-treatment" of different conditions (comorbidity): besides sexual desire and related sexual disorders, it may have a very positive impact on mood disorders, fatigue, cognitive impairment, osteopenia, and age-related muscle loss, caused or worsened by the lack of testosterone, giving cancer survivors a boost of well-being, even more appreciated as a life-gift after years of sorrow, pain, fatigue, and loss of vital energy.

When oncologically appropriate, testosterone, either alone or in combination with estrogen, should be considered after surgical menopause and in those women who complain of AIS and/or specific sexual symptoms (excluding dyspareunia) after chemo- or radiotherapy, as the Leydig cells of the ovaries could have been destroyed, even if the gonads are still on site. Further studies are needed to support this claim.

Synthetic Steroids

Tibolone is a synthetic steroid with estrogenic, androgenic, and progestogenic properties. It is indicated for the relief of climacteric symptoms in postmenopausal women. Studies have shown that tibolone treatment (one capsule per day) yields significant improvements in sexual fantasies, arousability, desire for sex with a steady partner, and vaginal arousal after erotic stimulation [40].

A further study comparing tibolone and continuous estradiol/norethisterone acetate (E2/NETA) showed that the former resulted in better improvement in frequency of sexual activity, sexual enjoyment, and satisfaction compared with the latter [41].

Treatment with tibolone has demonstrated good overall tolerability with a low incidence of vaginal bleeding and breast tenderness. Sexuality, defined by frequency of sexual interest, frequency of orgasm, frequency of sexual responsiveness, and frequency of general sexual satisfaction, overall significantly improved with HT [41]. However, tibolone and HT with androgenic progestins increased scores to a greater extent

than estrogen replacement therapy. Of note, at the time of writing this, tibolone is marketed in more than 70 countries worldwide, but not in the USA.

In practice: The main indication of Tibolone is the cancer survivor with nonhormone-dependent cancer, complaining of postmenopausal and sexual symptoms, either after a iatrogenic or spontaneous menopause.

Topical Hormonal Therapies

Topical estrogen therapy (estradiol, estriol conjugated estrogens, promestriene) may variably contribute to improve genital arousal disorders contributing to vaginal dryness and post-coital cystitis (complained of 24–72 h after intercourse), comorbid with vaginal dryness and/or introital dyspareunia.

Topical Testosterone therapy: Anecdotically, testosterone propionate powder 2% in vaseline jelly, when applied in minimal quantity to the clitoris and labia once a day, may improve a woman's genital sexual response in 8–10 weeks, with a plateau of response in 16–24 weeks. Specific effects include increased vulvar congestion, more rapid genital arousability, more intense clitoral orgasm, increased number of orgasms, and a sense of "getting back" to a more satisfying and rewarding physical response.

In practice: When oncologically appropriate, topical hormonal treatments may be considered to improve the quality of genital sexual response in women cancer survivors. However, controlled studies in cancer survivors are lacking.

In summary, skilled gynecologists and GPs may tailor HT, when oncologically appropriate, according to the woman needs, with a careful choice of the more appropriate estrogen type (estradiol, estriol, conjugated estrogens) and dose; type and dose of progesterone or progestins; and testosterone, when indicated to maximize the benefit on the general well-being and specifically on sexuality of cancer survivors. Tibolone may be a valid alternative. Careful choice of the route of administration, with preference for transdermal and/or vaginal treatment to reduce liver first pass, may further enhance compliance, adherence, and consistency of use with increasing satisfaction on both general and sexual well-being, while contributing to minimize long-term side effects of cancer-related treatments.

Nonhormonal Central Nervous System Acting Drugs

The role of the CNS in women's sexuality is strong, but has remained underresearched. Critical aspects include a better understanding of contributions to sexual response of the neuroanatomical, neuroendocrine, and neurochemical systems, including the interrelated role of sex steroids and neurotransmitters in the CNS and periphery. Neurotransmitters modulate the secretion of many hormones (e.g., gonadotropin-releasing hormone, luteinizing hormone, testosterone, prolactin, and endorphins) involved in sexual functional capacity.

Antidepressants in Sexual Problems and Depression

Cancer survivors face mood changes, including potentially, clinically relevant depression in the many cases (Table 40.3). Contributors include physical, emotional, and relational factors. Depression is comorbid with loss of desire in more than 50% of cases. Unfortunately, the majority of antidepressants, with the exception of bupropion, have an antisexual effect in a dose-dependent pattern [42, 43].

Bupropion

This is an antidepressant with a peculiar effect of sexual function. There is some evidence that bupropion does not share the inhibiting effect other SSRI have on sexual function [42]. Bupropion may have different impact on dopamine transport than other antidepressants [44]. In addition, some studies have shown that bupropion

Table 40.3 Depression and anxiety as cofactors of FSD in cancer survivors [38]

Depression and anxiety reactive to cancer per se and secondary complications (e.g, after radiation-induced diarrhea or voiding disorders, when they persist after radiotherapy) may further affect erotic perception, self-esteem, and sexual self-schema. Women are more vulnerable than men to depression, from puberty onwards. Hormonal changes during menopausal transition may contribute to a specific "window of vulnerability," more severe in women with iatrogenic premature menopause.
Gender differences, related to varying sexual hormone levels and hormone secretion patterns across the lifespan, contribute to women's vulnerability to mood disorders and major depression. Depression across the menopause has a multifactorial etiology, which is complicated by cancer-related factors in cancer survivors.
Predictive factors include: previous depressive episodes such as premenstrual syndrome and/or postpartum depression; comorbidity with major menopausal symptoms, especially hot flashes, nocturnal sweating, and insomnia; menopause not treated with HT; major existential stress; elevated body mass index; low socioeconomic level and ethnicity. Postmenopausal depression is more severe, has a more insidious course, and is more resistant to conventional antidepressants in comparison with premenopausal women.

can have a beneficial effect on sexual dysfunction commonly reported in patients receiving SSRIs for treatment depression [42, 44]. In addition, the usefulness of bupropion in sexual dysfunction not caused by SSRI medical therapy is still an open question. Perhaps the most beneficial use of bupropion is one of augmentation. Bupropion supplementation may assist in maintaining an antidepressant benefit for the patient, as an offending SSRI is reduced in dosage, so that a better balance can be obtained between elevating mood and minimizing the antisexual side effects.

Depression has a different severity and responsiveness to treatment according to the estrogenic state. Specifically, postmenopausal depression is more severe, has a more insidious course, is more resistant to conventional antidepressants in comparison with the premenopausal women, and has better outcomes when antidepressants are combined with hormonal therapy [38, 45].

It has been suggested that a chronic hypoestrogenic state that impairs neuroplasticity may contemporaneously reduce the response to antidepressant drugs. Controlled studies indicate that postmenopausal women with major depressive disorder (MDD) based on DSM-IV criteria, who were not on HRT, showed a significantly poorer response to antidepressants over 6 weeks of treatment, compared to the response of premenopausal women. Menopausal status and older age are predictors of a poorer response to antidepressant treatment [45].This suggests as well a poorer response to pharmacologic treatments aimed at reducing HSDD associated with depression in postmenopausal cancer survivors.

Synergy Between Antidepressants and HRT in Addressing Sexual Disorders

An increasing body of evidence suggests that a hypoestrogenic postmenopausal status increases the vulnerability to depression and decreases the effect of antidepressant drugs [45–47].

Animal studies support the synergistic role of estrogen and SSRI in optimizing the antidepressant response, evaluated through specific behavioral tests [48]. In line with this, Thase et al. investigated whether differences in antidepressant efficacy are moderated by an interaction of age and gender. A pooled dataset from eight randomized, controlled trials of patients with MDD was reanalyzed. Among women, there was a significant interaction reflecting poorer SSRI response in the older age group; HT appeared to eliminate this difference. These findings provide further evidence that age, gender, and HT moderate response to antidepressant medications [49].

Estrogen therapy (ET) may also play a role in antidepressant response in postmenopausal women with major depressive disorder by accelerating the antidepressant response [50] or even potentiating antidepressant medication effect thus improving mood. ET demonstrates a specific efficacy in those depressive disorders during iatrogenic menopause consequent to chemotherapy [51].

In practice: The synergy between antidepressants and hormone therapy in women with either

natural or iatrogenic menopause and depression is of the highest importance to improve their QOL. However, to these authors' knowledge, no specific studies focused on response to treatment in postmenopausal cancer patients with comorbidity between depression and sexual symptoms have been conducted. Meanwhile, the authors' clinical experience indicates that low dose of antidepressant combined with well-tailored HT may maximize the QOL and sexuality of cancer survivors, while minimizing side effects and risks.

Antidepressant Drugs in the Treatment of Menopausal and Sexual Symptoms

Antidepressants can reduce some menopausal symptoms (specifically hot flushes and insomnia) when they act on common neuro-biological denominators. Soares and colleagues found a similar efficacy between HT and escitalopram in curing depressive symptoms and menopausal symptoms as vasomotor symptoms and insomnia [52]. After hormone therapy discontinuation, paroxetine offers a better control of menopausal hot flushes over placebo [53, 54]. These observations may prove useful for those women who have a contraindication to HT [55–59] such as breast cancer patients or those who prefer to stop HT and address their neurovegetative and affective symptoms in a nonhormonal way. However, it should be remembered that SSRI addresses only a few neurovegetative symptoms, beside depression, but cannot modulate the many other symptoms caused by the estrogen loss (such as joint pain, vaginal dryness, worsened urge incontinence, etc.).

Nonhormonal Topical Treatments

Vasoactive Agents in Women

The development of PDE5 inhibitor (PDE5i) therapy for erectile dysfunction in men in 1998 revolutionized the treatment of male sexual dysfunction [60]. Preclinical work with clitoral tissue baths suggested a rationale for use of these agents in female dysfunction [61]. Research to date regarding use of PDE5i in women has not shown a consistent benefit to this approach [62]. Attempts to gain a regulatory indication of any of the available PDE5i for female sexual dysfunction seem to have been abandoned. Anecdotically, there may remain a PDE5i indication in women with maintained sexual desire who complain of vaginal dryness specifically due to vascular genital factors (in synergy with topical estrogen/androgen treatment) after genital radiotherapy.

Botulin Toxin

Since the late 1970s, botulinum toxin (BoT) has been used as a therapeutic tool. BoT reduces muscular activity by inducing a presynaptic block of the cholinergic synapse and reduces local pain probably by decreasing the release of substance P. Because the adverse effects are very rare and transient, BoT is well tolerated. More recently, this therapy has been employed for pelvic floor disorders, including pelvic muscle spasms, chronic pain syndromes, and genitourinary disturbances [63]. Historically, vaginismus was considered a typical "psychogenic" disorder, treated with a psychosexual/psychodynamic approach. Later, a sexo-behavioral treatment was considered more appropriate. More recently, SSRI and anxiolytic agents have been proposed to reduce the systemic phobic arousal and anxiety associated with the disorder. Physiotherapy has been used to work more effectively on the pelvic floor. This multimodal treatment has proven successful in a variable percentage of cases, between 72 and 85%.

A subset of patients with severe phobic attitude and a tightened pelvic floor with a myogenic component do not respond to the current multimodal treatment. For these patients, no effective treatment was available before BoT. BoT injected under electromyographic (EMG) guidance in the pelvic floor muscles (levator ani or outer third vagina muscles) improves symptomatology in

patients with vaginismus, addressing the specific myogenic hyperactivity of the levator ani [64, 65]. A multimodal treatment (pharmacologic with SSRI and benzodiazepines, pelvic floor physiotherapy, and focused psychosexual therapy) contributes to restore the possibility of intercourse leading to a more complete sexual life. BoT injections also improve the pelvic floor hyperactivity associated to vestibulodynia and vulvar vestibulitis. Though sometimes periodic injections are needed, the benefit is permanent in approximately 60% of affected women [64, 65].

In practice: BoT treatment may have a role in hyperactive pelvic floors of cancer survivors who: (a) have a primary vaginismus they decided to treat after having being diagnosed with and treated for cancer; (b) have a recurrence of vaginismus after cancer treatment and/or for coexisting biological triggering factors; (c) have a hyperactive pelvic floor associated with vulvar vestibulitis/vulvodynia, not responding to standard pharmacologic and rehabilitative treatments. However, specific studies on cancer patients using BoT have not been carried out so far.

Future Treatment Options

Ongoing research suggests that new central nervous system (CNS) acting drugs may be of interest in the medical treatment of FSD in cancer survivors.

Flibanserin

Flibanserin is a postsynaptic 5-HT_{1A} agonist, a very weak partial agonist of dopamine D(4) and a 5-HT_{2A} antagonist [66]. As current antidepressants exert an acute effect at the presynaptic level, almost all block the uptake of monoamines or inhibit the activity of the enzyme monoamine oxidase, more or less selectively. However, the therapeutic effect of the current antidepressants is achieved only after repeated administration. The net effect of the antidepressant is credited to be the increase of monoamine concentrations in the synaptic cleft and, consequently, to induce changes in those receptors upon which a particular monoamine acts. These phenomena need time for induction [67]. Recently, a new potential therapeutic combination has been proposed in which a serotonin 5-HT_9 uptake blocker is administered together with pindolol, an antagonist of the presynaptic dendrosomatic 5-HT_{1A} receptor. This combination allows achievement of an increased 5-HT synaptic concentration in the cortex within a shorter period of time.

Acting at postsynaptic receptor level, a drug could mimic the effects exerted by long-term antidepressant treatments, thus avoiding the delay due to adaptation of pre/postsynaptic mechanisms. Moreover, several lines of evidence indicate the frontal cortex as a possible target for the therapeutic effect of antidepressants or as an important area for the occurrence of depression.

Given the high comorbidity between depression and HSDD, an antidepressant with a specific action on the prefrontal cortex (besides hippocampus and midbrain) could represent a new option for HSDD.

Flibanserin seems to satisfy the need of a short-acting drug and is currently under development for hypoactive sexual desire disorders (HSDD) and female central sexual arousal disorders [66–69]. Flibanserin may be of special interest in cancer survivors of hormone-dependent cancers, who complain of FSD and cannot use conventional HT. However, to the authors' knowledge, no studies on this important subset of cancer survivors have been carried out at the time of this chapter writing.

In practice: Once and if efficacy is proven, the greatest utility of a CNS-acting agent might be found in assisting a patient to open up to higher levels of desire and/or arousal within the context of strategic use of other complementary forms of sexual therapy. The future of sexual medicine in general and of the treatment of FSD in particular may be aided most when centrally acting compounds, which enhance sexual response, are combined with hormonal supplementation, vasocongestive agents, and sexual counseling in a manner individualized

to the needs of the patients [68, 69]. Such a multifaceted approach would certainly result in an exciting new era for sexual medicine and the treatment of various forms of female sexual disorders, specifically in cancer survivors. Unfortunately, research on Flibanserin as being recently stopped by the owner Company.

Psychosocial Interventions

Psychosocial interventions include basic counseling, physiotherapy, and psychosexual intervention. Basic sexual counseling is an integral part of medical consultation. An initial session can involve the practitioner providing the patient with information on anatomy and physiology, sexual development and function, fertility, sexuality in different life phases, the spectrum of human sexual behavior and cultural norms, and communication of sexual needs. This information is intended to elicit understanding and encourage questions with the hope of increasing the patient's knowledge of and self-confidence in their sexuality, more so after the difficult and challenging experience of being diagnosed with and treated for cancer.

Psychosocial interventions are excellent tools for addressing FSD and it is normally the case that biomedical and psychosocial interventions are combined to provide an optimal outcome. This type of therapy is best considered as a step-by-step approach with continuous adaptation of diagnosis and therapeutic strategies, more so in cancer survivors.

Conclusion

Cancer is increasingly more of a chronic than a fatal disease. More attention should be focused on restoring a satisfying QOL, which includes physical intimacy, sensuality, and sexuality. Unfortunately, sexual problems are usually neglected in female cancer survivors, with a specific denial of their biological basis, with symptoms being attributed to the negative psychological effect of cancer diagnosis and treatment per se and their negative affective consequences such as depression and anxiety. Opposite to this psychologically oriented approach, medical and rehabilitative treatments can offer substantial improvements, certainly more so when combined with appropriate psychosexual counseling. Indeed, the contextual sensitivity of female sexual response tends to more frequently require the use of a combination treatment, where sexual pharmaceuticals and sex coaching are integrated more frequently for women than these have been for men.

In clinical practice, hormonal treatments, currently used to treat menopausal symptoms, should be considered more often to improve sexuality as a critical part of a rewarding quality of life and aging in nonhormone-dependent cancer survivors. When oncologically appropriate, different hormone combinations, inclusive of estrogen/androgen or testosterone alone, may be tailored according to the individual needs. Combinations of antidepressant and HT may further aid women with depression and sexual symptoms after a natural or iatrogenic menopause for cancer.

New nonhormonal agents are currently investigated and could offer an option for younger cancer survivors with HSDD who cannot or would not take hormones to improve their desire and sexuality. However, data in cancer patients have not been produced so far.

While the recent data supporting the therapeutic use of centrally acting agents, as a monotherapy for FSD, are cautiously encouraging, there is a promise for these centrally acting compounds to be integrated into treatment approaches that utilize other pathways in a multilayered, individualized approach to care.

In parallel to this spring in the scientific research, there should be a parallel growth in physicians' attitude to take care of FSD in the clinical setting, whatever the disease the patient is complaining of. The goal is to give women and couples the full potential of a joyful sexuality in their lifespan, in spite of and over the challenge of the cancer experience.

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Chapter 41
Surgical Treatments for Sexual Problems in Women

Lara J. Burrows and Andrew T. Goldstein

Keywords Vulva • Vestibulodynia • Hysterectomy • Vestibulectomy • Clitoris • Phimosis • Perineoplasty • Bartholin's gland

Introduction

Millions of women suffer from dyspareunia. Sexual pain disorders can interfere with quality of life, strain interpersonal relationships, and may preclude sexual activity. There are many causes of dyspareunia. Depending on the etiology of the pain, different treatment modalities should be considered.

In general, most female sexual pain disorders can be initially managed conservatively. After a complete history and physical examination, there are many medical and behavioral treatments that may be employed. As many of the physiologic causes of dyspareunia have only recently been elucidated, most of the efficacy data to support treatment regimens are in small case series which are neither randomized nor placebo-controlled.

In the event that conservative treatments are unsuccessful, more invasive measures, such as surgery may be considered. This chapter will review the surgical management of female sexual pain disorders of the vulva. The aim of this chapter is to provide information to health care practitioners who treat women with sexual pain disorders secondary to vulvar pathology and who have failed conservative treatment options.

Vulvar Anatomy

The main anatomic structures of the female vulva include: the mons pubis, urethral meatus, labia majora, labia minora, hymen, vestibular glands, clitoral prepuce, clitoris, Bartholin's glands, and the vulvar vestibule. The mons pubis is the subcutaneous fat pad over the bony symphysis pubis. At puberty it becomes progressively thicker and is covered with pubic hair. The clitoris is the erectile body of the vulva, corresponding to the penis in the male. This firm, rubbery, moveable shaft is connected to the pubic bone and is covered by a small called the prepuce. It is innervated with thousands of nerve fibers and is vital for sexual arousal. The urethral meatus is the opening of the urethra and is found just anterior to the vaginal introitus. The opening may be either star shaped or slit-like. On either side of the meatus are the small openings of Skene's glands.

The labia majora are the large outer lips which are hair-bearing. The labia minora are the thin, inner, pigmented lips of the vulva, containing loose connective tissue. The purpose of the labia is to protect the sexual organs,

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urinary opening, vestibule, and vagina. The hymen is the thin membrane of connective tissue separating the vestibule and the vagina. It may be prominent at birth, but it is lacerated with sexual intercourse and parturition, leaving only remnants.

The vulvar vestibule warrants specific mention as it is the site of many causes of dyspareunia. The vulvar vestibule is the tissue between Hart's line and the hymen (it is usually at most a centimeter wide). Hart's line marks the histologic transition from the squamous mucosa of the vestibule to the more keratinized mucosa of the labia minora. The vestibule extends from the frenulum of the clitoris anteriorly to the fourchette posteriorly.

The vulvar vestibule is of particular interest because it is embryologically different from the adjacent tissues. The labia, which are lateral to Hart's line are derived from the genital tubercle. The hymen and vaginal mucosa which are proximal to the vestibule are derived from Müllerian tissue. The vestibule itself develops from the lower most part of the urogenital sinus, making the tissue of the vestibule similar to the mucosa of the urethra and bladder, which are also derived from the urogenital sinus. This difference in embryologic origin has several implications: congenital abnormalities may occur in this tissue that lead to dyspareunia and this tissue may respond differently to hormonal or allergic insults that may also cause dyspareunia.

Terminology

When referring to vulvar pain, it is easy to confuse terminology. The term "vulvodynia" is discomfort or burning pain in the vulvar area, occurring in the absence of visible pathology or a specific, clinically identifiable disorder; it may be generalized or localized and provoked or unprovoked [1].

Vestibulodynia is a type of vulvodynia (formerly known as the vulvar vestibulitis syndrome or vestibular adenitis) in which pain is localized only to the vulvar vestibule; it is classified as primary or secondary. In the primary subset, the pain has been present since the first tampon use or intercourse, and with secondary vestibulodynia, women have had painless tampon insertion or intercourse, with the subsequent development of vestibular pain.

Vestibulodynia

As noted earlier, vestibulodynia may be primary or acquired (secondary). Recent research indicates that primary vestibulodynia is due to a defect in the primitive urogenital sinus and may be thought of as a congenital disorder [2]. In patients who have vestibulodynia, it is crucial to make this distinction. In women who have acquired vestibulodynia it is important to search for an underlying cause and make every attempt to treat with conservative measures. Often times, the underlying disorder can be identified and treated. Alternatively, for women who have the primary (congenital) form, in the author's experience, this is less likely to respond to conservative management and will most often be effectively addressed surgically. The procedure of choice is a vestibulectomy and when performed correctly, it is a highly effective treatment option. There are 37 published reports on this procedure, comprising more than 1,500 patients. In aggregate, most of the studies have demonstrated at least an 80% success rate for the surgical management of vestibulodynia. A recent series of 104 women who underwent vulvar vestibulectomy showed that 93% were satisfied with the procedure and would recommend the procedure to other women with similar symptoms [3].

Prior to vestibulectomy, it is important to evaluate the patient for levator ani spasm (pelvic floor dysfunction) which may occur in 50–60% of patients with vestibulodynia [4]. If levator ani spasm is present, this should be treated prior to surgery since surgery may be is less successful in this subgroup of patients. Additionally, erotophobia is a predictor of poorer outcome after a vestibulectomy [5]. Therefore, counseling may

enhance postoperative improvement by reducing pelvic floor hypertonicty and poor sexual arousal, which can develop after long-standing dyspareunia or in women who have never had pain-free intercourse.

A vestibulectomy is performed by removing the mucosal layer of the vulvar vestibule medial to Hart's line, extending approximately 3 and 5 mm distal to the hymenal ring [6]. This procedure may be done as an outpatient. Complications from vestibulectomies are uncommon, but may include clinically relevant blood loss (<1%), wound infection or separation (1–3%), granulation tissue (1–3%), decreased orgasm (8%), Bartholin's duct cyst formation (1–3%), unfavorable cosmetic changes (4%), decreased lubrication (20%), and continued significant dyspareunia (12%) [3].

It is of great importance to counsel patients preoperatively that they will be on modified bed rest for about 2 weeks after this procedure and must take care not to separate the thighs in order to avoid disruption of the sutures. Ice packs are applied to the perineum postoperatively for 7 days and at approximately 6–8 weeks postoperatively, the patients begin dilator therapy. Intravaginal intercourse may usually be attempted 4 months or so postoperatively depending on progress with dilator therapy and any psychosocial factors that may need to be addressed.

Clitoral Phimosis

Phimosis (or "burying") of the glans clitoris by scar tissue may be caused by a chronic inflammatory dermatologic condition called lichen sclerosus. Lichen sclerosus is a lymphocyte-mediated inflammatory dermatitis that most commonly occurs in the anogenital epithelium. Although the exact prevalence of lichen sclerosus is not known, it has been reported that it affects 1 in 300 to 1 in 1,000 of all patients referred to a community-based dermatology practice to approximately 1 in 70 women in a general gynecology private practice [7–9]. The chronic inflammation associated with this condition often leads to scarring and distortion of the vulvar architecture. Clitoral phimosis of the clitoris is often problematic because smegma can accumulate in the space between the clitoris and prepuce, leading to formation of a smegmatic pseudocyst. These pseudocysts can become inflamed or infected. In addition, clitoral phimosis frequently causes loss of clitoral sensitivity, which may cause secondary anorgasmia. Lastly, women with clitoral phimosis often complain of psychologic trauma caused by the distortion of their vulvar anatomy and a perceived diminution of their sexuality or femininity.

When treating clitoral phimosis secondary to lichen sclerosus, it is important that medical management of the lichen sclerosus has been optimized. In the past, surgery to correct the architectural changes associated with lichen sclerosus was contraindicated because of a process known as the Koebner phenomenon. Koebnerization in lichen sclerosus is a pathologic process in which normal skin becomes sclerotic after it is injured or traumatized (such as with surgery) [10]. Thus, it is important to continue topical corticosteroids in the postoperative period.

The procedure, sometimes known as "dorsal slit surgery of the clitoris", may be performed by placing a lacrimal duct probe between the clitoris and the prepuce and bluntly lysing any adhesions [11]. A dorsal incision approximately 5 mm in length is made in the prepuce and any remaining adhesions are lysed. No tissue is excised during the procedure. Postoperatively, patients should apply clobetasol ointment daily to the surgical site. After the surgical site has healed, patients may decrease the frequency of clobetasol application to twice weekly. In the most recent case series, subjects expressed a high degree of satisfaction with the procedure [12].

Perineoplasty

Another cause of introital pain is granuloma fissuratum which is characterized by recurrent splitting of the skin of the posterior fourchette

with subsequent pain with vaginal penetration. Granuloma fissuratum is a poorly described condition. It may result from dermatologic conditions, such as lichen sclerosus, it may occur secondary to vulvovaginal atrophy, after episiotomy, or it may occur as a primary finding. A recent case series reporting on women with granuloma fissuratum found that these women were frequently misdiagnosed; however, once the correct diagnosis was made, surgical management with a superficial perineoplasty yielded very satisfactory results [13].

The procedure is typically performed in the outpatient setting. After administration of adequate anesthesia, an examination is performed, and tension is placed on the posterior fourchette to reproduce the fissure. The extent of the fissure must be identified to ensure complete excision of the lesion. The skin is incised in a *vertical* plane from the inferior aspect of the hymen to 1–2 mm beyond the fissure; care must be taken to excise the base of the fissure to ensure optimal wound-healing. The distal vagina is then mobilized to facilitate advancement of the vaginal muscosa and closure without tension. The lesion is then closed in a *horizontal* plane. Complications of this procedure include hematoma formation, infection, and residual dyspareunia. Kennedy et al. have reported that this procedure has a 95% success rate for curing granuloma fissuratum [13]. In a series which reported on perineoplasty for introital stenosis caused by lichen sclerosus, the authors reported that 90% of patients reported improvement in dyspareunia [14].

Bartholin's Gland

A cyst or an abscess of the Bartholin duct or gland is common. Management of a symptomatic Bartholin's duct cyst or abscess can be challenging for the clinician and frustrating for the patient. There are several treatment options ranging from sitz baths, ablation, and simple drainage to surgical marsupialization, fistulization, and excision of the gland.

Marsupialization of a Bartholin gland may be done in the office or in an outpatient surgery center. According to a review by Wechter et al., there were no reported recurrences at least 1 month after marsupialization [15]. In the author's opinion, it is likely that the recurrence rate after marsupialization of a Bartholin gland is low, but it is most likely not zero.

Another surgical option for a Bartholin duct or gland cyst is fistulization. This procedure creates an epithelialized tract for the obstructed Bartholin duct. A Word catheter is placed through a 5-mm stab incision on the inner labium minus (just external to the hymen) in the region of the Bartholin gland duct. The bulb of the catheter is inflated with and the catheter is left in place for 4–6 weeks. Other techniques are similar, but utilize a foley catheter or a Jacobi ring instead of a Word catheter. In Wechter's review, recurrent Bartholin gland pathology was noted in 4–17% of patients after fistulization.

Excision of Bartholin duct cysts and abscesses was evaluated in three studies including one randomized trial [16–18]. The duration of the procedure ranges from 20 to 60 min. With at least 2 years follow-up for 168 patients in aggregate, recurrence rates were up to 3%. Complications included bleeding, hematoma formation, and fever. Persistent dyspareunia was present in up to 16% of patients.

Conclusions

The psychological impact of sexual pain is well-described; feelings of hopelessness, depression, and anxiety are common. Frequently, this condition stresses marriages and interpersonal relationships. Sometimes, even when vulvar pain resolves, psychological and sexual dysfunction often persist. Therefore, in addition to treating the underlying pathophysiologic process that is causing sexual pain, it is imperative to address any associated psychosexual and relationship dysfunction.

The treatment of female sexual pain may be confounded by the fact that in many cases, the cause is unknown. Management options should be tailored to the patient's symptoms while addressing any psychosocial concerns with

compassion. Although it may be tempting to offer surgical treatment in the setting of a patient who has not responded to more conservative options, it is imperative that an appropriate diagnosis is firmly established before attempting a surgery.

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Chapter 42
Sex Therapy in Female Sexual Dysfunction

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Keywords Sex therapy • Counseling • Cognitive behavioral therapy • Psychotherapy

Introduction

In the hierarchy of life, sexual pleasure is one of the pivotal drivers within all of us as human beings [1]. However, there is also a sense of survival that can overpower the need for pleasure. Hence, when people feel threatened due to the diagnosis of cancer and their survival becomes a matter of question, it is natural for their sense of pleasure associated with physical intimacy to be threatened. For women, whose sexual appetite is not the same as for men [2], the need to survive can have a more profound impact on their ability to be relaxed and have good sexual function. Additionally, women's sexual response has been defined with a more contextual model than a linear model of desire, arousal, and orgasm [3].

Cancer as a disease is described as "uncontrolled growth and spread of abnormal cells" [4]. Since treatment outcomes can be varied for each person with their given type of cancer, simply hearing the word "cancer" can be enough to frighten many people. It is reported to increase activation of the amygdala and insular cortex [5]. The oncologist working in a multi-disciplinary setting is able to provide the most complete care for their patients when they receive the diagnosis of cancer [6]. The physician must remember that "treating the cancer" is only one aspect of treating the problem. The patient's body is attached to her psyche and frequently her psyche, and her emotional being, is in a relationship with another human. Hence, when treating the body, we must also treat the psychosocial aspects of the disease. This includes ruling out anxiety and depression, addressing the concerns of their partner and family members, and exploring their fears and concerns about making the "right" decision in the treatment options for their specific kind of cancer.

In this chapter, topics to be covered include: a discussion about gender differences that impact the diagnosis and treatment choices with cancer, variables the treating clinician should be aware of when helping women with a diagnosis of genital and breast cancer, psychosocial aspects and methods for treating women with cancer, and how treatment choices can impact a woman's sense of sensuality and sexuality. In addition, perspectives on cultural differences and influences in treating women with cancer and its impact on their sexuality will be presented.

Gender Differences with Sexual Function After Cancer and Physician Impact with Patient Response

Men and women are quite different not only in the kinds of cancer they experience, but also in their inner motivation for fixing their sexual

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function when they have the diagnosis of cancer. While it is true that men tend to get more cases of cancer and have more deaths due to cancer each year [4], it is also true that their need to "fix the sexual plumbing" is more significant because of their gender identity being tied to their sexual function [7]. When women receive a diagnosis of cancer they are often concerned about survival, fertility and procreation, the well being of their family, and body image. The age and type of cancer diagnosis a woman receives will influence a woman's desire for maintaining her sexual function. Also, the precancer sexual function will typically influence the postcancer functioning. Hence, women who had sexual difficulties prior to a cancer diagnosis and treatment should expect to have some sexual difficulties after treatment for cancer, regardless of the type of cancer.

When exploring cases of genital system cancers, men and women have similar numbers. However, when the number of deaths from breast and genital cancers combined was compared, there were more women than men that died from these two types of cancers in 2009 [4]. The impact of treatment for breast versus genital cancers can show a more profound impact on the woman's body image with the treatment of breast cancer, than the treatment of genital cancer for women or prostate cancer for men. Hence, it is important for the treating clinician to be mindful of the impact of treatment choices on the patient, especially when it is a woman. One report focused on the impact of oncologist comfort or discomfort in discussing sensitive areas, such as: fatigue, distress, fertility, and sexual function, for women facing breast cancer and the importance of clinicians developing skills in the evaluation, counseling, and treatment of their patients [8]. Additional studies have evaluated physician characteristics and how these might influence the outcomes of older women with breast cancer. One report showed the specialty of the physician, length of time in practice, and fear of malpractice had some influence on the clinician's decision-making for older women with breast cancer [9].

Sexual function after treatment of childhood cancers has a more significant impact on women's sense of sexuality than for a man's sexual function after childhood cancer [10]. Another aspect of the gender differences when women have cancer is the impact the patient's cancer has on her partner. These ramifications can range from increased exhaustion due to being the primary caregiver, increased anxiety and depression due to the patient's increased anxiety and depression, seeing the patient/partner as "sick," and decreased sexual intimacy [11–13]. Partners of women with breast or gynecological cancer report their partner (the patient) has a decreased desire for sex and presents as "the patient." Hence, the partner may be conflicted about their frustrations due to lack of physical intimacy after the diagnosis and treatment for cancer [14]. They also reported more disappointment, anger, and sadness due to the loss of physical intimacy with their partner [14].

Clinical Considerations for Diagnosis and Treatment of Women with Genital and Breast Cancer

When women go through the diagnosis and treatment for cancer of the breast or genitalia, there are numerous complications and considerations for the patient, her partner, and the treating physician in the decision-making process. Usually, the woman and her partner are most interested in survival, and quality of life issues are secondary in this process. Hence, it is important for the treating clinician to help keep the patient and her partner focused on all aspects of this complex and multi-factorial experience.

Women experiencing gynecological cancers are very likely to experience significant sexual disorders due to several factors. Some of these factors include: crampy abdominal feelings, worse sexual response, urinary leakage, and early onset of menopausal symptoms [15, 16]. These symptoms were exacerbated by the use of radiotherapy with the surgical cancer treatment for up to 10 years postdiagnosis [15]. The literature is unclear about the impact of radical hysterectomy on women for cervical cancer [16, 17]. One report suggests that women with radical hysterectomy had a worse sexual response,

whether performed by means of laparoscopic or laparotomic methods, compared to controls [16]. And, another study suggested that cervical cancer survivors faired quite well with their sexual response posthysterectomy [17]. Another variable in this sexual response discrepancy may be the age of the patient and whether any radiation was involved postsurgery. Typically, if the woman was younger and more educated, she had more sexual difficulties [18] and if she had radiation associated with her medical treatment, she was more likely to have sexual difficulties [19].

The rationale behind these findings is not difficult to understand. Younger women may still be close to their sexual prime – usually around age 30 – and the need for procreation and sexual pleasure may be more significant for them. However, older women are likely to have less natural interest as there tends to be a decrease in testosterone and libido with menopause, and the impact on their sexual function may no longer be as important for them. It is natural that radiation would have a more significant impact on sexual function because it changes the tissues of the cancerous cells as well as the surrounding cells. Regardless of the factors influencing women's sexual response after treatment for their cancer, it is important to remember that this woman may have a partner and the physical intimacy may be an important aspect of their relationship. This is the issue that must be addressed with the patient and her partner in the treatment option decision-making process.

Breast cancer can also have a profound impact on the woman's self-esteem, quality of life, and sense of well being. One study described it as a loss of "…femininity, maternity and sexuality, as the mammary gland is perceived by patients, is a highly traumatic experience, frequently resulting in re-evaluation of life and functioning…" [20]. For women with breast cancer, there are numerous choices, whether to do a lumpectomy, radical mastectomy alone, a mastectomy with chemotherapy and or radiation-therapy, and whether to do reconstruction after or with the mastectomy. There are a number of variables that can influence her choices, including: her age, tumor stage, prognosis, and psychosocial issues.

The treatment choice a woman, her partner, and her physician make for her breast cancer is difficult because of the variables listed. The result of her decision is reflected in the literature when studies show the impact on sexual function, quality of life, and cancer recurrence. Two studies reported that completing a radical mastectomy had significant impact on aspects of the woman's physical, emotional, cognitive, and social life and it was labeled "posttraumatic stress," which is known to increase levels of anxiety and depression [20, 21]. Other studies showed that breast conservation surgery had less negative impact on the woman for areas of quality of life, sexual function, and body image 5 years postdiagnosis [22, 23]. When comparing treatment choices based on age and early-stage cancer, one study reported the younger women (less than 55 years old) had a decreased quality of life with complete mastectomy – probably for the reasons previously stated. And older women (over 55 years old) who had the lumpectomy also had a decrease in quality of life issues [24]. Also, probably for the reasons previously stated.

Regardless of the type of cancer a woman faces, it is imperative for the patient, her partner, and the physician to work collaboratively to find the best treatment choice for her specific case with the multi-factorial method outlined in some clinical settings [6]. While it may not be feasible for all clinical settings to provide this multidisciplinary approach for patients, it should be part of the discussion in the decision-making process for the patient to be aware of other resources as part of their treatment regime.

Psychosocial Implications of Cancer on Women and Their Sexual Function

When women are diagnosed with cancer, their first thought is usually quite emotional and it relates to their sense of survival [5], then they are concerned about their family and fertility, and depending on the kind and treatment for the cancer, it may influence their body image. One of the

most under-diagnosed comorbid components in this process is the impact of anxiety and depression on the female patient. If the female patient is not familiar with medical practices, she is more likely to have grave concerns and a significantly increased level of anxiety and depression [25]. She is left to wonder about her choices with various treatment options. Basic anxiety is described as the difference between being "normal" and having to face her new reality, having to decide about cancer treatment options. It is easy to understand why women would have enormous anxiety in this difficult time. In addition, she may feel a sense of anger and frustration because she could not control her life enough to avoid the cancer, she is feeling out of control with her treatment choices, and naturally, she feels a sense of depression and loss of her "normalness." She has to face a sense of loss – the loss of her life as she used to know it. She may face her fear of the unknown – what her life will be like after the treatment choice – assuming there is a life after treatment of the cancer. The female cancer patient will more-than-likely be an enormously anxious and depressed woman-feeling confused and conflicted about her life in the present or the future [25]. This is why it is important to have a treatment team to help the patient and her partner through this difficult time [6].

Mental Health Interventions (Table 42.1)

In addition to the medical treatment options for women with cancer, there are other psychological options that should be explored with the female patient. Some of the psychosocial options include: support groups, guided relaxation, meditation, or hypnosis [25–27].

Support Groups

When support groups were used in conjunction with guided relaxation or hypnosis they have shown a significant impact on helping women to decrease the intensity of pain and suffering over time when compared to a control group of education only for breast cancer patients [28].

Hypnotherapy

Clinically, having practiced with hypnotherapy for nearly 20 years, patients have reported a benefit to have a recording of the guided relaxation or hypnosis to listen to over and over with time. Basically, this is another cognitive-behavioral method to teach patients how to focus their attention, learn to relax, reduce stress, allow for better sexual function, and reduce pain. Other traditional cognitive-behavior therapy interventions, couples therapy, and brief cognitive-behavior sex therapy are all indicated for the female patient and her partner or family when treating cancer [29–31].

The guided relaxation component should be the cornerstone in the psychological treatment options for a cancer treatment program because it helps patients learn to reduce stress, which has been linked to a decrease in the functioning of the immune system [27, 32]. Hence, managing stress more effectively can help a woman maintain and strengthen her immune system to fight off disease. Even if a clinician does not have a well-trained professional to collaborate with locally, it is appropriate to refer the patient to guided relaxation or meditation recordings for listening and training while she is developing the skills to quiet her anxiety and stress [33]. One study reported the value of teaching female patients mindfulness to improve their sexual function with gynecologic cancer [34].

Psychotherapy

Traditional cognitive psychotherapy includes giving the patient information about the disease, the treatment options and then putting the pieces together to understand how to make the most informed decision for their specific case ([35], p. 4).

Table 42.1 Psychosexual Interventions in women with cancer

References	Numbers	Methods	Results	Conclusion
Gross et al. [51]	*N* = 3,171 without Ca with Hx/ depression	24-Year follow-up	334 dev Ca	Statistically sig. women with depr dev breast Ca-link between hormonally mediated cancer and depression
Butler et al. [52]	*N* = 124 breast Ca	12 Months S/G, Hyp, Ed compared to ed only	Tx had less intensity/pain over time	Patients able to use Hyp outside S/G were able to manage pain and Hyp is adjunctive Tx for pain
Bartoces et al. [53]	*N* = 145 CAS (42 = invasive cervical Ca, 103 = noninvasive cervical Ca)	Telephone, struct-interview-MCS and PCS (QOL)	No differ in LT invasive/ noninvasive cervical CAS for QOL	SE associated with MCS not PCS for both Ca Tx-SE and mental health should be impt part of Tx for both groups of cervical Ca
Kroenke et al. [54]	*N* = 405 CAS	Telecare-homeMonitored-v-usual care	Eval at 1, 3, 6, 12 months44% CAS have pain and depression 44% unable to work due to symptoms	Pilot study to eval Tx interventions without conclusions
Muriel et al. [55]	*N* = 448 (oncologists)	E-mail/survey	1/3 Patients have psychosocial distress ½ have mental health in practice, ½ refer to mental health Tx, ½ refer and prescribe psychotropic meds	Most oncologists deliver some mental health care and only ½ had mental health affiliated

CAS cancer survivors, *Tx* treatment, *SE* self-esteem, *Ca* cancer, *Hx* history, *Hyp* hypnosis

Source: American Cancer Society booklet on women and cancer

When the behavioral component is added, it is a method to help patients practice more adaptive coping skills in dealing with the real world ([35], p. 215). Practically speaking, an example would be to educate the patient and her partner about her specific disease and the prognosis, pros and cons of the medical treatment options, course of treatment and recovery, ramifications on their personal relationship and physical intimacy, and some of their personal and familial histories that might be important in the decision-making process. For the behavioral component, the psychotherapist might give them specific homework or exercises to practice as they work through the decision-making and treatment-recovery process. An example might be to plan a relaxing, romantic, and pleasure focused evening and take turns being the "giver" and the "receiver." Basically, it takes the attention off the usual sexual experience and brings the endpoint to the emotional intimacy and feeling good together again [36].

Ideally, it would be desirable if the patient could learn to "turn lemons into lemonade" and that means to take this frightening experience of a cancer diagnosis as an opportunity to learn more about herself and develop healthy coping skills. For example, she might learn to meditate which could help her in all of her day-to-day activities, she could learn to have more intimacy in the physical relationship with her partner, she might even learn to help others in a support

group, and she might learn to find some positive aspects to the cancer experience as one study demonstrated [37]. Other reports of positive aspects of cognitive-behavior therapy and cognitive-behavior sex therapy for female cancer patients focused on their ability to learn to communicate more effectively as they developed better coping skills for dealing with the ramifications of the cancer including the sexual and body image concerns with breast cancer [38, 39].

In order for this to happen for patients, she has to be in a place to consider that there might be an opportunity to learn something positive with this otherwise frightening experience. Usually, when people are experiencing loss, such as a "normal" life before cancer, there is a tendency to pass through the stages of grieving: denial, anger, bargaining, depression, and acceptance [40]. Women and their partners have to wrestle with the loss of their life as they know it. How they manage this process is very telling of the resiliency within the relationship, which will help it sustain and grow over time. Dealing with the cancer diagnosis is the "crisis du jour" and only one of many crises that couples face in the course of their relationship over their lifetime together.

Cultural Differences in Sexual Functioning for Women with Cancer

While it can be said that as humans, we are generally the same worldwide, it is certainly clear that there are subtle cultural differences that should be acknowledged as we work with women and their families living with cancer from different parts of the globe. Studies show that Asian women with cancer tend to have some interesting beliefs about cancer. One report showed women in Malaysia believed that having sex could cause a recurrence of cancer and that it could be sexually transmitted [41]. This same report stated that 70–86% of women with cancer were reluctant to talk with their spouse or their physician about their sexuality [41]. The implications of this could be that physicians treating women from this part of the world should be mindful about directly questioning Asian women about their sexuality when they present with cancer concerns. Two other studies reported a correlation between numerous sexual partners and early sexual experience (less than 12 years old) as a precursor to developing human papillomavirus (HPV), which can lead to cervical cancer [42, 43].

There were numerous reports on implications and ramifications of breast cancer from around the globe. Some to be highlighted include those relating to women and sexual function after treatment for their breast cancer. In Sudan, Eastern Africa, one study showed that women with breast cancer reported better sexual function if they were more educated, had been in the relationship longer, and had hormone replacement therapy [44]. Consistently, around the world, women reported better body image, self-esteem, and sexual function with breast-conserving treatment for their breast cancer [45–47]. This would be a logical and expected outcome for the reasons previously stated. Basically, it preserves the woman's body image. Since her body image and the mammary glands are closely linked to her sense of femininity and sexuality, it is more disturbing when this part of her body is removed or mutilated and this can create embarrassment for the woman.

Women around the globe that have to fight cervical cancer have some similar experiences. Women in Korea reported more problems with body image, sexual function, and finances than the controls [48]. The rationale for the discrepancy in finances seems elusive. Another report about women with cervical cancer from Korea stated that more women with a less educated spouse, a family history of cancer, short height, and early sex and pregnancy had a higher incidence of cervical cancer [49]. This seems somewhat unusual – to discuss the spouse's education and her height as variables – except that it was a large-scale study over 3 year period of time from a major university hospital. One consistency also reported in an Indian study of women with cervical

cancer was the early age (under 12 years old) of intercourse [50]. The Indian study also reported that women who had extramarital sex were also more likely to present with cervical cancer. These reports seem consistent with reports from Western countries [51].

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Chapter 43
Erectile Function Preservation for Men with Cancer

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Keywords Erectile tissue • Cavernosal smooth muscle • Endothelium • Penile rehabilitation • Cavernosla oxygenation • Venous leak • PDE5 inhibitors • Intracavernosal injection therapy • Vacuum device

Introduction

Cancer is a major health concern in the United States and in other countries: not only is cancer the second leading cause of death in the United States, accounting for one of every four deaths, but also its treatment may be associated with significant morbidity [1]. Cancers involving the male pelvic organs and their treatments are notoriously associated with erectile dysfunction (ED) [2]. Such cancers include prostate, bladder, and ano-rectal cancers. Prostate cancer is the second most common cancer and the third most common cause of cancer-related death among men. According to the American Cancer Society, it is estimated that in 2009, 192,280 new cases will be diagnosed (25% of all new cancer cases) and 27,360 deaths (9% of cancer-related deaths) will be attributed to prostate cancer [3]. Currently, with prevalent testing for early detection, men are diagnosed in their fifth or sixth decades. The vast majority (91%) of men diagnosed with prostate cancer present with localized disease and have excellent chances of long-term survival [3]. Treatment of prostate cancer includes radical pelvic surgery to remove the prostate and the seminal vesicles – radical prostatectomy (RP), prostate irradiation (radiotherapy), delivered using various techniques or hormonal manipulation, aimed at suppression of testosterone, the principal male hormone. Reported ED incidence after RP varies greatly, from 14 to 90%, with a combined incidence reported by a recent meta-analysis to be 58% [4]. A recent prospective study reported an ED incidence of 47% a year after external beam radiotherapy for prostate cancer, however, it is must be remembered that radiation-induced damage may take more than a year to be fully manifested, thus, the eventual incidence is probably higher [5]. A long-term sexual function follow-up of men who had radiation for localized prostate cancer revealed that at 15 years from treatment the vast majority of men (78%) were not sexually active compared with 38% of controls and that 94% had severe ED compared to 64% of controls [6]. The addition of hormonal therapy, even short term, exerts additional deleterious effects on erectile function [7]. Bladder and ano-rectal cancers are less common, accounting for 7 and 0.3% of all male cancers, respectively, and their treatment may include extensive pelvic surgery, radiotherapy, and/or chemotherapy [3].

In addition to ED caused by a direct cancer treatment effect on structure and function of tissues and organs involved in the process of erection, organic ED, ED in cancer patient may also be psychogenic, secondary to cancer-related concern, depression, loss of self-esteem, change in body image, relationship changes, and other

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psychogenic factors [2]. ED of organic origin may be secondary to hormonal, neural, or vascular insults, but also may involve penile erectile tissue damage. Erectile tissue damage is irreversible; hence, prevention of such damage is of utmost importance if permanent ED is to be prevented in men with cancer.

The purpose of this chapter is to present our current understanding of the erectile tissue structure and function, to detail the pathophysiology of cancer treatment-induced erectile tissue damage, and to review the currently available strategies for erectile tissue preservation and the scientific evidence to support interventions aimed at erectile tissue protection.

Erectile Tissue Structure and Function

Erection is a complex event involving hormonal, neural, and vascular components. The inciting stimulus, visual, tactile, or mental, leads to activation of neural pathways, eventually triggering nitric oxide synthase (NOS) activation, nitric oxide (NO) synthesis, and activation of guanylate cyclase. These events lead to increased levels of the intracellular second messenger cGMP with a resultant decrease in intracellular calcium levels and smooth muscle relaxation [8]. The end target of the erectile process is the erectile tissue. The erectile tissue is a spongy-like structure, composed of endothelium-lined sinusoids (lacunae), which fill with blood during erection. The sinusoids to fill with blood upon smooth muscle relaxation as described previously.

Erection involves not only expansion in penile volume, but also increase in penile axial rigidity to allow for penetration. This is achieved as the expansible erectile tissue is bounded by the dense fibrotic covering sheath, called the tunica albuginea. The tunica albuginea limits the erectile tissue expansion volume and leads to pressure elevation inside the erectile chambers that is translated to rigidity [9]. The expansion of the erectile tissue against the relatively inexpansible tunica albuginea and the increase in pressure compress the subtunical veins that drain the erectile tissue, preventing blood from leaving the erectile chambers, further contributing to maintenance of erection. This interaction between the expanding erectile tissue and the nonexpansible tunica albuginea that generates subtunical vein compression (known as the veno-occlusive mechanism) is crucial in achieving and maintaining erection.

Penile detumescence involves the above process in reverse: cessation of NOS release by nerve endings lowers NO levels and cGMP production. Intracellular cGMP is degraded in an enzymatic process by the enzyme phosphodiesterase type 5. Reduced levels of intracellular cGMP lead to release of calcium from the sarcoplasm, smooth muscle contraction, and opening of the subtunical veins facilitating blood outflow, resulting in flaccidity.

Cancer Treatments and Erectile Tissue Damage

Cancer therapies, specifically for pelvic organs cancers such as prostate, bladder, and rectum/anus, cause ED and erectile tissue damage by a combination of different mechanisms. Eventual ED is a result of injury to nerves, blood vessels, endothelium, and erectile tissue, with differences in the relative contribution of each mechanism and in time course of onset, unique to each treatment modality. A comprehensive evaluation of the cancer treated patient for ED mandates careful review of the treatments given, their timing, dose and duration, and the pathophysiology of ED with each treatment and with a combination of treatments. Understanding the pathophysiologic processes in the individual patient, their extent and reversibility, is essential to individually tailor treatment to each patient and to provide men with a prognosis for erectile function preservation.

Pelvic Surgery

Our current understanding of the pathophysiology of ED following pelvic surgery is primarily derived from RP research; however, the mechanism

of injury in radical pelvic surgery for bladder or ano-rectal surgery is similar. Prior to 1982 virtually all men who underwent surgical treatment for prostate cancer were incapable of achieving functional erections after surgery. Following the discovery of the anatomy of human cavernous nerves by Walsh and Donker, the first purposeful anatomic nerve-sparing RP was performed with complete recovery of sexual function within 1 year following surgery [10]. The cavernous nerves, a paired structure, are autonomic nerves that travel on either side of the bladder and the prostate towards the penis to innervate the erectile tissue. Nerve injury is the primary insult in radical pelvic surgery. It is well appreciated that transection of, or extensive thermal injury to the cavernous nerves will result in permanent loss of erectile function after surgery. However, traction and/or percussive injury to the nerves may be just as deleterious.

With complete nerve transection, the loss of erectile function is complete and immediate. Men lose their ability to achieve erections in response to sexual stimulation as well as their sleep erections. Men, who have had non-nerve-sparing surgery, are likely to have a postoperative course of erectile function deterioration, rather than recovery and development of early ED refractory to medical interventions [11]. Response to oral erectogenic medications is not to be expected with complete nerve resection and recovery of nerve function and eventual spontaneous erection does not occur. Men who had their cavernous nerves transected are able to achieve erections with direct inhibition of the erectile tissue smooth muscle contraction by intracavernosal injection (ICI) of erectogenic vasoactive agents. Unlike the erectogenic oral medication effect, which is largely dependent on partial residual nerve function, ICI acts directly on the erectile tissue smooth muscle and does not require intact neural pathways. With nerve-sparing surgery, the cavernous nerves are not transected, however, some degree of stretch injury cannot be avoided and thus nerve sparing is not synonymous with erectile function sparing, and patients may confront the burden of ED postoperatively, even after successful nerve-sparing surgery performed by skilled surgeons. After surgery, slow, gradual erectile function recovery is expected, over the course of 18–24 months. The course of recovery has been shown to be determined by the degree of nerve trauma, the patient's age, and the quality of erections before surgery [12]. Clinical experience has shown us that some men can achieve non-medication-assisted partial erections and respond to PDE5 inhibitors within 2–6 weeks after surgery but by 12 weeks no longer respond, possibly due to ongoing postoperative Wallerian degeneration, which is a slow degeneration of the distal nerve stump in response to nerve injury, involving degeneration of the myelin sheath that envelops the nerve fiber and infiltration by inflammatory cells such as macrophages.

Neural damage, prolonged or even transient, has complex consequences for the cavernosal tissue. Histologically, neuropraxia/neurotomy leads to cavernosal biochemical, morphological, and functional changes at the level of both smooth muscle and endothelial cells [13]. The first consequence of injury is the absence of erection and cavernosal oxygenation [14]. When penile smooth muscle cells are exposed to a prolonged hypoxic environment, there is a significant overexpression of hypoxia-related pro-fibrotic substances, like transforming growth factor-β1 (TGF-β1) and TGF-β1 dependent endothelin-1 (ET-1), which promote the deposition of collagen I and III within the corpus cavernosum [14–16]. The increased level of TGF-β1 demonstrated in cavernosal tissue exposed to low oxygen tension seems to be mediated by the inhibition of prostaglandin-E_1 (PGE_1). These structural erectile tissue changes are the basis for development of erectile tissue damage.

Vascular injury in radical pelvic surgery revolves around damage to accessory pudendal arteries (APAs), which potentially have a role in penile blood supply. These arteries are variable in their incidence, their origin, and their course in the pelvis, and they are predisposed to injury at the time of RP. Droupy et al. have shown in a small study using transrectal and transperineal ultrasound that these arteries are functional [17]. Nine of 12 patients studied had periprostatic arteries coursing forward towards the penis. Upon ICI the hemodynamic changes that were

seen in the cavernosal arteries were mirrored in the periprostatic arteries suggesting that the APAs were functional. Rogers et al. have shown that APA preservation at the time of open RP translates into an improvement in erectile function recovery and possibly even shortening of the time to recovery of erections [18].

Pelvic Radiation

Pelvic radiotherapy is a curative treatment for prostate cancer and is commonly used to downstage rectal cancer before radical pelvic surgery and may be used in the treatment of bladder cancer in protocols of bladder preservation, when bladder resection is not desired. Pelvic radiation is clearly associated with ED whose primary cause is vascular injury [19]. Goldstein et al. found that while men who had undergone pelvic radiotherapy did not have neurological damage, they consistently had vascular abnormalities and even demonstrable occlusive pudendal artery lesions [20]. Zelefsky et al. evaluated men with ED after RT using Doppler ultrasound and corroborated that ED after pelvic radiation is of arteriogenic origin and suggested that its presentation is delayed, with a median time to presentation of 14 months [21]. Mulhall et al. studied erectile hemodynamics and found that arteriogenic etiology is not the only vascular pathology following RT, but in 85% abnormalities of the penile veno-occlusive mechanism are found, which is consistent with erectile tissue damage [22]. Carrier et al. showed that radiation injury involves not only vascular and erectile tissue damage but also neural damage: in a rat model study, radiation was found to reduce the number of NOS-containing nerve endings within the penis [23]. Unfortunately, unlike surgery where a nerve-sparing technique was developed and used with significant reduction in the extent of neural injury, a nerve-sparing radiation technique does not exist and unlikely to be developed due to the close proximity of the cavernous nerves and the prostate. Mulhall et al. demonstrated that even with advanced radiation technique of 3D conformal radiotherapy, not only the prostate and the adjacent cavernosal nerves are included in the radiation field, but 43% of the total dose is delivered directly to the most proximal erectile bodies [24].

Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) is a treatment for metastatic prostate cancer, as well as for high-risk localized prostate cancer in conjunction with RT. Androgen deprivation can be accomplished either surgically by castration (orchiectomy) or medically, and its aim is to reduce testosterone to a castrate level. Testosterone is pivotal in maintaining penile tissue integrity and ADT causes direct erectile tissue damage: castrate levels of testosterone result in significant reduction in trabecular smooth muscle content, marked increase in connective tissue deposition, and resultant ED [25]. The tunica albuginea also exhibits morphological changes with lack of androgen, and appears thinner, with fewer elastic fibers and collagen disorganization. In a castrate animal model, fat-containing cells have been observed in the subtunical region with reduced erectile function. It has been postulated that these structural alterations may interfere with normal function of the subtunical veno-occlusive mechanism. Testosterone has an important role in erectile tissue function, mediated through the NOS-cGMP-PDE5 pathway, a key player in erectile tissue smooth muscle relaxation. Testosterone regulates NOS isoforms and PDE5 expression and activity in the corpus cavernosum, which determine erectile tissue cGMP levels and smooth muscle tone [25].

Testosterone has also been shown to play a role in neural pathways, hence the mechanism involved in ADT-associated ED may also be neurogenic. Testosterone has repeatedly shown to be contributory to both nervous structure and function. There is an evidence to support the role of testosterone in preservation of neural structures involved in the erection process. Schirar et al. reported that androgen receptors are present in

about 40% of the major pelvic ganglion cells and that androgens modulate the synthesis of NOS in neurons [26, 27]. Rogers et al. studied the effects of castration in a rat model and strategies to prevent castration-associated damage and found that castration causes endothelial, smooth muscle and nerve damage, and that testosterone replacement therapy (TRT) led to nerve regeneration [28]. Syme et al. compared the results of unilateral genitofemoral nerve grafting following cavernous neurotomy in intact, castrated, and castrated-testosterone-treated rats and found that castrate animals had poorer erectile response and lower neuronal NOS (nNOS) while animals receiving TRT had comparable outcomes to those of intact animals [29]. These findings suggest that there are neural structures whose regeneration and function is androgen dependent.

Erectile Tissue Damage and Erectile Dysfunction

The pathophysiology of ED after pelvic cancers treatments, radical pelvic surgery, pelvic RT and ADT, is multifactorial and involves injury of neurogenic, vascular, and hormonal natures. With progressive injury, the final common pathway is erectile tissue damage (Fig. 43.1). As previously stated, erectile tissue damage may be a consequence of direct treatment effect: neuropraxia/denervation of the corporal tissue following radical pelvic surgery and resultant atrophy and degeneration, direct radiation effect on the erectile tissue causing structural changes, and loss of androgen trophic effects. Erectile tissue damage may also be an indirect consequence of prolonged periods without regular erectile activity. Normally, men obtain 3–6 erections lasting 10–15 min, during REM sleep each night, without sexual stimulation [30]. While during erection the penis is oxygenated with the pO_2 rising to 70–100 mm of mercury; while, in the flaccid state, the pO_2 is only 25–40 mm hypogonadism (Fig. 43.2). It has been postulated that chronic absence of oxygenation results in upregulation of fibrogenic cytokines including TGF-beta. TGF-beta results in collagen production which eventually leads to erectile tissue damage [31]. Histologically, erectile tissue damage is characterized by smooth muscle cell apoptosis, reduction in elastic fiber number, and deposition of collagen with impaired bundle organization – all contributing to loss of the delicate erectile tissue architecture and its unique properties.

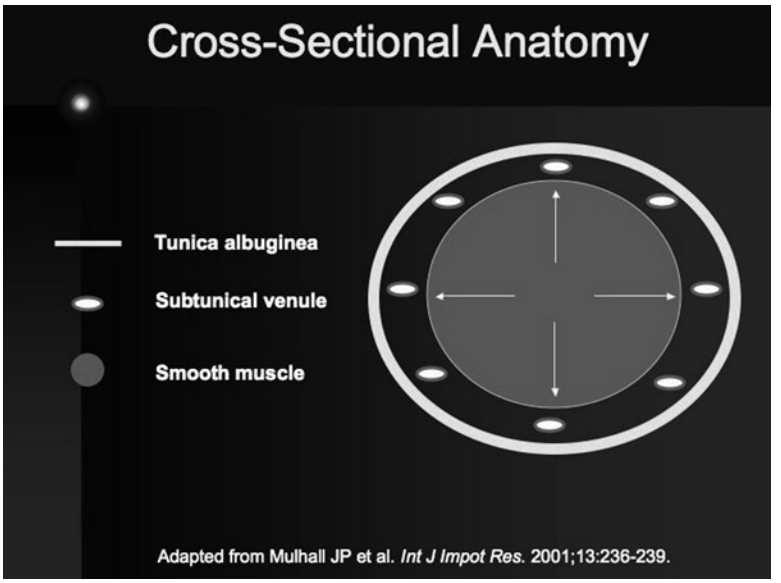

Fig. 43.1 Schematic representation of the corpus cavernosum and the venocclusive mechanism

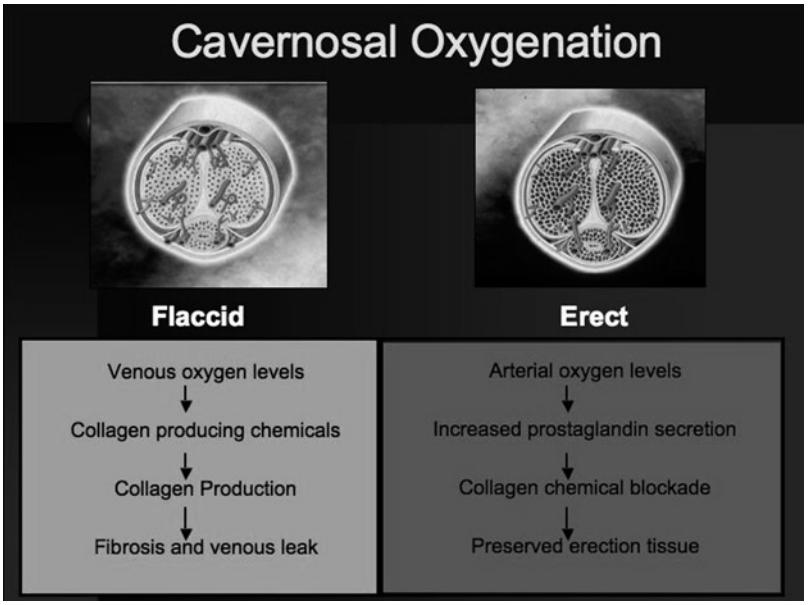

Fig. 43.2 Schematic representation of the concept of cavernosal oxygenation

Erectile tissue damage is the underlying pathology of permanent veno-occlusive ED. During erection, the damaged corporal erectile tissue fails to adequately expand against the tunica albuginea, the veins draining the erectile chambers are not tightly compressed and occluded and blood escapes from the erectile chambers. This phenomenon is termed *venous leak* (Fig. 43.1), defined as failure of the veno-occlusive mechanism to trap the blood within the erectile chambers during erection. Nehra et al. have shown in human corporal tissue biopsies taken at the time of cavernosometry, once smooth muscle content in the corpora cavernosa drops below 40%, venous leak occurs and this leak correlates well with the amount of smooth muscle loss [32]. Iacono et al. have shown that as early as 2 months after RP in untreated men (no rehabilitation) there is a marked increase in collagen deposition and a marked decrease in elastic fiber content in erectile tissue [33]. This is in keeping with the animal data that suggest even in the earliest stages after cavernous nerve injury, structural changes occur.

Mulhall et al. have shown in a series of 16 patients who had preoperative and postoperative hemodynamic assessment that more than half of the men had venous leak after surgery [34]. In a more recent analysis by Mulhall et al. [35], in men who had partner-corroborated excellent erectile function prior to surgery, who underwent duplex Doppler penile ultrasound after surgery, there was an increase in the incidence of venous leak (based on elevated end diastolic velocities during duplex Doppler penile ultrasound) as time progressed after surgery. The incidence of venous leak less than 4 months after surgery was approximately 10% and rose to 35% between 8 and 12 months after surgery and 50% after 12 months. The importance of this information is that in the same series, men with normal erectile hemodynamics were more likely to have recovery of natural erectile function. However, only 8% of men who had venous leak had recovery of natural functional erections after surgery. We also know from other data that men with venous leak are far less likely to respond to PDE5 inhibitors than men with arterial insufficiency [36]. Another study from the same group clearly demonstrated the association of non-nerve-sparing surgery with higher incidence and an earlier onset of venous leak [11].

Venous leak has unique characteristics and clinical course (Fig. 43.1). It is not an "all or none"

phenomenon: the further the smooth muscle content drops and the more extensive the collagen deposition is, the greater is the magnitude of leak. Normal smooth muscle content ranges 40–50%. In the range of approximately 25–40%, as smooth muscle content drops, the magnitude of venous leak steeply increases. Below smooth muscle content of 25%, maximal leak is evident, and further reduction is clinically not meaningful [32]. Erectile tissue damage is irreversible and therefore once it is extensive enough and venous leak is evident, recovery is unlikely. Erectogenic pharmacotherapy is capable of increasing penile blood inflow, however, it is ineffective in reversing erectile tissue damage, prevention of venous leak, and reducing the amount of escaping blood. Indeed, increasing penile inflow can overcome low-grade leak and allow men to achieve satisfactory erections, however, with significant high-grade leak, pharmacotherapy, both PDE5 inhibitors and ICI are largely ineffective and a penile implant is the only effective measure to restore penile rigidity and allow penetration. Attempting to get an erectile tissue damaged penis erect can be compared to an attempt to fill a bucket with a hole: ideally, to fill a bucket a good inflow is needed and no fluid should leak out. If there is a small hole in the bucket, analogous to limited erectile tissue damage and low-grade leak, increasing the inflow can overcome the leakage and the bucket can eventually be filled. This is the mechanism by which pharmacotherapy works: increasing penile blood inflow. With a large hole, even maximal inflow cannot overcome the leakage and the bucket cannot be fully filled, analogous to extensive erectile tissue damage, high-grade leak and inability to achieve erection even with maximal penile inflow achieved with high-dose ICI.

Erectile Tissue Preservation and Cancer Treatments

Erectile tissue damage involves irreversible structural tissue alterations and is secondary to the treatment itself and to subsequent ED with prolonged absence of erectile activity. Hence, erectile tissue preservation strategies include (1) interventions to prevent or minimize treatment effect, (2) erectogenic therapies to obtain erections consistently, and (3) other interventions that have been shown to protect erectile tissue from the deleterious effect of cancer treatment.

Minimizing treatment effect can be achieved in several ways: if radical pelvic surgery is to be performed, any attempt should be performed to preserve the cavernous nerves. It has been shown that failure to recover spontaneous erections, poor response to PDE5 inhibitors, and early development of venous leak are closely associated with non-nerve-sparing surgery [11]. A prevalent misconception is that in men facing radical pelvic surgery with pre-existing ED, an attempt to perform nerve-sparing surgery is futile, as they need ED therapy anyway. However, if such men are responding to erectogenic pharmacotherapy, nerve-sparing surgery should be attempted to avoid venous leak development, loss of the ability to respond to medical treatment, thus avoiding surgical treatment. In cases of salvage surgery after primary curative treatment failure, nerve-sparing surgery is technically more demanding, and erectile tissue damage is more likely to occur and recovery of erections is less likely [37, 38]. Adjuvant radiotherapy after RP has a synergistic effect on erectile tissue health, and its use should be limited if possible, especially under certain clinical circumstances when its oncologic benefit is unclear [39]. Similar approach should be the rule also with ADT: careful consideration should be practiced, the treatment goal should be clearly defined and the benefits should be weighed against the potential harms, one of which being its effect on erectile tissue. Recently, the role and the timing of ADT as primary treatment and as adjuvant immediate treatment after RP have been questioned [40, 41].

The second principle of erectile tissue preservation revolves around the concept that obtaining erections consistently, on a regular basis, preserves erectile tissue health. Soon after pelvic surgery, the cavernous nerves are traumatized and the majority of men cannot achieve

spontaneous erections: Rabbani et al. found that after RP, only 25% of their study population recovered satisfactory erections at 4 months and only 50% at 30 months [12]. The first clinical evidence to support the use of regular erectogenic treatment after RP came from a prospective randomized study by Montorsi et al., in which men after RP who received regular ICI have better recovery of their spontaneous erectile function when compared with men who used no therapy early after surgery. Although this study has certain limitations, such as small study population, lack of vascular assessment before and after RP, and lack of documentation of the effects of ICI, the Montorsi study gave the first signal that erectogenic treatment on a regular basis is of benefit [42]. Indeed, as previously detailed, lack of erection favors erectile tissue hypoxia, expression of fibrogenic cytokines, smooth muscle cells apoptosis, collagen deposition, and erectile tissue damage. The time dependency of venous leak development after RP is consistent with the concept of progressive erectile tissue damage after RP with lack of erections. The Montorsi study was conducted before PDE5 inhibitors were introduced, and today there are oral erectogenic agents that can be used to help men to obtain erections. Recently, it has been demonstrated that cavernosal oxygenation is achieved, even in the initial stages of erection, before full rigidity has been achieved [43]. This principle has important clinical implications: not infrequently, men after cancer interventions are struggling to achieve full erections. If preservation of erectile tissue is the goal, it seems that we can provide adequate oxygenation even with partial erection and the question can be raised should we be driving our patients to achieve fully rigid erections.

Over the past decade, there is a growing interest in research of the beneficial effect of PDE5 inhibitors, beyond their erectogenic properties, to facilitate erectile function recovery. The first clinical study evaluating regular, nonerectogenic use of sildenafil was conducted by Padma-Nathan et al. and found improved recovery of spontaneous erections with 50 or100 mg sildenafil administered nightly, not on-demand for sexual activity [44]. This pioneering study triggered extensive basic research that led to the discovery of the erectile tissue protective properties of PDE5 inhibitors and other compounds.

Erectile Tissue Preservation: Animal Study Data (Table 43.1)

Emerging scientific evidence suggests that persistently elevated levels of NO and cGMP may have an antifibrotic effect on a variety of tissues, including the tunica albuginea and corporal tissue [45, 46]. Because PDE5i work by inhibiting the enzyme that degrades cGMP, this may be a key means of the antifibrotic action of PDE5i. In this context, several studies have demonstrated a reduced amount of collagen deposition and fibrosis in penile tissues of animals chronically treated with PDE5i [13, 47–51].

Ferrini et al. found that chronic vardenafil was effective in preventing both the fibrosis and loss of smooth muscle seen following bilateral cavernous nerve resection [47]. Compared with the sham group, rats exposed to nerve injury demonstrated a threefold increase in corporal smooth muscle apoptosis, a 60% reduction in the smooth muscle:collagen ratio, a twofold increase in inducible NO synthase (iNOS) expression and development of venous leak. When vardenafil was given daily for 45 days to the animals that underwent bilateral nerve resection, the corporal smooth muscle:collagen ratio was normalized and the subsequent venous leak was prevented. The authors suggested that the effect of vardenafil in preventing corporal fibrosis might be mediated by changes in iNOS expression and activity. Prolonged endogenous induction of iNOS seems to produce sufficient NO to reduce collagen synthesis, inhibit TGF-β1 expression and myofibroblastdifferentiation,andactivatemetalloproteinases that break down collagen [52].

Mulhall et al. [13] demonstrated that chronic administration of sildenafil in the rat cavernous nerve crush model, given subcutaneously daily resulted in preservation of the smooth muscle–collagen ratio. In this series of experiments, the investigators also showed increased expression

Table 43.1 Laboratory research (animal) data

Authors	Publication year	Species	Methods	Treatment	Duration	Main outcomes
Mulhall et al.	2008	Rat	Cavernous nerve crush	Sildenafil	3, 10, 28 days	Improved erections Smooth muscle/collagen ratio ↑ CD 31 ↑ eNOS ↑ Apoptosis ↓ Akt phosphorylation ↑ eNOS phosphorylation ↑ Improved myelinated nerves architecture
Kovanecz et al.	2008	Rat	Bilateral/Unilateral cavernous nerve crush	Sildenafil ± iNOS inhibitor	45 days	Smooth muscle/collagen ratio ↑ Apoptosis ↓ Venous leak ↓ With iNOS inhibition – damage ↑ Sildenafil effect independent of iNOS inhibition
Ferrini et al.	2006	Rat	Bilateral cavernous nerve crush	Vardenafil	45 days	iNOS expression ↑ Smooth muscle proliferation ↑ Smooth muscle/collagen ratio ↑ Venous leak ↓
Vignozzi et al.	2006	Rat	Bilateral cavernous nerve crush	Tadalafil	3 months	Smooth muscle/collagen ratio ↑ Hypoxia ↓
Kovanecz et al.	2008	Rat	Bilateral/unilateral cavernous nerve crush	Tadalafil	45 days	Papaverine response ↑ Venous leak ↓ Smooth muscle/collagen ratio ↑ Collagen III/I ratio ↑ No effect on: TGF-β1, iNOS, xantine oxidereductase
Lysiak	2008	Mouse	Bilateral cavernous nerve crush	Tadalafil	2, 4, 6 weeks	Smooth muscle and endothelial cell apoptosis ↓ Akt phosphorylation ↑ ERK1/2 phosphorylation ↑

of the endothelial factor CD31 and increased phosphorylation of Akt and eNOS, which may account for the endothelial protection mediated by these agents. Similarly, Vignozzi et al. [51] found that chronic tadalafil administration to rats reversed the decline in the cavernosal smooth muscle:collagen ratio that occurred after bilateral cavernous neurotomy. Interestingly, the magnitude of the benefit of sildenafil after neural injury seems to be directly related to the timing of its administration [53].

Chronic treatment with PDE5i might exert at least some of its beneficial effects through much more complex mechanisms than a simple sustained increase in intracellular cGMP, such as neuromodulatory effects. The effect of chronic administration of PDE5i might be associated with structural and functional changes, which may involve not only smooth muscle cells but also endothelial function. The first proof of such association was given by Behr-Roussel et al. [54] who showed that a daily, 8-week treatment with sildenafil (60 mg/kg) administered subcutaneously to neurally intact rats was associated with enhanced endothelium-dependent relaxations of cavernosal strips to acetylcholine after chronic treatment with sildenafil. Conversely, relaxations in response to sodium nitroprusside were unchanged after sildenafil treatment. Moreover, the erectile responses to acute sildenafil were greater in chronically sildenafil treated rats. The findings suggested that the endothelium-dependent response is promoted by long-term PDE5i treatment and that the therapy does not confer an adverse effect on cavernosal tissue responsiveness involved in physiological erection. The investigators concluded that long-term sildenafil treatment might have long-lasting, physiologically significant erectile tissue benefits. The effect of chronic treatment with PDE5i seems to be mediated by increased Akt-dependent endothelial NOS (eNOS) activation [55]. This is key, since the predominant data suggest that endothelial NOS (eNOS) plays a major role as homeostatic regulator of penile vascular function and health [56]. Similar results reporting improved eNOS activity and endothelial relaxations after chronic treatment with sildenafil have also been demonstrated in animal models of diabetes and age-associated ED [54, 57, 58].

The effect of chronic PDE5i on endothelial function might not be only mediated through increased eNOS activation. Indeed, recent studies have suggested a restoration of endothelial progenitor cells (EPCs) to normal levels in patients with ED treated chronically with PDE5-I (sildenafil, tadalafil, or vardenafil) [59–62]. The role of NO in EPC mobilization as well as activation has been recently demonstrated. Moreover, it has been demonstrated that a lack of eNOS induces defective hematopoietic recovery and PC mobilization [63]. The effect of chronic PDE5i in increasing the number of circulating EPCs might be the effect of the inhibition of PDE5 in the bone marrow. Of note, reverse transcriptase-polymerase chain reaction analysis showed that human bone marrow expresses PDE5 messenger RNA [64].

Finally, chronic administration of PDE5i has also been shown to reduce the cavernosal apoptotic process after cavernous nerve injury [13, 65]. The effect of PDE5i in decreasing the number of penile apoptotic cells in cavernous injured models appears to be mediated by the phosphorylation of the survival associated kinases Akt and extracellular signal-regulated kinase (ERK) 1/2 [65]. The effect of chronic PDE5i in reducing apoptosis has also been studied in clinical scenarios other than post-RP models. Salloum et al. demonstrated that both sildenafil and vardenafil reduced the area of cardiac necrosis in a rabbit model of cardiac ischemia-reperfusion [66, 67]. Das et al. using mouse cardiac myocyte cells exposed to hypoxia and reoxygenation showed that sildenafil-treated cells demonstrated less necrosis and apoptosis than control cells [68, 69]. Interestingly, sildenafil-treated myocytes demonstrated an early increase in the ratio of the antiapoptotic protein Bcl-2 compared with the pro-apoptotic protein Bax, which may have been responsible for the antiapoptotic effect of sildenafil. The increase of Bcl-2/Bax ratio, as well as the antiapoptotic effects of sildenafil, was inhibited by treatment with the NOS inhibitor l-nitro-amino-methyl-ester, suggesting the role of NO signalling in the protective effect of the drug against apoptosis [68].

Erectile Tissue Preservation: Human Study Data (Table 43.2)

Direct evidence of erectile tissue preservation would require studies involving erectile tissue biopsy and analysis that, understandably, are difficult to conduct. The only human interventional study to provide direct evidence to support an intervention to preserve erectile tissue was performed by Schwartz et al. which was a randomized, non-placebo-controlled trial evaluating the impact of sildenafil on corporal smooth muscle integrity in men after RP [70]. Twenty-one patients used sildenafil every other day at either 50 or 100 mg. They had corporal biopsy performed prior to RP and 6 months postoperatively. Histopathological analysis showed significant preservation of smooth muscle content with sildenafil use at both the 50 and 100 mg level, in stark contrast to the afore-mentioned Iacono study. Nevertheless, the rapidity of the acute histologic findings correlates with a study demonstrating a virtual complete loss of nocturnal penile tumescence activity within 1 month of nerve-sparing prostatectomy [71].

Indirect evidence supporting interventions effective in promotion of erectile tissue preservation may be derived from studies showing improvement in long-term erectile function or reduction in the prevalence of venous leak. However, in case of indirect evidence, the beneficial effect may be related to neurological, hormonal, or other unknown factors. An example of studies providing indirect evidence to support the concept of erectile tissue preservation are the previously described rehabilitation studies addressing the concept of regular rather than on demand use of PDE5 inhibitors to promote eventual erectile function recovery after RP [44, 72].

Bayer sponsored the REINVENT study which was an analysis of nightly vs. on demand vardenafil post-RP. The study was very complicated in its design: specifically, within 14 days of bilateral nerve-sparing RP, patients were randomized in 1:1:1 ratio to receive either 9 months of treatment with 10 mg nightly vardenafil (which could be decreased to 5 mg if required) plus on-demand placebo for sexual relations; 9 months of treatment with flexible-dose on-demand vardenafil for sexual relations (starting at 10 mg with the option to titrate to 5 or 20 mg), plus nightly placebo; or 9 months of treatment with nightly placebo plus on-demand placebo for sexual relations. After this a 2-month single-blind phase was conducted where all patients received only placebo for sexual relations and this was, in turn, followed by a 2-month open label phase where all patients received vardenafil for sexual relations. The inclusion/exclusion criteria were standard for ED post-RP trials.

The primary end point was the proportion of patients achieving an IIEF erectile function domain (EFD) score ≥22 after the 2-month washout, single-blind placebo phase. Some readers may be concerned that this figure does not represent good erectile function, but there is data that suggests that the majority of men with such an EFD score consider themselves functional [10]. Indeed, the classically described normal score of 26 is likely overly rigorous. Secondary endpoints included the SEP (sexual encounter profile) question 3 (which asks about the ability to penetrate and keep an erection to the completion of intercourse) outcomes and the proportion of men achieving normal erectile function (EFD score ≥26).

While the proportion of patients achieving an EFD score ≥22 at the end of the 9-month double-blind phase was greater for the on-demand vardenafil group compared to placebo and nightly vardenafil groups, at the end of the 2-month single-blind phase there was no significant difference between the three groups, indeed the authors state that the "primary efficacy variable was not met." The proportion of patients achieving a score of ≥22 on the EFD was 28, 24, and 29% for the placebo, nightly vardenafil, and on-demand vardenafil groups. Likewise, there were no significant differences in SEP3 outcomes at the end of the single-blind placebo phase (months 9–11) between the three groups, with rates between 35 and 42% (p = ns).

The authors conclude that "this robustly designed and evidence-based multi-center study provides data to support a paradigm shift towards

Table 43.2 Clinical research (human) data

Authors	Publication year	Design	No. of subjects	Treatment	Duration	Main outcomes
Montorsi et al.	1997	Prospective Randomized Controlled	12 – treatment 15 – control	ICI (PGE1)	12 weeks	Recovery of spontaneous erections: 67 vs. 20% (control)
Mulhall et al.	2005	Nonrandomized review of prospective database	58 – treatment 74 – control	3 erections per week, with ICI or PDE5i	18 months	Nonmedication assisted functional erections: 52 vs. 19% Sildenafil response: 64 vs. 24% ICI response: 95 vs. 76%
Padma-Nathan et al.	2008	Randomized, double-blind, placebo-controlled	28 – Sildenafil 100 mg 23 – Sildenafil 50 mg 25 – placebo	Sildenafil nightly	36 weeks on drug 8 weeks off drug	IIEF Q3+Q4 score ≥8, spontaneous erections: 29 vs. 26 vs. 4%
Schwartz et al.	2004	Prospective uncontrolled	10 – Sildenafil 100 mg 11 – Sildenafil 50 mg	Sildenafil nightly	6 months	Smooth muscle preservation post op vs. preop: 100 mg group: 56.9 vs. 42.8% 50 mg group: 52.7 vs. 51.5
Bannowsky et al.	2008	Prospective randomized controlled	23 – Sildenafil 25 mg 18 – control	Sildenafil nightly	1 year	Spontaneous erections: 47 vs. 28% Sildenafil response: 86 vs. 66%
Montorsi et al.	2008	Randomized, double-blind, double-dummy, multicenter	149 – On demand 143 – Nightly 153 – Placebo	Vardenafi on demand, vs. vardenafil Nightly, vs. Placebo		IIEF ≥22 at after drug washout: On demand – 29.1% Nightly – 24.1% Placebo – 28.9%

on-demand dosing with PDE5 inhibitors for the treatment of ED in men in this patient group." However, the purpose of the study was not to define whether on-demand drug was better than placebo for sexual relations as this study shows (an entirely intuitive and expected outcome) but rather whether nightly vardenafil was efficacious in increasing erectile function recovery after RP. The fact that there was no difference in the three groups in the primary and main secondary outcome measures between the three groups means one of three things (1) that regular PDE5i use after RP is no better than on-demand use for erectile function recovery, (2) that vardenafil is inferior to sildenafil, supported by a small post-RP randomized, placebo-controlled trial [8] and a pulmonary hypertension study [11], or (3) that the REINVENT trial was not designed in such a fashion as to answer the main question at hand, which is what I believe this study indicates.

There were a number of methodological problems with the study (as it is presented in the paper). (1) The study was conducted over an almost 3-year period at 87 centers. With 423 patients completing study (there was in excess of a 30% dropout rate), this means that the mean patient number enrolled per center was less than five. It is unknown how many surgeons were performing the surgery, but it is at least 87 and this raises issues of surgeon stratification. One of the key factors in designing such a study is assuring homogeneity of nerve-sparing capabilities and with the large number of surgeons used in this study, this is questionable. Indeed, the SEP3 rates at the end of the single-blind placebo phase support this with rates of around 40% representing very poor response to a PDE5i and thus raising questions about the nerve-sparing status of the population. (2) There was no indication of the frequency with which each of the treatment groups was actually using the vardenafil given to them. For example, it is unknown how often the on-demand group actually used their vardenafil for sexual relations and likewise, it is unknown how often the nightly group actually used their vardenafil. It is conceivable that the latter may not have used their vardenafil every night (as is my clinical experience in my rehabilitation program). The closer the number of vardenafil pills used was between the two treatment groups the less likely such a study is capable of answering the question posed. (3) Can such a study ever be truly blinded? It is well known that patients receiving placebo in an ED drug trial are more likely to dropout (as is the case in this study with a dropout rate in the placebo arm 2–3 times higher than that in the treatment groups) because they achieve a poor erection during sexual relations. Indeed, it is somewhat surprising that the dropout rate was not even higher given the fact that the placebo and nightly groups used placebo for sexual relations for 9 months after surgery. In my clinical experience, the sexually motivated patient is clamoring for another treatment by 6 months after RP, thus, this raises questions about what the motivation level of the population was in this study. The presence of a placebo group in such studies is a major challenge. I believe that the presence of a true placebo group in such a study is nonviable and actually undermines the data.

Some of these issues are difficult to control for the design team. However, allowing all groups to use a PDE5i on demand for sexual relations would limit the dropout rate and will increase enrollment, which in turn may allow the use of a smaller number of centers and avoid the surgeon stratification concerns. This might also get around the concerns about blinding of which arm a patient is in and would permit in reducing the number of arms to two as opposed to three.

A number of other factors are worth commenting on: the key finding is that the use of a PDE5i, vardenafil in this case, results in a higher proportion of patients achieving an EFD score of ≥22 compared to using placebo for sexual relations. As previously stated, this is to be expected. The duration of the study is likely too short, as most men optimize their erectile function after RP between 18 and 24 months postoperatively. Supporting this is the significant difference in the proportion of patients achieving EFD score ≥22 and SEP3 rates between 11 (end of single-blind placebo phase) and 13 months (end of the open-label vardenafil phase). With regard to EFD ≥22 at 11 months,

the proportion ranged from 24 to 29% between groups while at 13 months these rates were 48–54%, suggesting significant nerve recovery in this 2-month period, a time frame entirely consistent with clinical experience. Furthermore, the SEP3 rates rose from 38–42% at 11 months to 57–62% at 13 months. This is a salutary lesson for all investigators, an ending time point of at least 18 months if not 24 months should be used in such studies. Finally, only one third of men completing the study returned to their baseline erectile function even with the use of a PDE5i.

Concluding as the authors do, that these data support the shift to using only on-demand PDE5i in a rehabilitation program is fallacious. In my opinion, the data do not in any way support such a shift but what it does indicate is that there remains room for the conduct of an appropriately designed study to address penile rehabilitation post-RP.

Summary

ED in the cancer patient involves complex pathophysiology and several different pathways. The final common pathway is irreversible erectile tissue damage. Structurally, erectile tissue damage involves loss and disorganization of cavernous tissue elastic fibers, death of smooth muscle cells, and collagen deposition. These structural alterations lead to loss of the unique properties of the erectile tissue, manifested mainly as failure to expand during erection, veno-occlusive dysfunction, and venous leak. Clinically, ED associated with erectile tissue damage is associated with poor response to medical treatment, PDE5 inhibitors or even high dose ICI, leaving a surgical treatment as the only option. Recent research provides evidence to support interventions aimed at erectile tissue preservation in men undergoing cancer treatments. As to our current knowledge, minimizing exposure to cancer treatments if possible, erectogenic

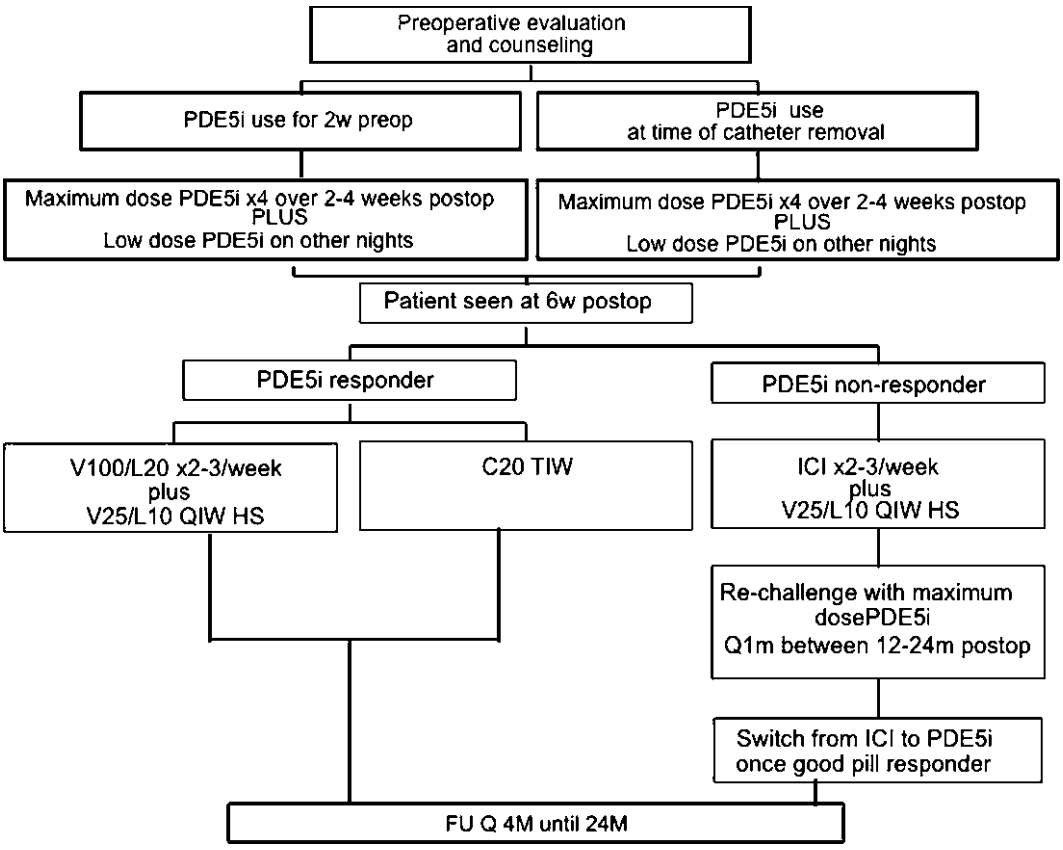

Fig. 43.3 Mskcc penile rehabilitation regimen

treatment to achieve erections on a regular basis during and/or soon after treatment and regular PDE5 inhibitor administration appear to have some potential to prevent erectile tissue damage associated with cancer treatments (Fig. 43.3).

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Chapter 44
Erectile Dysfunction: Pharmacological Therapy

Tariq F. Al-Shaiji, Eric Chung, and Gerald B. Brock

Keywords PDE5 inhibitors • Intracavernosal injection therapy • Prostaglandin • Nitric oxide • Priapism

Introduction

Erectile dysfunction (ED) associated with cancer therapy is commonly encountered whenever surgical interventions, radiotherapy, or systemic chemotherapy compromise the pelvic blood vessels or nerves. Currently, available treatment modalities frequently achieve long-term cancer remissions, and as a consequence, with advancing age patients are likely to face sexual dysfunctions and suffer their devastating effects on quality of life (QoL) long after the cancer treatment has been completed. The diagnosis of cancer is tough to overcome, but when its therapy results in alteration of basic bodily functions, it can be hard to deal with for patients and their partners.

Dramatic advances have been achieved in our ability to treat ED over the past five decades with new agents emerging. In spite of these novel agents, many men and their partners suffer the impact of ED on their QoL frequently without requesting information or treatment leaving the condition underevaluated and untreated. This chapter highlights the pharmacological approaches that are currently available, highlighting their risks and benefits.

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Historical Review of Modern Erectile Dysfunction Pharmacotherapy

Sexual function and dysfunction has been an area of great personal and societal interest throughout history, but interestingly has been a taboo subject in most cultures for thousands of years. In some instances, ancient cultures have reported a belief of psychological or supernatural origin to sexual function [1, 2]. Indeed, Porter and Hall reported many examples of British physicians who have published information about sex for the general public and were subsequently penalized or ostracized within their profession [3]. Although the term "impotence" has been used for centuries, it generates much confusion and has been largely replaced by "erectile dysfunction" since 1992 [4]. A search of the English language literature published on or before 1970 failed to find any reference to sexual medicine in a title, but of course this does not mean that the term had not been used verbally, in non-English language literature or in nonindexed literature [5]. The first book written in the English language with sexual medicine in its title was *Basic Sexual Medicine*, written by Eric Trimmer and published in 1978 [5].

Many interesting remedies have been tried and recommended by different mythologies all

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over the world for many centuries to treat what was recognized to be a problem with erection. Specifically, over the last four decades, a rise in the available options to treat ED have become available, with a particularly steep growth in published reports in the last 15 years. This change coincides with the development of surgical and medical therapies for the condition, encouraging both patients and physicians to diagnose and treat ED.

In 1668, Regnier de Graaf discovered that the injection of saline into the penile blood vessels of cadavers could induce an erection [6]. In 1980, Virag, a French vascular surgeon, discovered intracavernosal therapy almost by accident when he mistakenly performed an intra-arterial injection of papaverine and produced an erection in his patient [7]. At almost the same time, and quite independently, an English neurophysiologist named Giles Brindley described an erection after the intrapenile administration of the alpha-blocker phentoxybenzamine [8]. In a dramatic demonstration in 1983, Brindley went a step further at the American Urological Association conference in Las Vegas when he stepped in front of the podium while presenting his work and demonstrated to the audience his own erection from self-injection [1, 9]. This event led to a rapid rise in the scientific interest within the field with Zorgniotti and Lefleur pioneering the use of a combination of papaverine and phentolamine as intracavernous pharmacotherapy for ED [10]. The first report on the intracavernous injection (ICI) of prostaglandin E1 (PGE1) to induce pharmacologic erection was published by Ishii et al. in 1986 [11, 12]. In 1993, Wolfson et al. were the first to report on the efficacy of intraurethral prostaglandin E_2 cream given as suppositories offering a possible less invasive alternative treatment for ED compared to injections [13]. Alprostadil (prostaglandin E1) was the first ED drug to receive regulatory approval and began to be marketed in 1995. It is available as a local injection or an intraurethral pellet [1].

The last three decades have been witness to a transition from little real understanding of the physiologic basis of ED, to the recognition that it is a complex neurovascular event amenable to pharmacologic manipulation. This has had a considerable impact on sexual medicine worldwide. This knowledge coupled with the concept of "naturalness," searching for therapies that are less invasive, has been a driver for the development of oral agents in preference to injectable or surgical treatments. In 1980, Furchgott discovered that endothelial cells produce an endothelium-derived relaxing factor (EDRF) in response to stimulation by acetylcholine in vessels with intact endothelium [14]. In this study, EDRF acted on vascular smooth muscle to produce relaxation. Seven years later, separately, Ignarro et al. and Palmer et al. proved that EDRF is nitric oxide (NO) [15, 16]. The next crucial chapter in the history of ED pharmacotherapy started in the United Kingdom with the serendipitous discovery that sildenafil, a phosphodiesterase 5 (PDE5) inhibitor which was being investigated as a vascular relaxant, increased blood flow to the penis and therefore enhanced erections based on the NO–cGMP pathway [1, 17, 18]. Subsequently, following an elaborate and detailed clinical trial program involving thousands of human subjects over the course of 6 years in 1998, the U.S. Food and Drug Administration (FDA) gave approval to sildenafil citrate as the first oral ED drug and the era of Viagra was born [19]. The successful introduction of sildenafil into clinical practice was shortly thereafter followed by the launch of two other PDE5 inhibitors: tadalafil and vardenafil, which obtained FDA approval in 2003 [20].

Goals of Pharmacological Therapy

Cancer-related ED may interfere with several different components of the normal erectile cascade (neural, vascular, or end organ) and also be related to the stress of the cancer diagnosis. An understanding of the underlying etiologies is essential for the physician prior to tailoring the appropriate treatment to the individual patient. A patient and partner-centered approach based on needs and expectations

is ideal. The development of ED can significantly affect QoL through reduced self-esteem and sense of masculinity leading to embarrassment and personal relationship conflict. Although complete cure from ED may not be possible, the primary objectives should include restoration of satisfactory physical functioning and improvement in sexual satisfaction and relationships to restore QoL. Current pharmacological options are focused on two main targets: relaxing the corpus cavernosum smooth muscle and influencing the central regulatory mechanisms of erection [21]. A treatment algorithm for ED is presented in Fig. 44.1.

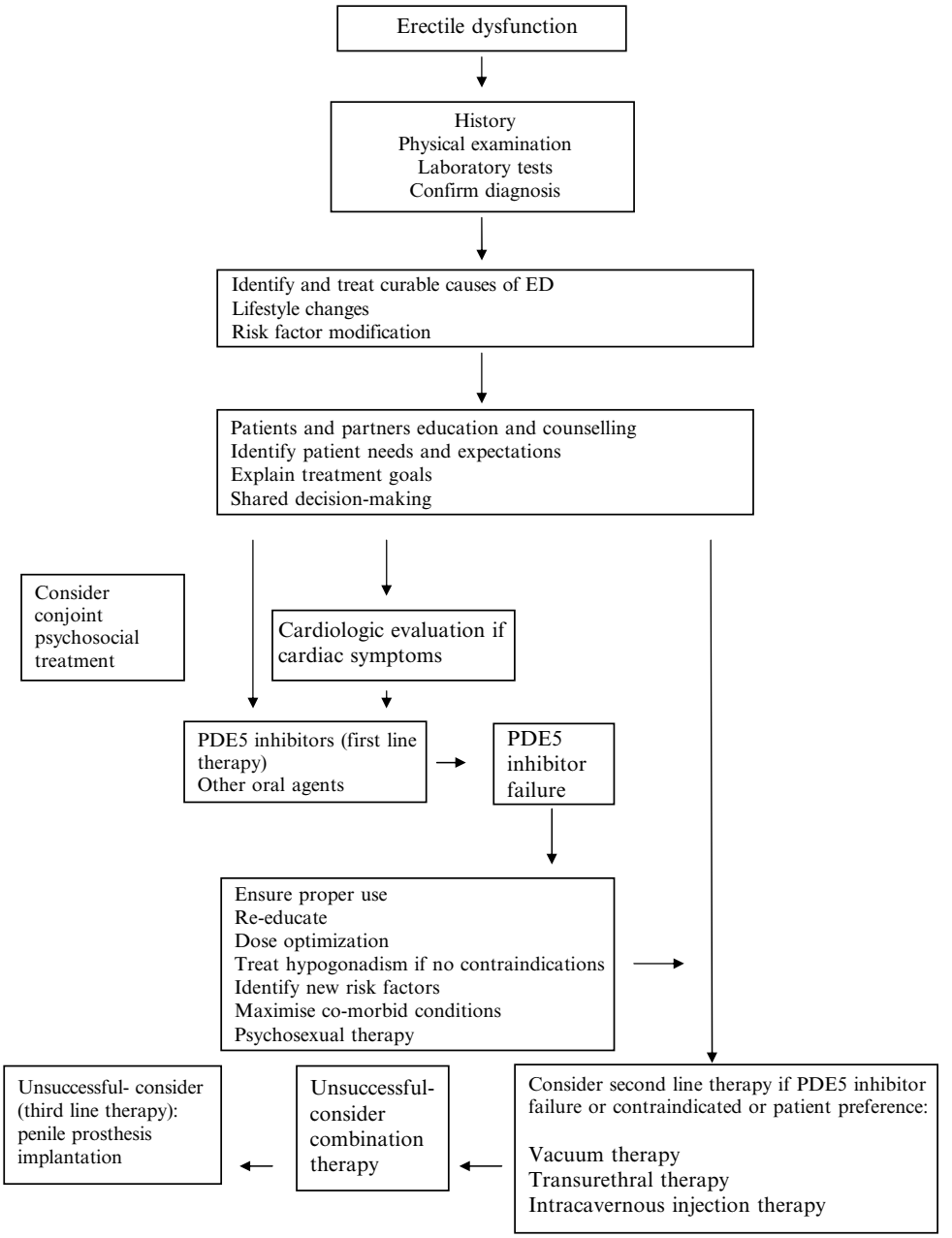

Fig. 44.1 Treatment algorithm for ED

Oral Agents

Phosphodiesterase 5 Inhibitors

During normal erection, NO activates guanylate cyclase, which facilitates the conversion of guanosine triphosphate to cyclic GMP (cGMP) and leads to a cascade of events culminating in decreased intracellular calcium and subsequent smooth muscle relaxation. At the same time, cGMP is broken down to GMP by the enzyme phosphodiesterase, the type 5 isoform, which is abundant in the corpora cavernosa. PDE5 inhibitors act at this level, competitively inhibiting the breakdown of cGMP, resulting in higher cGMP levels which act as amplifiers of the normal erectile physiology. This pathway is dependent on an intact libido, adequate sexual stimulation, functional sensory pathways, and a multitude of other factors that must be present to produce a normal erectile response [22]. Consistent with the effects on the NO/cGMP pathway, the PDE5 inhibitors augment the hypotensive effects of organic nitrates [23]. Given nitrates increase cGMP levels, concomitant use of nitrates and PDE5 inhibitors produces a synergistic effect leading to excessive vasodilation and signifiant hypotension [23]. Currently, there are three commercially available PDE5 inhibitors: sildenafil citrate (Viagra, Pfizer, New York, New York), tadalafil (Cialis, Lilly, Indianapolis, Indiana), and vardenafil (Levitra, Bayer, West Haven, Connecticut). These agents remain the first-line therapy for the treatment of ED in men with no contraindications to their use [24]. All the agents have shown in clinical trials to improve erectile responses supported by demonstrated improvements in international index of erectile function (IIEF) scores among other end-points [25].

Sildenafil

Sildenafil was the first PDE5 inhibitor to receive regulatory approval and be marketed worldwide. It is estimated that more than 50 million men have been treated over a 10-year postmarketing experience [26]. It is available in 25, 50 and 100 mg doses and administered orally on demand. The recommended starting dose for most patients with ED is 50 mg taken about 1 h before sexual intercourse [27]. The dose can be increased or decreased, depending on patient's response and side effects. The patient should use the starting dose at least four times, to evaluate the efficacy and tolerability of the drug. If the starting dose is considered insufficient to obtain a satisfactory erection, the patient can titrate to a higher dose [28]. Dose-finding studies have defined clearly that there is dose-response relationship with sildenafil, and the best results in terms of improvement of erections have been obtained with the maximum dose (100 mg) [19]. It has been reported that 63% of patients taking a 25-mg dose describe improved erections, whereas 82% report improvement with 100 mg [29]. It is usually effective within 30–60 min from the time of administration with a therapeutic window that can last for up to 12 h [30]. The maximal recommended frequency is once per day [31]. Taking sildenafil with food (especially fatty food) reduces the rate and extent of its absorption; however, there is no significant interaction of sildenafil with alcohol [21]. It is metabolized primarily in the liver, mediated by two cytochrome P450 isoforms (CYP2C9 and CYP3A4) [32]. In patients with hepatic or renal impairment and those over 65 and on concomitant use of p450 CYP3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole, protease inhibitors), a dose adjustment may be needed since these groups of patients are expected to have reduced clearance of the drug [31, 33]. On the other hand, agents such as rifampin, phenobarbital, phenytoin, and carbamazepine may induce CYP3A4 pathway and enhance the breakdown of sildenafil, so that higher doses may be required [25]. The pharmacokinetic data of sildenafil are shown in Table 44.1.

A number of mild class-specific side effects are linked to sildenafil [34]. These are due to inhibition of PDE5 causing vasodilation within the capillary smooth muscle of the brain (causing headache), nasal cavity (rhinitis), sinuses (sinusitis), dermis (flushing), and gastroesophageal junction (dyspepsia) [21, 22, 26, 35]. Of these, headache, flushing, and dyspepsia are the most

Table 44.1 Comparison of the available oral PDE5 inhibitors [24, 33, 41, 49, 56, 68, 149–151]

Parameter	Sildenafil	Tadalafil	Vardenafil
Available doses (mg)	25, 50, 100	5, 10, 20	2.5, 5, 10, 20
Maximum dose (mg)	100/day	20/day	20/day
C_{max} (μg/L)	411	378	17
Mean T_{max} (h)	1	2	0.7–1
$t_{1/2}$ (h)	4	17.5	4–5
Duration of action (h)	≥8	24–36	≥8
Bioavailability (%)	41	NA	15
Food interaction	Yes with high-fat foods; possible with low-fat foods	None	Yes with high-fat foods; possible with low-fat foods
Alcohol interaction	None	None	None
Metabolism	CYP3A4 major, CYP2C9 minor	CYP3A4 major, CYP2C9 minor	CYP3A4 major, CYP2C9 minor
Excretion	Feces major (80%), urine minor (13%)	Feces major (61%), urine minor (36%)	Feces major (91–95%), urine minor (2–6%)
Contraindications	*Absolute*:	*Absolute*:	*Absolute*:
	Organic nitrates (regularly or intermittently)	Organic nitrates (regularly or intermittently)	Organic nitrates (regularly or intermittently)
	Known hypersensitivity to any component of the tablet	Known hypersensitivity to any component of the tablet	Known hypersensitivity to any component of the tablet
	Relative:	*Relative*:	*Relative*:
	Postrelease labeling cautions use in patients not studied, including men with MI, stroke, life-threatening arrhythmia within 6 months	Postrelease labeling cautions use in patients not studied, including men with MI, stroke, life-threatening arrhythmia within 6 months	Postrelease labeling cautions use in patients not studied, including men with MI, stroke, life-threatening arrhythmia within 6 months
	Resting BP < 90/50 or >170/110 mmHg	Resting BP < 90/50 or >170/110 mmHg	Resting BP < 90/50 or >170/110 mmHg
	Cardiac failure	Cardiac failure	Cardiac failure
	Unstable angina	Unstable angina	Unstable angina
	Retinitis pigmentosa	Retinitis pigmentosa	Retinitis pigmentosa
			Associated with minor prolongation of QT interval, avoid in patients with congenital prolonged QT interval
			Those on Class I (quinidine, procainamide) or Class II (amiodarone, sotalol) antiarrhythmics

(continued)

Table 44.1 (continued)

Parameter	Sildenafil	Tadalafil	Vardenafil
Use with alpha blockers	Concomitant use of selective alpha blockers does not present a risk for significant hypotension	Concomitant use of selective alpha blockers does not present a risk for significant hypotension	Concomitant use of selective alpha blockers does not present a risk for significant hypotension
	There is a potential risk of significant hypotension when using nonselective alpha blockers	There is a potential risk of significant hypotension when using nonselective alpha blockers	There is a potential risk of significant hypotension when using nonselective alpha blockers
Side effects (top five in order of frequency when compared to placebo)	Headache	Headache	Headache
	Flushing	Dyspepsia	Flushing
	Dyspepsia	Back pain	Rhinitis
	Nasal congestion	Myalgia	Dyspepsia
	Alteration in color vision	Nasal congestion	Sinusitis

Pharmacokinetic data based on fasted state and higher recommended dose

C_{max} maximum plasma concentration; t_{max} time to C_{max}; $t_{1/2}$ half-life; *NA* not available

common adverse events, but rarely lead patients to discontinue treatment [36]. In addition to these effects, sildenafil is specifically associated with visual disturbances (blurred vision, flashing lights, blue haze, and changes in color perception) secondary to the relative selectivity of sildenafil for the PDE6 isozyme found in both the rod and cone cells of the retina [21]. PDE type 6 plays an important role in the conversion of light impulses into nerve impulses in the retina (phototransduction) [37]. No chronic visual impairment has been reported, and the incidence of visual side effects was similar in diabetic and nondiabetic men [38]. Such visual disturbances have not been seen to persist beyond 6 h after administration of sildenafil and rarely constitute a reason to discontinue treatment [26]. In men with retinal diseases (retinitis pigmentosa, macular degeneration), an ophthalmologic consultation may be warranted before sildenafil treatment is initiated [22].

Patients with ischemic heart disease and hypertension experience a higher incidence of adverse events than diabetes (3.6, 2.3 and 1.9%, respectively) [39]. Clinical safety data pooled from more than 3,700 patients with 1,631 patient-years of exposure to sildenafil have shown that most adverse events were mild to moderate and self-limiting in nature by continuous use [40], with the drop-out rate due to adverse events similar to placebo [41]. The incidence of adverse effects tends to increase with larger doses [31]. A major concern with use of sildenafil is its interaction with organic nitrates, such as nitroglycerine or volatile nitrates (isoamyl nitrite and "poppers") [42]. The combination of nitrates and any PDE5 inhibitor can lead to a potentially serious fall in systemic blood pressure and thus sildenafil is contraindicated in patients who are using nitrates, regularly and/or intermittently, for cardiovascular disease [43]. Despite this fact, many patients appear to be willing to accept this risk, obtaining and using PDE5 inhibitors against the recommendation of their physician, if it means that they can regain even some degree of sexual function [35]. The consensus report published in conjunction by the American College of Cardiology and the American Heart Association examining the safety of sildenafil recommended that, after men take sildenafil, a minimum of 24 h must pass before nitrates can be used to relieve angina or other potentially life-threatening cardiovascular situations [42]. Clinical trials and postmarketing data of all available PDE5 inhibitors have demonstrated no increase in myocardial infarction rates in patients who received these agents as part of either double-blind, placebo-controlled trials or open-label studies, or compared with expected rates in age-matched populations of men [44]. If a patient develops angina while taking sildenafil, other agents may be administered instead of nitroglycerine until the appropriate time has passed and this is true for all available PDE5 inhibitors [25]. In response to the rising concern of physicians, the American Heart Association published guidelines for sildenafil therapy which is shown in Table 44.2 [45]. One proposed rule of thumb is that patients who have cardiovascular disease may be stratified into high, intermediate, and low risk; low-risk patients may be treated with first-line agents,

Table 44.2 Sildenafil use recommendations for men with cardiac disease [45]

Sildenafil is absolutely contraindicated in men taking long-acting or short-acting nitrate drugs
If the man has stable coronary disease and does not need nitrates regularly, the risks of sildenafil should be carefully discussed with him. If the man requires nitrates because of mild to moderate exercise limitation due to coronary disease, sildenafil should not be given
All men taking an organic nitrate (including amyl nitrate) should be informed about the nitrate–sildenafil hypotensive interaction
Men must be warned of the danger of taking sildenafil 24 h before or after taking a nitrate preparation
Before sildenafil is prescribed, treadmill testing may be indicated in some men with cardiac disease to assess the risk of cardiac ischemia during sexual intercourse
Initial monitoring of blood pressure after the administration of sildenafil may be indicated in men with congestive heart failure who have borderline low blood pressure and low volume status and men being treated with complicated, multidrug antihypertensive regimens

Table 44.3 Cardiac risk stratification [46, 152]

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic ≤3 risk factors for CAD – excluding age and gender	Asymptomatic but >3 risk factors for CAD – excluding age and gender	Severe or unstable or refractory angina
Mild valvular disease	Recent MI or CVA (i.e., within last 6 weeks)	Recent MI or CVA (i.e., within last 14 days)
Controlled hypertension	LVD/CHF (II)	Uncontrolled hypertension (SBP > 180 mmHg)
Minimal/mild stable angina	Moderate stable angina	High-risk arrhythmias
CHF (I)	Murmur of unknown origin	Hypertrophic cardiomyopathy
Postsuccessful coronary revascularization	Heart transplant	CHF (III, IV)
	Recurrent TIAs	Moderate/severe valve disease

CAD coronary artery disease; *CHF* congestive heart failure; *MI* myocardial infarction; *CVA* cerebral vascular accident; *LVD* left ventricular dysfunction; *TIA* transient ischemic attack; *SBP* systemic blood pressure

whereas high-risk patients (patients who have unstable angina, uncontrolled hypertension, or a myocardial infarct or stroke within the last 2 weeks) should have their cardiovascular status stabilized before resuming sexual activity [46] (Table 44.3).

The administration of sildenafil in doses greater than 25 mg should be postponed for at least 4 h after taking any alpha adrenergic antagonist [47, 48]. The interactions that may result are more pronounced when sildenafil is given to healthy volunteers not previously taking alpha blockers, but are rarely of clinical significance when the drugs are not started simultaneously [27]. Nevertheless, concomitant use of selective alpha blockers does not present a risk for significant hypotension [49]. Coadministration of all PDE5 inhibitors including sildenafil with other antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium blockers, beta-blockers, diuretics) may result in small additive drops in blood pressure, which are usually minor [25]. Generally, the adverse event profile of sildenafil is not worsened by the concomitant use of antihypertensive medicines [27]. Adverse events and safety data for sildenafil are shown in Table 44.1.

Tadalafil

Tadalafil is a more recently approved PDE5 inhibitor which is distinguished by its long-acting property. It is available in 10 and 20 mg doses with a recommended starting dose of 10 mg taken 30 min to 12 h prior to anticipated sexual activity. The dose can be increased to 20 mg if necessary [50]. In January 2008, the FDA approved the use of once-daily tadalafil at doses of 2.5 and 5.0 mg for men who anticipate more frequent sexual activity [24]. McMahon showed that in patients who were unresponsive to on-demand tadalafil, treatment with daily tadalafil significantly improved all treatment outcomes [51]. This improvement is probably related to improved endothelial function [52]. It is effective from 30 min after administration, but its peak efficacy is expected in about 2 h time [26]. Efficacy is maintained for up to 36 h [53]. Patients have been shown to respond even after 36 h and this may offer them more freedom in choosing when to initiate sexual activity as well as engaging in sexual activity more than once after a single administration of tadalafil [54]. Its efficacy is not affected by food or standard doses of alcohol [55, 56]. Tadalafil is predominantly eliminated by the liver, mostly by cytochrome P450 3A4 [21]. The pharmacokinetic properties of tadalafil are discussed in Table 44.1.

Side effects encountered with tadalafil are generally mild in nature, self-limiting by continuous use, and the drop-out rate due to adverse events is similar to placebo [56]. Although they share common side effects, tadalafil differs from sildenafil in its lack of inhibition of PDE type 6 [33]. The FDA reports that tadalafil induces

somewhat less flushing than the other medications, but may result in pain at different sites, most prominently the back and limbs, and may result in general myalgia [20]. Cross-inhibition of PDE type 11 is theorized to be responsible for myalgia and back pain [55]. Because PDE type 11 is found in the testis, safety concerns regarding effects on sperm were raised; however, a study conducted in men older than 45 years revealed no effect on spermatogenesis or reproductive hormones after administration of tadalafil (10 and 20 mg) for 6 months [57]. Tadalafil is contraindicated in patients who are using nitrates, regularly and/or intermittently. In patients taking tadalafil who require nitrate administration for a life-threatening cardiovascular situation, a minimum of 48 h should pass between dosing with tadalafil and administration of nitrates [58]. Tadalafil is contraindicated in patients taking alpha blockers, except for tamsulosin 0.4 mg [59]. More recent updates, however, stated that for patients currently stabilized on alpha adrenergic antagonist therapy, it is advised that tadalafil be initiated at the lowest recommended starting dose. Likewise, when initiating alpha adrenergic antagonist therapy in patients whose tadalafil therapy is already stabilized at a specific dose, the lowest possible starting dose should be prescribed and dosage titration should be closely monitored [35, 60]. Adverse events and safety data for tadalafil are shown in Table 44.1.

Vardenafil

Vardenafil is another PDE5 inhibitor, with higher in vitro potency (tenfold), more rapid binding to PDE5, and slower dissociation from this enzyme than sildenafil or tadalafil [61, 62]. Its higher potency, however, does not necessarily imply greater clinical efficacy [63]. It weakly inhibits PDE type 6, but does not inhibit PDE type 11 to any significant degree [37]. Vardenafil has demonstrated efficacy in patients who have previously undergone radical prostatectomy for localized prostate cancer and in patients with diabetes [64, 65]. It is available in 2.5, 5, 10, and 20 mg doses. The recommended starting dose is 10 mg taken as needed approximately 25–60 min before sexual activity and, as with all PDE5 inhibitors, with sexual stimulation which is a prerequisite [21]. It acts within 30 min and lasts for at least 8 h [66, 67]. As with sildenafil, the absorption of vardenafil is delayed if taken after a meal containing >30% fat [28]. Therefore, patients should be advised to use vardenafil with an empty stomach, to maximize its efficacy [66]. It is metabolized primarily in the liver by CYP3A4 and, to a lesser extent, by 2C9 isoforms [68]. Vardenafil shares similar pharmacokinetic properties with sildenafil and are presented in Table 44.1.

Vardenafil has similar side effects profile to sildenafil with headache, cutaneous flushing, dyspepsia, and rhinitis being the most common [65, 69]. The drug has also been associated with minor visual disturbances, mainly transient increases in brightness and haziness [21]. Based on clinical findings to date, visual disturbances do not seem to be a major problem with vardenafil [70]. Treatment emergent adverse events are generally of mild to moderate intensity and rapidly decreased during long-term treatment with a drop-out rate similar to placebo [68, 71]. Vardenafil is contraindicated in patients who are using nitrates, regularly and/or intermittently. If vardenafil is taken and the patient develops chest pain, nitroglycerine must withheld for at least 24 h [25]. Vardenafil is not recommended in patients who take type-1A antiarrhythmics (quinidine or procainamide) or type-3 antiarrhythmics (sotalol or amiodarone) or in patients who have congenital prolonged QT syndrome due to its effect on the QT interval [20, 24]. Vardenafil can be used at any time with tamsulosin [72]. On the other hand, it should only be initiated at the lowest dose, only if the patient is stabilized on other alpha blocker therapy, and dosing of the two drugs should be separated by at least 4 h [72]. Likewise, when initiating alpha adrenergic antagonist therapy in patients whose vardenafil therapy is already stabilized at a specific dose, the lowest possible starting dose should be prescribed and dosage titration should be closely monitored [35]. Adverse events and safety data for vardenafil are presented in Table 44.1.

Nonarteritic Ischemic Optic Neuropathy

Spontaneous nonarteritic ischemic optic neuropathy (NAION) is the most common acute optic neuropathy and ranks second only to glaucoma as a cause of acquired optic neuropathy for men aged 50 years and older [73]. The vast majority of patients do not become legally blind, but the degree of visual acuity and visual field loss is usually significant [74]. Recent media reports have linked PDE5 inhibitor use to a small increase in the incidence of NAION which is felt to be unrelated to PDE6 inhibition [24, 75]. As of May 2005, there were 43 cases of NAION reported to the FDA after the use of PDE5 inhibitors, including 38 associated with sildenafil, 4 with tadalafil, and 1 with vardenafil [24, 76]. The FDA noted that most, but not all, of the individuals had underlying anatomic or vascular risk factors for the development of NAION [24]. Since risk factors for NAION include age over 50, heart disease, diabetes, hypertension, dyslipidemia, nicotine use, and a congenital predisposition, patients at risk of NAION would be the patients more likely to suffer from ED and require a PDE5 inhibitor [75]. Review of safety data from over 100 clinical studies of sildenafil did not identify any cases of NAION, with similar findings have been reported with vardenafil and tadalafil [73, 77, 78]. At present, the FDA have concluded that there is insufficient data to establish a causal effect; however, patients need to be appropriately counseled [24]. Men should be instructed to stop taking any PDE5 inhibitor at once and contact their physician if visual changes or loss occur and any man who reports a history of NAION should not be prescribed any of these medications.

Sudden Sensorineural Hearing Loss

Sudden sensorineural hearing loss (SSHL) is a relatively common condition with an estimated incidence of 10/100,000 people per year [79] and is considered to be generally of idiopathic ideology [80]. In 2006, Mukherjee and Shivakumar were first to report a case of bilateral SSHL in a patient taking sildenafil [81]. This report prompted the FDA to investigate its database of adverse events and discovered 29 other reports of sudden hearing loss in patients taking PDE-5 inhibitors [80]. The problem was sometimes accompanied by tinnitus, vertigo, or dizziness and in most cases the hearing loss involved one ear [82]. It was temporary in approximately one third of patients and ongoing in the remaining patients at the time of the report [83]. The FDA mentioned that medical follow-up information was often limited for the reported cases, which makes it difficult to determine whether these reports are directly related to the use of one of these drugs, an underlying medical condition, other risk factors for hearing loss, a combination of these factors, or other factors [82]. Although there is currently no direct evidence for a mechanism of this side effect, Maddox et al. postulated that it is related to the prolonged effects of intracellular cGMP within the cochlea [80]. Based on its review of these unpublished cases, the FDA now requires more prominent labeling of this potential side effect to consumers. The revised label will advise clinicians to let patients know that sudden hearing loss may be due to the drug and to stop taking the drug and seek medical attention if they experience any sudden decrease or loss of hearing [82].

PDE5 Inhibitors Failures

Approximately 30–35% of patients are nonresponders to PDE5 inhibitors [52]. The reported 62% prescription renewal rate at 3–4 months of follow-up, which drops to around 30% by 6–12 months, suggests that patients stop taking the drug for reasons other than failure of treatment [84]. Before moving to second-line treatments which are more invasive in nature, some strategies may be pursued to salvage these nonresponders. Several measures are described in the literature and they are summarized in Table 44.4.

Table 44.4 Measures to salvage PDE5 inhibitors nonresponders

Adequate patients follow-up, ideally within 6 weeks of commencing therapy [72]
Patient reeducation and counseling on the correct use of the medications [52, 153, 154]
Adequate sexual stimulation
Timing of administration and response to medications
Food interactions
Exposure to a minimum of 4 doses before optimal response occurs (taken sequentially, not concurrently)
Dose optimization to a maximum dose to achieve maximum response [52, 72]
Daily dosing [51]
Switching oral agents [155]
Chronic usage [156, 157]
Optimization of comorbid conditions and modifiable risk factors [158]
Management of concurrent hypogonadism if no contraindication [159, 160]
Combination with non-PDE5 agents that act synergistically [52]
Combined psychosexual therapy [161]
Referral to erectile dysfunction specialist [52]

Dopamine Receptor Agonists

Apomorphine

Apomorphine is a centrally acting nonselective dopamine receptors agonist with modest efficacy and good tolerability [85]. Oxytocinergic neurons located in the paraventricular nucleus and medial preoptic area of the hypothalamus are rich in these receptors and the administration of apomorphine activates them, which subsequently induces a cascade of events that reach the periphery and causes penile erection [28]. The oral route of administration of this drug is undesirable because of the high degree of hepatic metabolism [86]. It has a rapid speed of action with 10–25 min to erection onset [70]. The most common adverse events are nausea/vomiting, headache, and dizziness [87]. Since it is a potent emetic, apomorphine was reformulated into a sublingual preparation, allowing a lower dose, which is administered on demand in 2 or 3 mg doses [88]. Interestingly, patients who experienced nausea seemed to develop a tolerance because the majority of these episodes occurred only in the first few administrations [86]. Clinical trials revealed that apomorphine possesses greater efficacy than placebo in men with ED [87]. Efficacy rates (erections sufficient for intercourse) range from 28.5 to 55% [87, 89, 90]. The drug is only available in certain non-US markets.

Adrenergic Receptor Antagonists

Yohimbine

Yohimbine is an alpha-2-adrenergic–receptor antagonist produced in the bark of Yohimbe trees and presumably acts at the adrenergic receptors in brain centers associated with libido and penile erection [22]. Its effect on erectile function is at best marginal and may be more useful in patients with psychogenic than with organic ED [20, 70]. A metanalysis of seven randomized, placebo-controlled studies of 419 men with ED from various causes found that yohimbine was better than placebo for all types of ED combined, and its effects were most noticeable with respect to nonorganic ED [91]. A controlled randomized study of patients with organic ED taking 18 mg of yohimbine per day showed no significant difference from placebo [92]. Side effects include gastrointestinal intolerance, headache, palpitation, fine tremor, elevation of blood pressure, and anxiety [20]. Since this agent may induce nervousness, it is contraindicated in patients who are under psychiatric care and/or are taking

antidepressants [70]. The place of yohimbine in therapy for ED has been dismissed by the American Urological Association Clinical Guidelines Panel on ED [93].

Phentolamine

Oral administration of 40–80 mg of the alpha1 and alpha2-antagonist phentolamine has been shown to improve erections in 37–45% of men, respectively, vs. 16% of those receiving placebo [94]. The time to maximum concentration is 30–60 min, and the half-life is 5–7 h requiring patients plan their sexual activity [95]. Reported side effects include headache, facial flushing, and nasal congestion [22]. Oral phentolamine has failed to obtain FDA approval, although it is available in several South American countries.

Serotonergic Receptor Agonists

Trazodone

Trazodone is a serotonin antagonist and reuptake inhibitor, used as a sedative and antidepressant [22]. It is associated with the unusual side effect of spontaneous priapism and has been used empirically for the treatment of ED [96]. Its effect on erection is thought to be the result of serotonergic and alpha-adrenolytic activity [22]. The medication is used at a dose range of 50–200 mg orally each night at bedtime (no relationship to timing of intercourse) with the most common side effects being drowsiness, fatigue, and dry mouth [96]. The drug has been shown to enhance nocturnal erections [97] and was reported to improve ED when combined with yohimbine [98]. Nevertheless, trazodone's beneficial effects could not be substantiated in a double-blind, placebo-controlled, multicenter trial using a dose of 150 mg/day [99]. In addition, its sedative effect may render sexual activity more difficult [31]. This agent may be useful not to treat sexual dysfunction, but as an alternative for antidepressant-induced ED [88].

Other Oral Agents

Androgen replacement therapy may be of benefit to those with hypogonadism and ED and is discussed elsewhere in this book. A number of other oral agents have been used in the treatment of ED with various mechanisms of action [100]. Examples include delequamine (selective alpha2-adrenergic antagonist), l-arginine (NO donor), nalmefene/naltrexone (opioid-receptor antagonist), limaprost (alprostadil derivative), red Korea ginseng (unknown mechanism of action), and melanotan-II (a cyclic analog of alpha melanocyte-stimulating hormone) [25, 101]. Excluding androgen replacement, there is no place for the above-mentioned drugs in the treatment of ED since efficacy data are lacking [25, 101].

Transdermal Agents

Nitroglycerine cream or paste; alprostadil cream; and a cream containing aminophylline, isosorbide dinitrate, and codergocrine mesylate have been applied to the penile shaft to induce erection in pilot studies with varying results [102, 103]. In order to overcome the poor drug absorption through the thick and dense tunica albuginea, several drug absorption enhancers have been developed for combination with these vasoactive drugs [104]. Although tumescence has been documented with these agents, it is usually suboptimal and inadequate for vaginal penetration [105]. In addition to local adverse events such as glans erythema, burning sensation, and allergic reactions, systemic side effects such as hypotension and headaches are frequent and contamination of the partner is a potential problem [101]. Currently, no topical therapy has been approved and their role in the treatment of ED is unknown.

Intracavernosal Agents

ICI therapy is considered the most effective form of pharmacotherapy for ED and has been used for more than 20 years [106]. It is regarded as a

second-line treatment for ED secondary to its invasive local administration, but should be considered when oral treatment fails. The medication is usually delivered through the tunica using a 27-gauge or smaller needle at the lateral aspect of the penile shaft. The advantage over currently available oral agents is that these medications bypass the need for neural input of NO, and thus, patients with a largely neurogenic form of ED (postradical prostatectomy) who fail oral therapy are often successfully treated with low-dose ICI. ICI therapy can be broadly classified into four main groups: alpha-adrenoreceptor blocking agents, phosphodiesterase inhibitors, adenylate cyclase activators, and combination therapy.

Alpha-Adrenoreceptor Blocking Agents

Phentolamine

Phentolamine (0.25–2 mg) is a competitive alpha 1 and alpha 2-antagonist and a direct relaxant of smooth muscle. It has a plasma half-life of about 30 min, and it is almost totally metabolized before excretion [96, 107]. When used alone, phentolamine is minimally effective in producing penile erection [108]. It is best used in combination with other agents to augment efficacy, primarily papaverine [109]. Its major side effects include hypotension and reflex tachycardia [22].

Phosphodiesterase Inhibitor

Papaverine

Papaverine is a nonspecific phosphodiesterase inhibitor that increases cyclic adenosine monophosphate (cAMP) and cGMP concentrations in penile erectile tissue with subsequent smooth muscle cell relaxation [110]. The usual dose ranges from 15 to 80 mg [22, 72]. Its plasma half-life is 1–2 h, and its final metabolism occurs in the liver, which may result in reversible liver transaminase elevation [96]. It is more effective in psychogenic and neurogenic ED compared with vasculogenic etiology [20]. As a monotherapy, it produces adequate erections in fewer patients; however, it may be of use in patients suffering from spinal cord injury or neurologic disease, who tend to be younger than the average ED patient and need smaller doses of the agent for efficacy [111]. Because of its relative slow corporal clearance, it has been suggested there is a potential for priapism (persistent unwanted erection), which is reported in 0.5–6% of patients [112]. In addition, papaverine is an acidic substance (pH 3–4) and precipitates at a pH greater than 5 and it has been suggested that it may lead to corporal fibrosis, although robust evidence in favor of this is scant [113]. Its advantages; however, include its low cost and stability at room temperature [22]. Currently, its main use is in combination therapy.

Adenylate Cyclase Activators

Alprostadil (Prostaglandin E 1)

Alprostadil, a natural prostanoid synthesized from the lipid precursor dihomo-*a*-linoleic acid, is a more stable and synthetic form of prostaglandin E 1 (PGE1) [86]. It causes corporal smooth muscle relaxation and subsequent vasodilation by acting on adenylate cyclase to increase the intracellular cAMP concentration [114]. In addition, it may also inhibit the release of noradrenaline from penile adrenergic nerves [115]. As a monotherapy, alprostadil has the highest efficacy of any of the individual agents and results in erections in more than 70% of treated men [116]. The majority of patients will achieve a satisfactory response at a dose of 10–20 μg, but the dose ranges from 5 to 40 μg [25, 72, 117]. The erection occurs typically after 5–15 min and lasts according to the dose injected [25, 72]. Intracavernously injected alprostadil is largely metabolized by the enzymes of the cavernous tissue and has a

half-life of 5–10 min [118]. Any remaining drug that escapes local degradation is metabolized to inactive metabolites in the lungs (as much as 90% by the first pass) [119]. The inactive metabolites are degraded further in the liver and cleared through the kidneys [106]. The drug appears to be more effective, and smaller doses may be needed, in patients with neurogenic or psychogenic ED or spinal cord injury [120]. On the other hand, those with diabetes or venous leak may be less sensitive (responsive) to PGE1 alone compared with other ED patients and thus higher doses may be required [70]. Alprostadil ICI is also found to restore the ED patient's ability to experience spontaneous erection by enhancing penile hemodynamics [121]. Possible mechanisms of recovery include reduction in performance anxiety in those with psychogenic ED, episodic variations, improved cavernous hemodynamics, improved cavernous oxygenation, and prostaglandin-induced angiogenesis [31]. The most significant adverse factors are pain at the injection site or along the shaft of the penis during erection (7–50% of patients) and high cost [118, 122]. The hyperalgesic effect is most prominent in men who have partial nerve injury, such as patients who have diabetic neuropathy or after radical lower abdominal and pelvic surgery [123]. The drug has a relatively low incidence of priapism and corporal fibrosis and exhibits very few systemic effects [106, 120, 124].

Other Intracavernosal Agents

Other drugs that have been used in ICI therapy include vasoactive intestinal peptide (VIP), NO donors (linsidomine and sodium nitroprusside), forskolin, potassium channel openers, moxisylyte, and calcitonin gene-related peptide (CGRP), mostly in combinations with papaverine, phentolamine, and/or alprostadil [101, 125–127]. Sparse data in the literature support the use of these agents. In addition, most of the combinations are not standardized and some drugs have limited availability worldwide.

Intracavernosal Agent Combinations

The rationale for combination treatment is to take advantage of different modes of action leading to better effectiveness as well as to minimize side effects by using lower doses of each individual drug. In addition, the cost effectiveness is better since the doses of the single compounds can be decreased when these are used within a combination. The papaverine/phentolamine combination (Bi-mix) has been used with success rates ranging between 63 and 87% [111, 128]. Currently, the most common dose of Bi-mix is 30 mg papaverine and 0.5–1.0 mg phentolamine [31]. The Bi-mix combination has been also shown to be effective in older patients [129].

The success of Bi-mix stimulated interest in combination "cocktails" with alprostadil. Two-drug combinations such as phentolamine/alprostadil and papaverine/alprostadil have been shown to be very effective and superior to alprostadil alone [130, 131]. It was not until 1991 when Bennett et al. introduced a three-drug mixture (Tri-mix) containing 2.5 mL papaverine (30 mg/mL), 0.5 mL phentolamine (5 mg/mL), and 0.05 mL alprostadil (500 μg/mL) with a reported success rate of 92% in 116 patients [132]. The Tri-mix combination has become popular owing to its high efficacy, lower incidence of pain, and lower cost per dose. The incidence of penile pain is lower (due to lower doses of alprostadil); however, fibrosis is reported to be more common (5–10%) when papaverine is used (depending on total dose), and mild hepatotoxicity has been reported with papaverine [25, 133]. Of interest, smaller volumes of injections are needed with this triple combination therapy than with the individual treatments [111]. The usual dose of Tri-mix solution ranges from 0.1 to 0.5 mL [20, 22, 25]. Many clinicians, however, reserve the Tri-mix regimen for men with vascular ED who fail therapy with alprostadil, or the papaverine/phentolamine combination, or for patients who experience severe penile pain with alprostadil injections [106]. In spite of its widespread use, Tri-mix is not approved by the FDA. A 4-drug regimen that includes papaverine, phentolamine,

alprostadil, and atropine has been described by Montorsi et al. who obtained excellent results in 94 patients with a response rate of 96% [134]. Other agents used in certain settings of ICI therapy include VIP plus phentolamine. This combination, which is highly effective but results in vasoactive side effects (flushing) in 70–80% of patients, is currently available in some non-US markets and is undergoing trials in the USA at the moment [70].

Despite high efficacy rates, 5–10% of patients will not respond to combination ICI therapy [25]. McMahon et al. showed that the combination of sildenafil with ICI injection of the triple combination solution can salvage as many as 31% of patients not responding to the triple combination alone [135]. However, 33% of patients reported adverse events (including a 20% overall incidence of dizziness), which were largely mild to moderate in severity and responsible for the discontinuation of treatment in 14% of patients who responded to combined treatment. It appears that combined oral PDE5 inhibitors and ICI therapy, while not approved, can salvage men not responding to ICI therapy alone and should be discussed with carefully selected patients before consideration of penile prosthesis surgery [72]. Alternatively, in men for whom ICI therapy alone fails or is insufficient, its use in combination with a vacuum constriction device has been suggested [20].

Important Aspects of Intracavernous Injection Therapy

Prior to any ICI therapy, patients must be completely informed about the pros and cons of this treatment modality. Men (and possibly their partners) must receive adequate training and education by medical personnel before commencing home injections. Trial injection using a low dose of the desired agent or combination must be performed at the physician's office with a goal to produce an in-clinic erection of a maximum of 60% (barely adequate for penetration) that lasts for less than 1 h [70, 96]. Ideally, several office visits should take place to ensure that the patient is comfortable and competent with ICI. Patients must be able to understand the importance of proper administration and be dependable enough to take appropriate action should a side effect arises. Instructions on how to administer ICI therapy are summarized in Table 44.5.

There is a major side effect of ICI which is priapism. Priapism is usually preventable through careful dose adjustment [22]. Nevertheless, patients must be informed that prolonged erections constitute a medical emergency and any erection that lasts longer than 4 h that is not relieved by ejaculation requires a visit to the emergency department. Management of priapism is discussed in detail elsewhere in this book. Fibrotic changes have been reported and present as palpable nodules or plaques on or within the tunica albuginea. It is unclear if these changes represent Peyronie's disease and whether they are the direct result of ICI or not. To prevent fibrosis, men are instructed to compress the injection site for 3–5 min (up to 10 min in men taking anticoagulants) [20]. In addition, changing the site of injection with each dose may help to minimize the chance of scarring [96]. If fibrotic plaques or nodules are noticed on follow-up visits, ICI may be withheld until these changes regress, which may take several months [106]. Penile pain, which is reported with alprostadil injection, is usually self-limited after prolonged use [25]. Some investigators advocate mixing alprostadil with local anesthetics such as procaine or 1% lidocaine to ameliorate the pain [136, 137]. The addition of sodium bicarbonate to the solution to produce a neutral pH has been tried with some success [138]. Others suggest that injecting the medication more slowly over 60 s can decrease pain [31]. Another important aspect of ICI is needle phobia. Some patients prefer to use an autoinjector that avoids a view of the needle and can help with the fear of penile puncture [72]. Some men choose to alternate ICI with a PDE5 inhibitor or an intraurethral suppository, preferring injection in circumstances when an erection of longer duration is desired [20]. Well-versed nurses or other assistants, as well as educational videotapes, booklets, and telephone hotlines, can be

Table 44.5 Instructions on how to administer ICI therapy [28, 31, 70, 86, 96, 104]

Ensure a relaxed atmosphere
Prepare a conventional insulin-type syringe
Draw up the desired drug using a fine gauge needle (27–30 gauge)
Start with a small dose or as directed by the physician
Automatic self-injection system may be used instead
Clean the phallus
Cleanse the intended area of injection with an alcohol swab
The needle is inserted using a quick entry up to the hilt of the needle, so that the tip reaches the center of the right or left corpus cavernosum
The injection is at a 90-degree angle to the skin given at the ten or two o'clock position (away from the ventrally located urethra), away from visible veins, and never in the midline
Immediately after injection, the base of the penis is squeezed firmly between the right thumb and index finger, while the accessible portion of the penis is massaged for up to 5 min by squeezing it laterally along the length of the shaft between the left thumb and index and middle fingers, thus distributing the drug throughout the shaft
Inject the right and left cavernosal body alternately
If the injected dose does not produce a satisfactory erectile response, the dose is slightly increased with the next injection under clinician supervision
The titration process proceeds until the optimum dose is identified or the maximum injected volume is reached
Limit the use of injection to 3 times a week, with no more than one injection in any 24-h period
Refrigerate the drug or mixture if it contains PGE1
Examine the drug or solution for changes in color or the formation of a precipitate
Must seek prompt medical attention for prolonged erections (>4 h)

helpful resources for patients who have difficulty or concerns regarding this technique [70].

The use of ICI therapy is relatively contraindicated in patients with hyperviscosity syndrome (multiple myeloma, polycythemia, sickle cell disease or trait), schizophrenia or a severe psychiatric disorder, bleeding disorders, and a history of hypersensitivity to the agents used [22, 25, 139]. Anticoagulant therapy is not a contraindication to ICI, provided the prothrombin time or the international normalized ratio (INR) is within the therapeutic range [140]. In patients taking an anticoagulant or aspirin, compressing the injection site for 6–10 min after injection is recommended [31, 96]. For those with impaired vision, obesity, and poor manual dexterity, partner injection is advisable [70, 140].

Transurethral Therapy

A specific formulation of alprostadil in a medicated pellet (Medicated Urethral System for Erection [MUSE]) has been approved for use in ED patients [141]. The mechanism of action of transurethral alprostadil is based on its absorption from the urethra and transport throughout the erectile bodies by communicating vessels between the corpus spongiosum and the corpora cavernosa [28, 142]. MUSE consists of a polypropylene applicator with a hollow stem 3.2 cm in length and 3.5 mm in diameter. The tip (measuring 3 or 6 mm in length) contains a semisolid pellet of medication that is available in four dose strengths: 125, 250, 500, and 1,000 μg [104]. In two large, multicenter, double-blind, placebo-controlled clinical trials conducted in the United States and Europe, MUSE was effective in 43% of men with ED from various organic causes [141, 143]. In clinical practice, only the higher doses (500 and 1,000 μg) were encountered and consistency rates were low [144]. The application of an adjustable constriction device placed at the root of the penis may improve efficacy, cited as high as 69% in one study [145]. Transurethral therapy is slower to induce erection than ICI therapy [70]. Pharmacologic studies on the rate and extent of transurethral absorption of alprostadil have revealed that 80% of intraurethrally administered alprostadil is absorbed within 10 min [106]. The onset of

effect is within 5–10 min after administration and the duration is approximately 30–60 min before detumescence occurs [146]. Although the advantages of this approach include local application, minimal systemic effects, and the rarity of drug interactions [22], efficacy rates are significantly lower than ICI therapy [147]. It is then considered a second-line therapy, providing an alternative to ICI in patients who prefer a less invasive, but less efficacious, treatment.

A starting dose of 500 or 1,000 μg is usually used [96], which can be titrated up or down depending on response. The patient is instructed to urinate immediately before administration, because the medicated pellet has been developed specifically to dissolve in the small quantity of urine that remains in the urethra after urination [104]. This also lubricates the urethra and makes the administration of the suppository easier. The use of a small drop of K-Y jelly at the meatus facilitates insertion of the applicator as well. The stem of the applicator is inserted into the distal urethra. A button is depressed to deposit the pellet. A gentle rocking of the applicator from side to side will separate the medicated pellet from the applicator tip. To minimize venous leak and promote intracavernosal absorption, the patient is instructed to stand while the medication is absorbed. After removing the applicator, massaging the penis for 30–60 s allows the compound to distribute and be absorbed fully. If a constrictive ring to be used, it should be placed snugly around the base of the penis immediately before applying the suppository to slow venous return from the penis and to permit drug exposure for a longer period of time [106]. The first application should take place in the physician's office. As with ICI therapy, transurethral therapy may require extensive patient education and office visits to optimize therapeutic outcomes. In our experience, about 50% of the patients respond to some extent, significantly lower than that with direct intracorporal injections.

The most common side effects are local penile pain and urethral pain or burning [141, 143]. Other less common side effects include vasovagal reflex, hypotension, and priapism (occurring in <0.1%) [106, 148]. Urethral bleeding and urinary tract infections are adverse events related to the mode of administration and faulty technique [70]. The female sexual partner may experience vaginal burning or itching during unprotected intercourse [31]. MUSE has been shown to be embryotoxic when administered subcutaneously to pregnant rats and, thus, a condom barrier is strongly recommended if the female partner is pregnant [31, 106]. Contraindications to intraurethral alprostadil are summarized in Table 44.6.

Table 44.6 Contraindications to intraurethral alprostadil [31, 106]

Hypersensitivity to alprostadil
Inflammatory urethral diseases, such as acute or chronic urethritis
Abnormal penile anatomy
Severe hypospadias
Penile curvature
Urethral stricture
Balanitis
Propensity for priapism
Leukemia
Polycythemia
Thrombocythemia
Multiple myeloma
Sickle cell anemia
Conditions that make sexual activity inadvisable, such as acute myocardial infarction
Sexual intercourse during pregnancy, unless the couple uses a condom barrier

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Chapter 45
Erectile Dysfunction: Devices

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Keywords Penile implant • Inflatable • Non-inflatable • Malfunction • Infection • Vacuum device

Introduction

Normal male erectile function results from a complex interplay of neurologic, vasculogenic, endocrinologic, and psychologic influences. Misfired neurotransmitters, damaged blood vessels, altered hormone levels, or simple wayward thoughts can derail the erectile process, and men stricken with erectile dysfunction often present with a combination of these and other pathologic processes. Indeed, erectile dysfunction is a multifactorial condition, which is further complicated in the setting of cancer, a systemic disease that can disrupt virtually every normally-functioning organ system during its progression as well as its treatment. Inability to perform sexually profoundly impacts cancer patients, many of whom are already significantly displaced from normalcy by their malignancy and are saddled with anxiety regarding their cancer diagnosis.

As described in earlier chapters, treatment strategies for organic erectile dysfunction (ED) in the male cancer patient routinely begin with pharmacologic intervention. In our practice, oral phosphodiesterase type-5 (PDE-5) inhibitors, intraurethral prostaglandin pellets, and intracavernosal injection of vasoactive agents represent a stepwise pathway of medical therapy, and generally a patient that fails one treatment will progress to the next. Hypogonadal men are evaluated and treated with testosterone replacement. During PDE-5 inhibitor treatment, the vacuum erection device (VED) is introduced and taught as an adjunct to medical therapy. For many patients, however, erectile dysfunction persists despite these therapies, and definitive surgical intervention in the form of penile prosthesis implantation is pursued.

Vacuum Erection Devices

Although Dr. Otto Lederer patented the first VED in the United States in 1917 [1], it took over a half-century for the first VED to be made commercially available for use by men with erectile dysfunction. This device was patented and produced by a tire salesman from Augusta, Georgia, Geddings Osbon Sr. [2], who named his invention the "Youth Equivalency Device" and marketed it toward older couples as a marital aid [3]. Osbon later renamed his device "ErecAid." In 1986, Nadig published the first peer-reviewed study using VED in men with organic impotence and found 32/35 (91%) were able to achieve erection adequate for vaginal penetration, leading to enthusiasm for this treatment option within the Urologic community [4]. A subsequent large-scale study of over 1,500 users confirmed a 92% rate of efficacy [5], and soon other similar VEDs

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appeared on the market. Several years later, in its recommendations for treatment of erectile dysfunction, the American Urologic Association mentioned VED therapy as an acceptable alternative to medical therapy [6].

The VED consists of two parts: a cylindrical tube of plastic closed at the far end by a pump mechanism and a series of penile constricting rings (Fig. 45.1). The open end of the tube is placed over the penis directly against the body wall, which is lubricated with water-soluble jelly creating of an air-tight seal. The patient then activates the vacuum pump (either manually or through battery power), and negative pressure generated within the tube pulls blood into the penis, engorging it and causing erection. When adequate rigidity has been reached, the constricting ring at the end of the pump is slid over the proximal penis to occlude venous backflow of blood and maintain tumescence. Sexual activity may then occur, and the constricting band is removed within 30 min to avoid ischemic or hypoxic injury to the penis (Fig. 45.2). Prior to using the device for sexual activity, instruction from a device company representative as well as practice with the device is preferable.

Due to the mechanism employed, erections produced by a VED differ from those produced physiologically. Blood flow into the portion of the corpora cavernosa closer to the body from the constricting ring is not occluded, and thus this area of the penis is mobile and can pivot on itself. Decrease in penile blood flow can lead to cyanosis and cooling of the penile skin and glans, sometimes accompanied by decreased penile sensation. Likewise some men experience pain, especially at the ring site and during the early stages of use while others can develop petechiae and bruising of the penis. Compression of the urethra by the constricting ring can also prevent

Fig. 45.1 Vacuum erection devices. (Courtesy of Augusta Medical Systems LLC, Augusta, GA, USA)

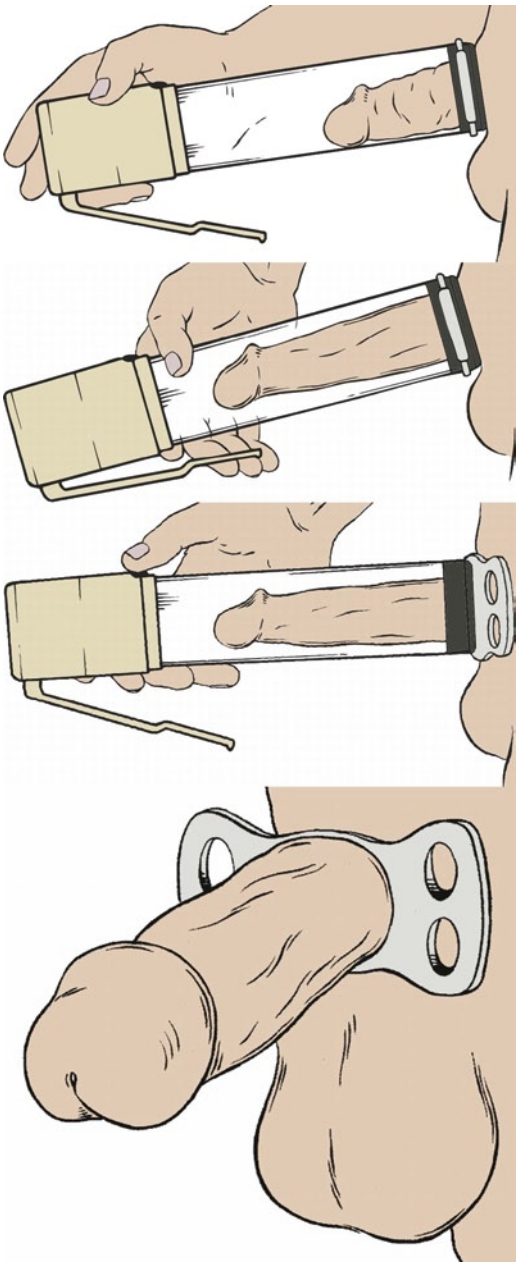

Fig. 45.2 Use of vacuum erection device. (Courtesy of Augusta Medical Systems LLC, Augusta, GA, USA)

ejaculation leading to "dry" orgasms. Men may have to shave their pubic hair to allow for an adequate seal from the cylinder. Patients with limited manual dexterity must rely on assistance from a partner to inflate the cylinder. Severe but rare complications of VED treatment have been reported and include skin necrosis [7], development of scarring and subsequent Peyronie's disease [7], testicular entrapment [8], urethral bleeding, and Fournier's Gangrene [9].

Despite these issues, the VED is generally well-tolerated and used successfully in men with erectile dysfunction. A review of seven published studies of VED as primary treatment for erectile dysfunction [10] showed success rates (ability to achieve erection adequate for intercourse) in those studies ranged from 52 to 100% in study populations numbering 26 to 5,847 patients [4, 11–15]. Along with high rates of success, studies have shown high levels of patient satisfaction and long-term use. An examination of questionnaire responses from men using the VED in short-term (median follow-up of 3 months) and long-term (median follow-up of 29 months) found regular use in 69% of the short-term group and 70% in the long-term group, and patient and partner satisfaction was 82 and 87%, respectively, in the short-term group, and 84 and 89% in the long-term group [17]. In a retrospective questionnaire-based study of 1,517 registered owners of Osbon vacuum devices, 77% reported using the VED at least every 2 weeks [5]; while a larger study of 5,847 registered owners found that 76% of these men were continuous users of the device and 84% had sexual intercourse as often as they desired. Furthermore, 65% had an improvement in self-image and 70% had an improved relationship with their partners [16]. Another report of 100 men at a mean follow-up of 8 months found a satisfaction rate of 68% [18]. Other studies, however, have suggested rates of acceptance of VED to be lower. In a group of 110 men with erectile dysfunction, only 54 accepted VED (49%) as a long-term treatment and after a median follow-up of 28 months, only 42% of patients were still using the device. Despite the decrease in device use, 98% of patients and 85% of their partners were satisfied with the therapy [19]. A prospective study of 129 men with ED, divided into three groups based on the severity of their disease, found only 35% rate of satisfaction with the device to continue long-term usage [20].

As discussed in earlier chapters, many patients with prostate cancer treated by radical prostatectomy experience sexual side effects after the procedure, including decreased or lack of erectile function as well as penile shortening. Several recent studies have evaluated the role of VEDs in this population. A prospective study published in 2006 randomized 109 men with erectile dysfunction after nerve-sparing or non-nerve-sparing radical prostatectomy to a 9-month period of either no intervention or daily VED usage (begun at a median of 4 weeks after surgery) [21]. In the group using VED, 80% of men reported successfully having had vaginal intercourse using the VED; 26% had a return of natural erectile function at 9 months, and 14% had natural erections sufficient for vaginal intercourse. This group had a statistically significant improvement in IIEF-5 score, a validated measure of self-reported indication of erectile function, and reported a spousal satisfaction rate of 55%. With regard to penile size, 65 and 85% of these patients were satisfied with their penile length and circumference, respectively, although 23% reported a decreased length and circumference at 6 months. In the 14 men who did not achieve erections with VED therapy and thereafter stopped using the device, 85% reported a perceived decrease in penile length. In the nonintervention group of 35 men, 37% of men regained spontaneous erections at a minimum of 9 months follow-up, however, in only 11% overall was the erection satisfactory for sexual penetration. The IIEF-5 score in these 13 patients was increased from baseline after surgery but was significantly lower than those in the VED group. Approximately 63% of patients reported a decreased penile length and circumference, and the overall spouse satisfaction was 54%. The authors concluded that early VED usage after radical prostatectomy facilitated sexual intercourse and patient/spousal sexual satisfaction as well as preserved perceived penile length and circumference, and potentially increased the return of natural erections sufficient for vaginal penetration.

Another study of 42 men with good preoperative erectile function undergoing radical prostatectomy examined daily VED use for 90 days beginning the day after urethral catheter removal [22]. At 3 months time, 97% of men that underwent measurement of stretched penile length (SPL) showed a loss of length of less than 1 cm. Of the three men who did have a reduction in SPL, two used the VED 25% or less of the possible days. The authors compared these findings to a previously published study from their group which found that 48% of men undergoing radical prostatectomy had a decrease in SPL greater than 1 cm at 3 months after surgery [23], and concluded that VED intervention significantly reduces penile shortening after radical prostatectomy.

Finally, Kohler and colleagues randomized 28 men undergoing radical prostatectomy to daily VED intervention starting either 1 month ("early VED") or 6 months ("late VED") after surgery. The study showed a preserved penile length in the early VED group versus a statistically significant loss in penile length of the late VED group at 3 and 6 months. At a mean of 9.5 months after surgery, after the late VED group had been using VED for several months, there was a nonstatistically-significant mean loss of penile length of 1 cm in this group, although several factors, such as earlier use of PDE-5 inhibitors in the late VED group and a small sample size, may have confounded these results. The early VED group also showed a significant improvement in IIEF scores at 3 and 6 months as compared to the late VED group, however, at the last recorded follow-up there was no overall difference in IIEF scores between the groups. Interestingly, once the late VED group began to use the device, the mean IIEF score in this group increased by greater than 4 points, an increase in function noticeable to the patient. The authors conclude that while sample size and potential confounders limit their study, the results indicate an early VED protocol after radical prostatectomy can help preserve penile length.

Published literature obviates a role for VED therapy in men with erectile dysfunction. VED provides an alternative to men for which surgery may not be possible due to medical comorbidities. It is also potentially more cost-effective than medical management as the patient pays a one-time fee for the equipment which may function for a number of years before needing to be replaced. Studies in general populations of men using VED have shown high rates of success in obtaining an erection satisfactory for penetration as well as adequate satisfaction among both patients and their sexual partners, with minimal side effects. Furthermore, studies of VED use in men with prostate cancer treated with radical prostatectomy suggest benefits to sexual rehabilitation of both improved erectile function as well as blunted loss of penile length after surgery. Thus, VED therapy is an important part of an urologist's armamentarium in the fight against erectile dysfunction.

Penile Implants

The era of penile prosthetic implantation was heralded by the Russian surgeon Nicolos A. Bogoras, who in 1936 described the reconstruction of an amputated penis with a graft made from tubularized abdominal skin into which he inserted a segment of rib cartilage to provide rigidity. This first penile prosthesis was adequate for both micturition and intercourse [24]. Surgeons faced with reconstructing penile amputations suffered by soldiers during the two World Wars employed this method with similar initial success, however, the development of complications such as cartilage resorption, infection, and significant curvature led to the search for a more permanent, synthetic material [25]. Over the next several decades, artificial penile implants made of acrylic and rubber were used with varying amounts of success.

In the early 1970s Small and associates, following the lead of contemporary plastic surgeon colleagues who were using silicone-gel filled breast implants, implanted into 31 patients with erectile dysfunction a new silicone-gel filled penile prosthesis placed directly into surgically dilated corpora cavernosa through a perineal incision [26]. The authors reported "excellent"

results in 27 patients and "good" results in one patient; they further concluded that their malleable prosthesis "closely mimicked" physiologic erection in shape and consistency, with the added benefit of providing extra width and length to the phallus. Just a year before Small's report, Scott and colleagues from Baylor College of Medicine published their experience using an inflatable penile implant in five patients with erectile dysfunction [27]. The design of the implant was based on the implantable artificial urinary sphincter they had described several months prior [28], and consisted of four pieces connected by tubing: a silicone rubber prosthesis consisting of two cylindrical erectile bodies placed in the corpora, a fluid-filled reservoir placed in the prevesical space of Retzius, and two separate inflation and deflation pumps placed in the scrotum. Two of these five patients could achieve erections satisfactory for intercourse while the other three patients were in the period of postoperative recovery at the time of publishing. The successes reported by Small and Scott helped pave the way for modern penile prosthesis implantation, and in the years that followed advancements in device technology and in surgical technique allowed penile implants to become more efficient, more reliable, and more easily implanted (Table 45.1).

Table 45.1 Currently available penile prostheses. (AMS – American Medical Systems, Inc., Minnetonka, MN, USA; Coloplast – Coloplast Corporation, Minneapolis, MN, USA)

Currently available penile prostheses
Mechanical
Dura II (AMS)
Semi-rigid rods
AMS 600M (AMS)
AMS 650 (AMS)
Spectra (AMS)
Genesis (Coloplast)
Two-piece inflatable
Ambicor (AMS)
Three-piece inflatable
AMS 700 (AMS)
Titan (Coloplast)

Noninflatable Penile Implants

Several decades have passed since the Small-Carrion malleable penile prosthesis, and although technologic advances have changed the composition of today's implants, the design of the prosthesis itself has changed little. Two types of semi-rigid implants exist: a mechanical prosthesis and a malleable prosthesis. Devices are placed into the corporal bodies using a simple subcoronal or penoscrotal incision. The procedure is straight-forward and in many cases is performed on an outpatient basis; after 4–6 weeks the patient is cleared to use his new prosthesis for intercourse.

The Dura II mechanical prosthesis, produced by American Medical Systems (AMS), consists of two cylinders composed of a central metal cable with articulating polyethylene segments covered with a sheath of silicone (Fig. 45.3). The prosthesis has a "gooseneck" design, which allows it to be positioned upward for intercourse or downward for concealment with minimal springback. The patient accomplishes this by curving the penis into the desired direction, and the positional memory of the device allows it to maintain the position with strong axial rigidity for penetration. The device comes in two different diameters, and extension tips can be added to match corporal length. Four different malleable prostheses are available currently in the United

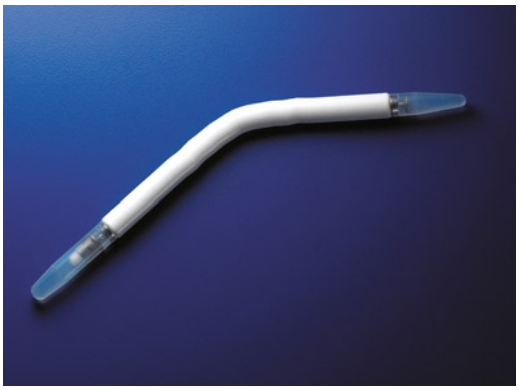

Fig. 45.3 The Dura 2 mechanical penile prosthesis. (Courtesy of American Medical Systems, Inc., Minnetonka, MN, USA)

States. AMS makes three models, the Spectra, the AMS 650 and AMS 600M, and Coloplast makes the Genesis implant (Figs. 45.4, 45.5). The basic design of these implants is the same; stainless steel wire core is surrounded by braided polyester suture, covered by a tapered silicone elastomer body. The Genesis implant is unique in that it offers a hydrophilic coating, which can be soaked in an antibiotic solution in the operating room prior to implantation. This antibiotic solution adheres to the implant, eluting the substance into the surrounding tissue bed and potentially allowing for easier implantation due to the lubricious nature of the device [29].

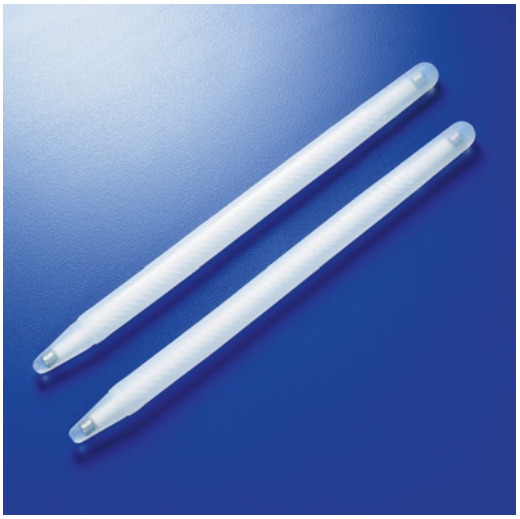

Fig. 45.4 The AMS 650 malleable penile prosthesis. (Courtesy of American Medical Systems, Inc., Minnetonka, MN, USA)

Fig. 45.5 The Coloplast Genesis penile prosthesis. (Courtesy of Coloplast Corporation, Minneapolis, MN, USA)

Noninflatable prostheses are well tolerated by patients who are generally satisfied with these devices. A long-term study of 85 patients receiving the Dura II mechanical implant found satisfactory rigidity and ease of concealing in 76 and 87%, respectively, at a mean of 5.7 years of follow-up. Continued sexual activity was reported by 76%, and 87% reported that the prosthesis improved their overall quality of life [30]. Because noninflatable implants are easy to use and require a minimal amount of manual dexterity, they are desirable options for patients with neurologic or musculoskeletal deficits, or morbid obesity. Kim and colleagues reported their experience with 48 patients with spinal cord injuries who received malleable penile implants, finding a 79% rate of patient satisfaction with the prosthesis as well as the added benefit of ease of applying a condom catheter or allowing for clean intermittent catheterization [31]. The lack of mechanical components makes these implants less prone to failure than the inflatable models, and the simplicity of design as well as of surgical implantation makes them a more affordable option as compared to inflatable prostheses.

Disadvantages of malleable prostheses include erosion, infection and potential for mechanical failure. A review of 372 malleable prosthesis implantations found a rate of 5% of erosion, 5% of infection, and 0.5% of mechanical failure in these patients [32]. Another drawback of the malleable implant is the persistent state of erection, a potential source of embarrassment for men who wear form-fitting athletic clothing or who shower in public at a health club or other athletic facility. Finally, although malleable implants are able to reproduce the increase in penile length seen with a normal male erection, they cannot provide the concomitant increase in penile girth, potentially limiting sexual satisfaction for patient and/or partner.

Inflatable Penile Implants

In contrast to malleable penile implants, which have changed little in design since their introduction, today's inflatable penile implants are markedly different than those first described by Brantley Scott in 1973. Advances in both technologic aspects of device design as well in surgical technique of implantation have helped make inflatable penile implants a reliable and safe option for the treatment of erectile dysfunction. The overwhelming advantage inflatable prostheses have over their semi-rigid cousins is the ability to simulate the physiology of the normal male erection. After implantation of an inflatable device, the penis can exist in its flaccid state in which the implant remains concealed with little evidence of its presence to the casual observer. Proper use of the device can be quickly and easily taught in the clinical setting; when the patient wishes to have an erection, he locates the hydraulic pump implanted into his scrotum, and after a few squeezes saline is transferred from the fluid reservoir into the implanted cylinders, expanding the phallus in both length and girth and providing an erection. When the sexual encounter has concluded, a deflation valve in the pump is activated, drawing the saline out of the cylinders and into the reservoir, leading to detumescence (Fig. 45.6).

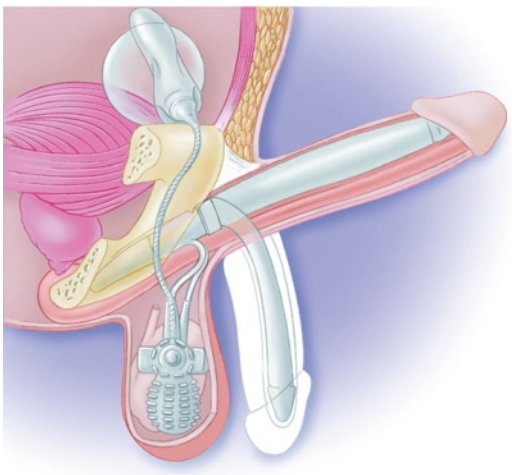

Fig. 45.6 The inflatable penile prosthesis. (Courtesy of American Medical Systems, Inc., Minnetonka, MN, USA)

Two types of hydraulically inflatable penile prosthesis exist today, two-piece and three-piece devices. Both consist of two inflatable cylinders implanted into the corporal bodies connected via tubing to a mechanical pump for inflation and deflation that sits in the scrotum. Both can be sized appropriately based on corporal length. The pump in the two-piece model (Ambicor by AMS) (Fig. 45.7) also acts as a fluid reservoir, while in the three-piece models (AMS 700 by AMS, Titan by Coloplast) a separate fluid reservoir is implanted into the prevesical space of Retzius (Figs. 45.8, 45.9). This fluid reservoir provides the capacity to fully expand the cylinders for increased length and girth, as well as rigidity for adequate penetration and sexual function. In men who are acceptable surgical candidates and lack contraindications, the three-piece model is the ideal option and the implant typically inserted by the experienced implant surgeon. Because they lack an implantable reservoir, the two-piece models are the prosthesis of choice in men with specific medical histories, for example, men who previously have had significant abdominal surgery, radiation, or episodes of severe peritonitis that likely have scarring or adhesive disease that would make surgical implantation technically difficult or men

Fig. 45.7 The Ambicor two-piece inflatable penile prosthesis. (Courtesy of American Medical Systems, Inc., Minnetonka, MN, USA)

Fig. 45.8 The AMS 700 inflatable penile prosthesis. (Courtesy of American Medical Systems, Inc., Minnetonka, MN, USA)

Fig. 45.9 The Titan inflatable penile prosthesis. (Courtesy of Coloplast Corporation, Minneapolis, MN, USA)

who are renal transplant recipients or who have undergone vascular grafting and in whom an infected reservoir and potential intra-abdominal infection could lead to compromise of the transplanted organ or graft. The lack of reservoir in the two-piece device also lessens the total amount of fluid available in the system, limiting inflation and the degree of girth expansion. To aid in inflation, a small amount of extra fluid remains outside the pump in the cylinders at all times, decreasing overall flaccidity in the detumesced state which some men may find problematic.

Surgical implantation of an inflatable penile prosthesis is more technically challenging than implantation of the malleable device. Surgical approach and type of incision vary by surgeon preference, and anatomical differences between patients may dictate the use of different methods. At our institution we routinely perform implantation in the uncomplicated patient under general anesthesia through a single penoscrotal incision that allows for implantation of the entire three-piece device. Briefly, a Foley catheter is placed per urethra into the bladder and a 1–2 cm transverse scrotal incision is made inferior to the base of the penis. Dissection exposes the corpora cavernosa, corporotomies are made bilaterally, and the corporal bodies are dilated and measured both proximally and distally for cylinder length. Appropriate sized cylinders with rear-tip extenders on the proximal end to adjust length are placed and the corpora are sutured closed. A subcutaneous pouch is made through blunt dissection to the dartos fascial layer of the scrotal wall and the pump is placed. Finally, dissection through the external inguinal ring is made medial to the spermatic cord, identifying the transversalis fascia. This layer is punctured and the reservoir balloon is placed in the prevesical space. All tubing is then connected, both inflation and deflation of the device is tested, and the scrotal incision is closed with absorbable suture and skin adhesive. The procedure is straight-forward and usually takes less than an hour to complete. It is our practice to leave the implant partially inflated and to keep the patient in the extended-stay unit overnight. In the morning the catheter is removed and the patient is discharged home after voiding. The patient is given 1–2 weeks of postoperative antibiotics and strict instructions to massage the pump down into the scrotum daily to prevent retraction. In 4–6 weeks, the patient returns to the office for activation of the device and instruction on use. Patients are then permitted to use the device and are advised to inflate and deflate it daily to allow tissue expansion around the implant.

Several studies have examined long-term patient satisfaction with their inflatable penile

implants. A group of 58 patients receiving the AMS 700 implant reported an 86% rate of satisfaction with their implant at 6 months [33]; while a study of 248 patients receiving both AMS and Mentor (now Coloplast) implants reported a 69% overall satisfaction rate with their implant [34]. Inflatable prostheses also have excellent long-term potential to treat erectile dysfunction; a study of 207 men who underwent prosthesis found 90% reported the device was functioning properly at a median of 100 months [35]. Furthermore, these men were pleased with the results their implant provided, with 87% of them saying they would undergo implantation again and 88% saying they would recommend the procedure to a friend or family member.

Individual patient characteristics and expectations must be reviewed prior to implantation of any penile prosthesis. Patients who desire an inflatable prosthesis must have adequate manual dexterity to operate the pump mechanism. Often patients with erectile dysfunction have significant cardiovascular comorbidities and assessment of cardiac risk factors is imperative prior to subjecting the patient to general anesthesia. Because inflatable prostheses are more expensive than malleable implants, patients with inadequate insurance coverage may have a more difficult time affording inflatable devices. Specific issues to address in preprocedural counseling include concerns about penile shortening after implantation, decreased penile sensation, chronic pain, device erosion, mechanical malfunction, and implant infection. Development of a pump with a fluid lock-out mechanism has lowered the rate of auto-inflation, a phenomenon in which increased intra-abdominal pressure causes device inflation. The risk of mechanical malfunction has sharply decreased as technical innovation has improved device longevity and reduced fluid leaks, and current devices have a 10-year rate of freedom from mechanical malfunction of greater than 60% [35, 36].

Infection is the most dreaded complication of any implant, and penile prostheses are no different. Infection rates for penile implants are estimated to be between 1 and 3% [37], and bacterial colonization is thought to take place at the time of implantation despite appropriate perioperative antibiotics and irrigation. Bacteria adhere to the implanted devices and form a biofilm, a multilayered bacterial microenvironment made up of slow growing bacteria with altered genetic expression that are more resistant to traditional antibiotic treatment [38]. Infections of penile prostheses are divided into clinically apparent infections (those presenting with symptoms such as new penile pain, erythema, induration, fever, drainage, and device extrusion, usually within 2 years of implantation) and sub-clinical infections (often presenting with chronic penile pain). In almost all cases of device infection, antibiotic therapy is required with subsequent removal and replacement. Recently, both manufacturers of penile prostheses have addressed infection through the use of antibiotic impregnated devices. Coloplast Corporation has developed a hydrophilic coating for its Titan prosthesis called Resist™ which is soaked in antibiotics intraoperatively that are then eluted over the next 1–3 days to reduce bacterial adherence. This has been shown to decrease infection rates at 1 year from 2 to 1% [29]. Likewise, AMS has developed a version of its 700 series prosthesis impregnated with a proprietary minocycline/rifampin coating called InhibiZone™, which contacts local tissue surfaces and elutes the antibiotics over 7 days to provide antibiotic activity in the area surrounding the implant. At 180 days, there is a significant decrease in prosthetic infection rates from 1.6 to 0.7% [39].

Patients with erectile dysfunction, unresponsive to traditional medical therapy, should be offered surgical therapies to restore erectile function. Implantable penile prostheses provide reliable long-term erectile function with high rates of satisfaction and low morbidity. Patients considering penile implantation should be counseled on the advantages and disadvantages of implantation, and the various devices and surgical techniques should be discussed. Expectations should be realistic and clearly delineated prior to surgical intervention. With open discussion between patient and surgeon encompassing these areas, optimal outcomes should be expected.

Conclusion

In the cancer patient, erectile dysfunction often develops as an unfortunate side effect of successful treatment of malignancy, leaving a debilitating reminder of disease and a further displacement from normalcy. Medical therapy represents the first-line treatment for men with erectile dysfunction. VEDs represent an adjunct to medical therapy that can sometimes aid in attaining success and may provide a novel rehabilitative pathway after radical prostatectomy in men with prostate cancer. In many instances, however, damage secondary to treatment is insurmountable with pharmacologic intervention alone, leaving surgical intervention as the sole path to regaining sexual function. Penile implants present a means of restoring a man's erectile function with minimal morbidity and excellent long-term success

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Chapter 46
The Management of Premature Ejaculation

Marcel D. Waldinger

Keywords Intravaginal ejaculatory latency time • IELT • Stopwatch • Prevalence • SSRI • Transdermal therapy • Serotonin • Synapse

Introduction

In general, men are able to control the timing of their ejaculation reasonably well, even if ejaculation may sometimes occur earlier than they would have wished. The probability that it may take a longer time at a next occasion makes most men not to worry about their ejaculation. However, this is not the case in men who suffer from premature ejaculation (PE). Males affected by PE are often continuously worried about and even obsessed by their ejaculation. As soon as ejaculation has occurred too early again, these males feel frustrated, are full of shame, or may feel guilty towards their sexual partner.

From a clinical and scientific point of view, one may wonder about what is exactly meant by PE. In other words, what is the definition of premature ejaculation? In recent years, an interesting debate has taken place in medical literature. Although probably every clinician may intuitively have a certain feeling about how to define PE, the debate has demonstrated that it still is difficult to come to a genuine consensus on this issue. This is not new. The same problems on how to define PE were present in the early 1980s after the publication of the first official definition of PE in the Diagnostic and Statistical Manual, third version (DSM-III), the classification system of mental disorders issued by the American Psychiatric Association (APA) [1].

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History of Premature Ejaculation

Since the beginning of last century, PE has been regarded as the expression of an unconscious psychological conflict. But at the same time, it has also been attributed to urological disturbances, such as a too short frenulum. Over the years, various treatments have been recommended [2]. In 1943, the German endocrinologist Bernhard Schapiro distinguished two types PE – Type A and B [3]. Both types have later been called primary (Lifelong) PE and secondary (Acquired) PE [4], and as such, included in the DSM-IV-TR [5].

Definition of Premature Ejaculation (Table 46.1)

Until 1980, there was no official definition of PE. In the first part of the twentieth century, psychoanalysts considered a man to be suffering from PE when ejaculation occurred so quickly after vaginal penetration that a woman hardly had any chance of getting sexually aroused.

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Table 46.1 Definitions of premature ejaculation

Organization	Publication	Year	Definition
ISSM	J Sex Med	2008	Ejaculation within about a minute Inability to delay ejaculation On all or nearly all vaginal penetrations Negative personal consequences
WHO	ICD-10	2004	Inability to delay ejaculation Insufficient to enjoy lovemaking Ejaculation before/very soon (15 s) after beginning of intercourse
AUA	J Urol	2004	Ejaculation occurring sooner than desired Before or shortly after penetration Causes distress to one or both partners
EAU	Website	2001	Inability to control ejaculation for sufficient time before vaginal penetration
APA	DSM-IV-TR	2000	Persistent or recurrent ejaculation After minimal sexual stimulation Before, on, or shortly after penetration Before the person wishes it
Masters & Johnson	Human Sexual Inadequacy		Inability to control ejaculation for sufficient time during intercourse Inability to satisfy partner on at least 50% of intercourse attempts

APA American Psychiatric Association; *WHO* World Health Organization; *ISSM* International Society for Sexual Medicine; *AUA* American Urological Association; *EAU* European Association of Urology

In the absence of any official definition, it was a sort of accepted idea that a man suffered from PE when he consistently ejaculated within 1 min after penetration. In 1970, William Masters and Virginia Johnson, two well-known American sexologists, rejected this idea by stating that a man has PE when he is not able to control his ejaculation to satisfy his female partner in more than 50% of intercourses [6]. Masters and Johnson strongly refuted a short ejaculation time as criterion for the definition of PE. Their view influenced the first official definition for PE made in the DSM-III in 1980 [1].

According to the DSM-III, a man is defined as having PE when "ejaculation occurs before the individual wishes it, because of recurrent and persistent absence of reasonable voluntary control of ejaculation and orgasm during sexual activity" [1]. As such, the DSM-III defined PE solely in terms of an absence of voluntary "control," without paying attention to the time that passes before a man actually ejaculates (the ejaculation time). After its publication, the DSM-III definition of PE has given rise to a fierce debate among psychiatrists about the meaning of the word control. The result of this debate was that in the next version of the DSM-III-R, published in 1987, the word control was no longer mentioned in the definition. Instead, PE was defined as "Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it" [7]. This defining criterion of a "short ejaculation time" remained in the two other DSM editions – the DSM-IV (1994) and the DSM-IV-TR (2000) [5]. However, as evidence-based research into the ejaculation time had hardly been conducted in the 1980s, a quantification of the "short" ejaculation time was not mentioned in the DSM-IV definition. In contrast, the definition of PE in the ICD-10, which is the classification system of the World Health Organization (WHO), does mention a cut-off point for the ejaculation time [8]. According to the ICD-10, a man has PE when he ejaculates "very soon after," e.g., within 15 s after penetration. However, the ICD-10 makes no reference to any study where this figure had been reported as outcome data [9]. So what actually is a short ejaculation time?

Research of Definition

For a long time, the question on what is actually meant by the criterion "shortly after penetration" (DSM-IV-TR) and "very soon after penetration"

(ICD-10) remained unanswered. In order to investigate the criterion of a short ejaculation time, in 1992, Waldinger et al. introduced the intravaginal ejaculation latency time (IELT), which is defined as the time between vaginal penetration and intravaginal ejaculation [10]. The same authors postulated that there is a continuum of the IELT in the general male population and that the IELT is neurobiologically and genetically determined [11]. However, it was only in 2005 that such a variability of the IELT was demonstrated in men [12]. In a stopwatch study, the IELT was measured in a random cohort of men in the general population of five countries (The Netherlands, United Kingdom, Spain, Turkey, and the USA) during a 1-month period [12]. The study demonstrated for the first time that in the general male population, the IELT is skewedly distributed with a median IELT of 5.4 min (range: 0.55–44.1 min). In a similar study in the same countries, performed a few years later, exactly the same results were found with a median IELT of 6.0 min (range: 0.1–52.1 min) [13]. From both studies, it may be concluded that the IELT in men is indeed distributed along a continuum.

Animal Model of Premature Ejaculation

Interestingly, a continuum of the ejaculation time has also been observed in various cohorts of laboratory male Wistar rats [14, 15]. Based on this continuum a new animal model for PE was presented in 2005, and with regard to ejaculation, it was postulated that there are three endophenotypes of male rats: (i) rats which always ejaculate after a very short time of copulatory behavior, i.e., rapid ejaculating rats; (ii) rats who ejaculate after a normal ejaculation latency time (ELT), i.e., normal ejaculating rats; and (iii) rats who ejaculate after a long ELT, i.e., sluggish ejaculating rats.

With reference to the existence of an IELT continuum in men and an ELT continuum in male rats, it was postulated that Lifelong PE in men represents a specific endophenotype and is characterized by specific symptomatology [16].

Normal and Abnormal Ejaculation Time

Men suffering from Lifelong PE frequently ask their treating physician what exactly is a normal ejaculation time. For many years, we have been unable to answer this question in a proper scientific way. However, the two aforementioned stopwatch studies in five countries provided a reliable scientific reply when applying statistics to the outcome data. According to statistics, any figure under the 2.5 or 0.5 percentile in a skewed distribution is regarded as abnormal or dysfunctional. In the five Nation study, it appeared that men under the 2.5 percentile had an IELT of less than 1 min [12, 17]. In other words, men with an ejaculation time of less than 1 min have, according to the statistics, an abnormal IELT compared to the IELT of the rest of men in the general population [17]. Interestingly, this IELT of 1 min or less was already known from a study in which a clinical cohort of Dutch men with Lifelong PE had measured their IELT with a stopwatch over a 1-month period at every intercourse; 80% of these men ejaculated within 40 s and 90% of these men ejaculated within 1 min after vaginal penetration [18]. Therefore, the majority of these men with Lifelong PE suffered from an IELT that was not only causing distress and frustration, but was also indeed statistically abnormally short compared to the rest of the normal male population.

Classification of Premature Ejaculation

Since 1943, it is known that there are two PE subtypes: Lifelong PE and Acquired PE. This distinction is important as it has consequences for the kind of treatment of both subtypes.

Lifelong Premature Ejaculation

Men with Lifelong PE suffer from early ejaculations ever since their first sexual contacts. At almost each coitus and with every woman or

sexual partner, they experience an early ejaculation. The aforementioned stopwatch studies, as well as studies in which PE was self-reported, it has been demonstrated that 90% of men with Lifelong PE ejaculate within 1 min and that another 10% ejaculate within 1–2 min [18, 19]. Similar results were reported in a retrospective Australian case series of 1,346 consecutive men with PE and a mean IELT of 43.4 s [20]. It is intriguing that many years after the times when men with PE were mainly treated by psychoanalysts, current evidence-based research has demonstrated that their definition in terms of 1 min after penetration had actually been correct. Recently, in 2008, the International Society for Sexual Medicine (ISSM) has reached consensus on a new definition of Lifelong PE by accepting the 1 min criterion and is as follows: PE is a male sexual dysfunction characterized by: (i) ejaculation which always or nearly always occurs prior to or within about 1 min of vaginal penetration; (ii) inability to delay ejaculation on all or nearly all vaginal penetrations; (iii) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [21]. It is likely that the DSM-V, which may become published in 2013, will also accept this 1-min ejaculation criterion [22]. Throughout their life, men with Lifelong PE usually ejaculate within the same short ejaculation time. However, it has been shown that about 20–30% of these men at some point in life get an even shorter ejaculation time after they reach the age of 30 or so [18, 19]. In other words, in some of these men, PE even gets worse with aging.

Acquired Premature Ejaculation

Men who start suffering early ejaculations at a certain age never having had this complaint previously and actually had been easily able to delay ejaculation may be diagnosed as having Acquired PE. Men with Acquired PE are rather more heterogeneous as a group when compared with those with Lifelong PE. This is due most probably to the different factors and dysfunctions that may lead to Acquired PE. It is not only psychological and relationship factors that may give rise to PE, but also hyperthyroidism, erectile difficulties, and urological problems like prostatitis that may be the cause of this PE subtype [23–26]. As there still is some lack of evidence-based research on Acquired PE, the Expert Panel Acquired PE meeting under the auspices of the ISSM which was convened in Hamburg in 2008 has agreed on the following interim position statement on Acquired PE: Acquired PE is a subtype of PE characterized by (1) substantial decrease in time-to-ejaculation compared to a man's previous sexual experience; (2) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (3) negative personal consequences, such as distress, worry, frustration, and/or the avoidance of sexual intimacy. The Expert Panel meeting agreed that further clinical research is required to obtain IELT data, as well as PRO data, for men with Acquired PE.

Two New Subtypes of Premature Ejaculation

Based on data obtained from large scale surveys on the prevalence of PE in the general population [27], Waldinger and Schweitzer postulated that in addition to Lifelong PE and Acquired PE, there are two other PE subtypes: Natural Variable PE and Premature-like Ejaculatory Dysfunction or Subjective PE [28–31].

Natural Variable Premature Ejaculation

In Natural Variable PE, a man only occasionally and incidentally experiences an early ejaculation. This incidentally occurring early ejaculation should not be regarded as a symptom of underlying psychopathology, but as manifestation of normal variation of the ejaculation time. Treatment consists of psycho-education and reassurement that there is no pathology involved.

Premature-Like Ejaculatory Dysfunction

It is well known that there are quite some men who are not satisfied with the duration of their ejaculation time. However, their dissatisfaction has often no clinical consequences, e.g., they do not seek treatment. But, on the other hand, there are men who do suffer from the idea that they have PE, while the duration of their IELT actually is in the normal range or even longer than the average IELT. Some of these men may seek medical treatment. As their IELT is normal, it has been suggested that one should clearly distinguish these men from men who have abnormally short IELTs, as is a major characteristic of men with Lifelong PE. Waldinger and Schweitzer proposed to distinguish these men and termed this subtype Premature-like Ejaculatory Dysfunction. According to these authors, treatment of this subtype should not immediately consist of prescribing medication, but should consist of counseling, psycho-education, and sometimes psychotherapy. Interestingly, while Lifelong PE is considered a mainly neurobiologically determined subtype of PE, Premature-like Ejaculatory Dysfunction has been considered a mainly psychologically determined subtype of PE. But it should be noted that, in contrast to Lifelong PE, there currently are no evidence-based outcome data of effective treatments in men with Premature-like Ejaculatory Dysfunction. More research into this subtype is warranted.

Men with Natural Variable PE and Premature-like Ejaculatory Dysfunction are rarely seen at urologic or sexologic outpatient clinics. The existence of these groups of men has mainly been derived from epidemiological surveys. As the prevalence of Lifelong PE and Acquired PE is probably rather low (about 5–10%), it may well be that the very high prevalence rates of 20–30% of PE in the general male population are determined by the large number of males who are dissatisfied with their sexual ejaculatory performance, while actually having normal ejaculation times [31].

Genetics of Lifelong Premature Ejaculation

In 1943, Bernhard Schapiro noted that family members of men with PE often have PE as well [3]. However, his interesting remark has never been quoted until 1998, when Waldinger et al. postulated that Lifelong PE, and particularly the short IELT, may be genetically determined [11]. Briefly, it was postulated that Lifelong PE is mainly a neurobiologically and probably also a genetically determined ejaculation disorder and that the very short ejaculation time in these men is related to a diminished serotonergic (5-hydroxytryptamine; 5-HT) neurotransmission in the central nervous system and some specific disturbances of serotonergic receptors [11, 16]. In 2009, Janssen et al. was the first to publish a DNA study performed in men with Lifelong PE [32]. This stopwatch study showed that 5-HTT polymorphism was involved in the IELT. It appeared that in men with Lifelong PE, males with LL genotype had a 100% faster ejaculation time than men with an SS genotype. It has been suggested that the IELT in Lifelong PE is influenced by more and perhaps even a multitude of gene factors. In the next decade, more genetic research will probably provide better insight into this intriguing matter.

Drug Treatment of Premature Ejaculation (Table 46.2)

The new classification of four PE subtypes shows that PE is not one clear disorder entity. On the contrary, it has recently been emphasized that PE has different underlying etiologies and pathogenesis [33]. This notion has consequences for its treatment. Treatment may consist of drug treatment, counseling, psycho-education, and psychotherapy. In general, drug treatment consists of daily and on-demand drug treatment.

Table 46.2 Characteristics of the most commonly used oral agents for PE treatment

Agent	Standard daily dose	*T½* (h)	Adverse effects
Clomipramine	25–50 mg/day	19–37	Dry mouth Constipation Blurred vision
Fluoxetine	20–30 mg/day	36	Nausea Anxiety Insomnia Libido loss ED
Paroxetine	10–40 mg/day	21	Yawning Nausea Anxiety Insomnia Libido loss ED
Sertraline	50–100 mg/day	26	Nausea Anxiety Insomnia Anhidrosis Libido loss ED
Dapoxetine[a]	15–60 mg[b]	1.5	Nausea Diarrhea Headache Dizziness Somnolence
Tramadol	25–50 mg[b]	5–7	Nausea Dizziness Insomnia Dyspepsia Seizures

T½ half-life; *SSRI* selective serotonin reuptake inhibitor; *MAOI* monoamine oxidase inhibitor; *TCA* tricyclic antidepressants

[a]Not currently FDA approved, but approved in Europe

[b]For on-demand use

Daily Oral Medication

Evidence-based psychopharmacological research has demonstrated that particularly the daily use of some selective serotonin reuptake inhibitors (SSRIs), such as 20 mg paroxetine, 50–100 mg sertraline, 20–40 mg citalopram, 10–20 mg escitalopram and 10–20 mg clomipramine, which is the most serotonergic tricyclic antidepressant, may clinically and statistically significantly delay ejaculation compared to placebo [34]. Of all SSRIs, daily use of 20 mg paroxetine exerts the strongest ejaculation delay [34].

The SSRIs and clomipramine block neuronal reuptake of serotonin from the synaptic cleft of central serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission and stimulation of postsynaptic membrane 5-HT receptors [35].

Despite the efficacy of SSRIs and clomipramine in delaying ejaculation, their use in the treatment of PE is off-label, which in some countries may cause problems for treating PE.

The daily intake of these serotonergic antidepressants has a number of advantages over the intake of drugs a few hours before intercourse (on-demand intake). By using a daily intake strategy, sexual contact may take place at every moment of the day with about 80% chance on a moderate to very strong ejaculation delay [36]. Moreover, the daily use of drugs does not interfere with the desirable spontaneity in having sexual contact on the spur of the moment, since ejaculation will be delayed for nearly all intercourses. In addition, the risk of nausea or other gastro-intestinal side effects during sexual contact is diminished after 1–3 weeks due to habituation of the gastro-intestinal tract to the serotonergic component of this group of drugs [36].

The side effects of the SSRIs and clomipramine vary according to the short and long term [36]. In the short term, SSRIs may give rise particularly to fatigue and yawning, but also to a vague feeling of nausea, flatulence, loose stools, and increased perspiration. Usually, these side effects diminish and disappear after 2–3 weeks of daily treatment. However, in the long term, SSRIs may give rise to increased weight and sometimes to erectile difficulties and decreased sexual desire. Besides these serotonergic side effects of SSRIs, clomipramine may also give rise to anticholinergic side effects such as dry mouth, blurred vision, and constipation. It is of relevance to inform patients about these side effects when prescribing the drug. If the side effects are too disturbing or continue for rather a long time, the patient should be

advised come off the drugs by reducing the daily dosage gradually in order to prevent the occurrence of SSRI discontinuation syndrome. After stopping the drug, one can prescribe another SSRI that may perhaps give rise to fewer side effects.

On-Demand Drug Treatment

SSRIs

In contrast with daily intake, the on-demand use of SSRIs a few hours before intercourse in general leads to less ejaculation delay in men with Lifelong PE compared to daily treatment with SSRIs. The on-demand use of these drugs also has an increased risk on gastro-intestinal side effects (particularly nausea) a few hours after drug intake. With regard to this time component after intake, the occurrence of nausea may cooccur with the moment of intercourse. Another disadvantage of the on-demand use of drugs is that it may have a negative effect on the spontaneity of a couple deciding to have sex. For many men and their partners, it is rather inconvenient to be thinking most of the time whether they dare have sex or not [19]. However, despite these drawbacks, the on-demand use of 20–40 mg clomipramine, about 4–6 h prior to coitus, may lead to a clinically relevant and satisfactory ejaculation delay. Besides its serotonergic properties, this is probably also due to its sympathicolytic properties.

It should be noted that the on-demand use of SSRIs, clomipramine, and dapoxetine may also have clear advantages over daily treatment. On-demand use of drugs reduces the chance of interactions with other drugs. It decreases the chance of interactions with alcohol and it may be prescribed to men who have no steady partner or are content in a relationship with a rather low coitus frequency. It surely is dubious to advise daily intake of SSRIs to men who have sexual contact perhaps only once or twice per month. For on-demand treatment, dapoxetine, tramadol, PDE-V Inhibitors, and EMLA cream are available, but besides dapoxetine, in a number of European countries, their use to treat PE is off-label.

Dapoxetine

Dapoxetine is a rapid-acting SSRI with a short half-life [37–39]. Particularly due to this pharmacokinetic property, the drug is suitable for on-demand use to treat PE. Dapoxetine has received regulatory approval as an on-demand treatment for PE in several parts of the world [37–39]. Three placebo-controlled trials have shown that when taken 1–3 h before intercourse, dapoxetine 30 or 60 mg taken 1–2 h before intercourse is more effective than placebo [37–39]. Although the extent of ejaculation delay induced by dapoxetine seems to be less compared to the daily use of SSRIs, the on-demand use of this drug is a good alternative for men who do not wish to use an SSRI every day, for men who suffer too much from SSRI-induced side effects, and of course for men who prefer to use a drug on an on-demand strategy.

Tramadol

Recently, two studies have been published on the ejaculation-delaying effect of tramadol 50–100 mg [40, 41]. Although both studies had a weak methodology, the on-demand use of the drug 1–3 h prior to coitus may lead to a delayed ejaculation. The precise cause of the induced ejaculation delay is unclear, but may be related to its serotonin reuptake inhibitory property as it is rather unlikely that it is caused by its antagonistic effect on the μ-receptor. Due to its opioid affinity, the patient should be informed about the risk of drug dependency when taking the drug on a more regular basis. Despite the publication of both studies, there still is too insufficient information on the general utility of tramadol to treat PE. For example, it is unknown whether the induced ejaculation delay remains on the long term and whether sexual side effects, such as erectile dysfunction or decreased libido, may impair its use on the long term. Therefore, head-to-head studies of a long duration, comparing tramadol with an SSRI, are warranted.

PDE5 Inhibitors

PDE5 inhibitors, like sildenafil, cialis, and vardenafil, may effectively treat the cause of PE, particularly in the case of Acquired PE which is the result of erectile difficulties. These drugs facilitate erectile function and because of that the drugs diminish the chance that a man decides to (prematurely) ejaculate as a way to mask his difficulty to maintain his erection. As the PDE-V inhibitors have no effect on the actual ejaculation time, these drugs are not useful in men with Lifelong PE and no erectile difficulties. However, there have been some publications in which PDE-V inhibitors are recommended for men with Lifelong PE. However, the methodology of these studies is rather weak [42].

Topical Anesthetics

The use of anesthetizing creams and sprays to delay ejaculation is the oldest known pharmacological method of treating PE [3]. A number of studies have demonstrated that lidocain- and prilocain-containing creams, like EMLA cream, may delay ejaculation [43–45]. Their effect is moderately effective [46]. Unless a condom is used, their use may be associated with penile hypoanesthesia and vaginal numbness. The use of a topical anesthetic may perhaps become more popular by the use of TEMPE, which is an eutectic anesthesizing topical spray containing lidocain and prilocain [47]. TEMPE has been developed to specifically treat PE. The spray immediately penetrates the skin of the glans penis, and by this property, it is distinguished from creams and sprays containing lidocaine and prilocaine which penetrate the skin at a much slower rate. The first study has demonstrated that the spray delays ejaculation without clinically relevant side effects [47].

Inadequate Intracavernous Self-Injection Therapy for PE

Unfortunately, some inadequate and expensive treatments of PE are recommended on the Internet. One of such inadequate treatments is intracavernous self-injection therapy. Currently, there is not any evidence for its efficacy of even safety. Only one study on intracavernous injection therapy for PE has been published [48]. However, the methodology and design of the study was extremely weak. In the absence of any well-controlled study, treatment of PE by intracavernous injection cannot be recommended.

Psychologic Treatment of Premature Ejaculation

For many years, the outcome objective of psychological intervention has been the prolongation of the IELT. However, the majority of studies investigating psychological interventions for delaying ejaculation lack the robust methodology as has been used in drug treatment studies of Lifelong PE. It is suggested that a better objective for psychological intervention would be the improvement of a mutually satisfying sexual relationship between the patient and his partner. As PE may result in sexual problems in the patient's partner or may lead to relationship problems, one should always assess the relationship and the partner's well-being.

Psychotherapy

A number of different psychotherapeutic approaches to PE have been described, but their efficacy has not been evaluated in properly controlled and adequately powered trials, and the different therapeutic modalities have not been compared in formal studies. It is likely that only some men seeking treatment for PE require in-depth psychotherapy [49]. In spite of hard evidence on the efficacy of psychotherapy, behavioral retraining is still often practiced by sexologists. Behavioral treatment is distinguished in the "stop-start" and the "squeeze" technique [6, 50]. The basis of behavioral retraining is the hypothesis that PE occurs because the

man fails to appreciate the sensations of heightened arousal and recognize the feelings of ejaculatory inevitability.

Stop-Start Method

In the first step of the "stop-start" process, the penis is manually stimulated until the man is fairly highly aroused at which point stimulation is stopped. When his arousal subsides, stimulation recommences and continues until a high level of arousal is again achieved when stimulation is stopped. This sequence is repeated at least four times before stimulation continues to ejaculation. The process is repeated three or more times a week. The aim is to increase the duration of stimulation the man can receive before needing to stop. The second step is almost identical to the first. The only difference is that the patient's partner applies the manual penile stimulation and the patient tells her when he wants her to pause and then restart. The next step is penile containment in the "quiet vagina," e.g., the man penetrates without any thrusting. The couple is encouraged to practice this position frequently in order that the man learn to enjoy the feeling of being inside the vagina. Finally, the woman starts gentle coital thrusting movement until the man tells her to stop because he is nearing ejaculation.

The Squeeze Technique

The squeeze technique is essentially the same as the stop-start process described above except that at the time stimulation is stopped, the penis is squeezed firmly between the thumb and the first two fingers applied at the glans penis. During the final step of the program when the penis is stimulated within the vagina, the woman lifts herself off the penis and applies the squeeze until the man's arousal subsides.

Sensate Focus

Concurrent with practicing the above-mentioned methods, the couple is encouraged to spend time in mutual pleasuring involving nongenital massage and caressing, following the program known as "sensate focus." This is suggested to reduce the genital-focused interaction of the ejaculatory control process. It should be noted that the man needs a cooperative partner and sufficient time to follow the program properly. Moreover, manual penile stimulation must be culturally acceptable.

Although there are many anecdotal reports of the efficacy of these aforementioned behavioral techniques and success rates in the short term have been reported from 60 to almost 100% [6, 51], the methodology and design of these studies have been weak and fail to meet the criteria of evidence-based research. In addition, long-term maintenance of ejaculatory control induced by these treatment has shown to be very low [52]. It is recommended that when discussing the various treatment options for PE with a patient and/or his partner, one should always inform the couple on the rather lack of scientific evidence that still exists on the efficacy of these behavioral techniques.

Clinical Interview of Men with Complaints of Premature Ejaculation

When taking a clinical interview of a man with complaints of PE, it is important to find out what he exactly means with being premature. The clinician should therefore ask the following questions:

- What exactly do you mean by premature ejaculation?

  Is it premature for you, for your sexual partner, or for both of you? Can you more specifically tell how long it takes to get an ejaculation after you have penetrated the vagina? After how many thrusts of the penis do you usually get an ejaculation?
- How often do you have a premature ejaculation?

  Is it always or nearly always at each intercourse? Is it only sometimes? In which percentage of attempts of having sex do you have premature ejaculation?

- Since when do you suffer from premature ejaculation?

  Has you experienced these early ejaculations from around your first sexual encounters? Or did you have no specific problems with ejaculation but only after a certain age? And if so, after which age?
- What exactly is premature?

  Can you estimate the time that usually passes after you have penetrated the vagina before you get an ejaculation? Is it so quick that you can count the number of penile thrusts? If so, after how many thrusts do you get an ejaculation?
- Do you also ejaculate outside the vagina when this has not been the purpose?

  How often do you ejaculate outside the vagina? Do you ejaculate at the moment or just after 2 or 3 strokes after penetration?
- Who's plan was it to seek treatment?

  Has it been your plan to seek for treatment? Or has it been on advise of your partner that you have been seeking treatment? What exactly do you expect from a treatment against PE?
- Do you talk about PE with your sexual partner?

  What did your partner told you? Does she agree that you have premature ejaculation?
- How is your relationship in general?

  Are you happy with each other? Are there any problems in the relationship? If so, do you think that this may interfere with your sexual relationship?
- How is your general health?

  Any problems with getting or maintaining an erection? Have you ever had some problems with your thyroid gland or with voiding? Did you ever had complaints of a prostatitis?

Relevant Questions for Considering Different Treatment Options

As there are different treatments available for PE, it is important to get an idea of the patient's willingness to accept a certain treatment. Moreover, one should carefully consider whether a certain treatment is also suitable for the patient. In case one decides to prescribe serotonergic antidepressants, one always have to ask questions about the use of other drugs that may interfere with the use of SSRIs, about previous treatments, and about contraindications for SSRI treatment. Obviously, it is important to know whether the patient has a preference for a specific treatment. To get more information about this preference, one can ask the following questions?

- What do you have in mind about treatment?

  What do you know about treatment? Have you read on Internet or in book about the available treatment options? What do you expect from a treatment? What are your partner's expectations?
- Would you prefer to take a drug on a daily basis or do you prefer to take it only a few hours before intercourse?

  How often do you have sexual contact? With a frequency of 2–3 times a week, I would advise daily treatment with an serotonergic antidepressant: what would you think of that? With a frequency of 2–3 times a month, wouldn't it be an idea to use a drug only a few hours before intercourse: what would you think of that?

Summary

Since the mid-1990s, there has been an increasing interest in drug treatment of premature ejaculation. Research into SSRI, clomipramine, and topical anesthetic treatment has been conducted by clinicians and neuroscientists and has remarkably been done without hardly any financial support from pharmaceutical companies. In a considerable number of studies it has been shown that daily use of some SSRIs and clomipramine delays ejaculation most effectively and that the initial side effects diminish and even disappear after about 3 weeks. Since the millennium, studies on the on-demand use of dapoxetine, tramadol, and PDE-V inhibitors have also been published. The use of PDE-V inhibitors is particularly useful in men who have PE on the basis of erectile difficulties.

Dapoxetine, tramadol, and topical anesthetics of lidocain and prilocain augment the various existing drug treatment options. Apart from the developments in drug treatment of PE, important progress has been made in the research of a better and more appropriate classification of PE. More research into the recently proposed new classification of four PE subtypes, genetic research, pharmacogenetic, and animal research may probably contribute to a better understanding of their etiology, pathogenesis, and treatments in the next decade.

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Chapter 47
Testosterone Therapy in the Male Cancer Patient

Abraham Morgentaler

Keywords Testosterone • Androgen • Prostate cancer • Hypogonadism • Testosterone replacement therapy • Libido • Erectile dysfunction

Overview

One of the more controversial issues over the last several years has been the use of testosterone (T) therapy (TTh) in men with prostate cancer (PCa). Many men 50 years or older suffer from symptoms of testosterone deficiency, including symptoms of erectile dysfunction, diminished libido, fatigue, depression, and sense of decreased vitality. TTh effectively treats these symptoms in many men, and may provide additional benefits such as increased strength, muscle mass, and bone mineral density (Table 47.1). Yet there has been a long-standing and widely held concern that higher serum T causes more rapid PCa growth. For this reason, any history of PCa has been considered an absolute contraindication to TTh, even in men with apparent cure.

However, the scientific literature fails to provide much support for this historical concept. Large population-based longitudinal studies have demonstrated that the risk of PCa is unrelated to serum concentrations of sex hormones, including T and other androgens. A meta-analysis of 19 controlled studies found that men who received TTh did not develop PCa more frequently than men who received placebo. And although the total number of men studied is quite small, several publications have now reported no cancer recurrences in men who received TTh following definitive treatment for PCa. These data indicate that the traditional view regarding T and PCa requires re-evaluation.

The origin of the concern that higher T necessarily leads to greater PCa growth may be attributed to the landmark work by Huggins and Hodges, who reported in 1941 that androgen deprivation, most commonly achieved via castration, caused regression of PCa. These authors and others in the pre-PSA era also administered T to men with metastatic PCa and noted evidence of cancer progression in some men, leading to the conclusion that higher T was dangerous for men with PCa.

These historical observations indicated that PCa is an androgen-dependent cancer. Yet PCa appears unaffected by variation in serum T concentrations in many studies. An important distinction that has only recently been appreciated is that an increase in serum T may have major effects on prostate growth in the androgen-deprived individual, but may have little or no effect in men who are hormonally intact. A Saturation Model provides a rationale for understanding this biphasic response, and is based

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Table 47.1 Benefits of testosterone therapy

Sexual
Erectile function
Libido
Intensity of orgasm
Nonsexual
Increased energy
Reduced fatigue
Improved/stabilized mood
Increased muscle mass/strength
Reduced fat mass
Increased bone mineral density

primarily on the finite ability of the androgen receptor (AR) to bind androgen. Maximal androgen-AR binding appears to occur at very low androgen concentrations. Once maximal binding is achieved, a critical pathway for androgen-mediated action on PCa cells is no longer susceptible to increased stimulation. Other mechanisms may also contribute to the lack of observed effects of androgen on prostate tissue at serum T concentrations within the naturally occurring range.

This modern reassessment of androgen action on PCa growth has important clinical ramifications for the growing number of PCa survivors who happen to be T-deficient and symptomatic. Since evidence now reveals that serum T concentrations within the normal range do not appear to confer added risk to men with PCa, it becomes more difficult to justify the withholding of TTh to men who are T-deficient and who desire symptom relief and improvement in their quality of life. Although no large, long-term studies of TTh in men with PCa are yet available, it seems reasonable to now offer TTh to symptomatic men with PCa, particularly to those who have undergone definitive therapy with a favorable prognosis. Patients should first be informed of the absence of long-term safety data and the unknown degree of risk of cancer recurrence or progression. Particular care should be exercised for the individual with severely depressed serum T, as these men may still have potential for significant androgen-mediated PCa growth.

Introduction

Testosterone Deficiency and the Prostate Cancer Patient

Testosterone deficiency, also termed hypogonadism, can cause a variety of symptoms and signs, such as erectile dysfunction, diminished libido, increased fatigue, depression, and decreased bone mineral density [1]. TTh is often effective in treating these symptoms and signs [2], however there has been a long-standing and widely held taboo against offering TTh to men with a history of PCa, regardless of disease status [3]. This taboo arose from the concern that higher serum T levels would "awaken" dormant PCa cells, thus causing disease progression or recurrence. The prohibition against TTh has particular poignancy for PCa survivors, who often have already experienced significant compromise of their sexual function from their cancer treatments, and also because their cancer treatment may have directly caused the reduction in serum T that has contributed to their symptoms.

The Origin of the Prohibition Against TTh in Prostate Cancer Patients

The origin of the prohibition against TTh in PCa patients arose from the work of Huggins and Hodges in 1941, who reported that castration or lowering of T by estrogen administration caused PCa to regress [4], and that T administration caused "enhanced growth" of PCa. This prohibition against TTh in men with a history of PCa reaches to the highest levels of medicine. Product labeling for T formulations includes a contraindication against using T in men with "a history of, or suspicion of, prostate cancer" [5]. Several years ago, the NIH temporarily halted T-related research,

in part due to prostate safety concerns, until the Institute of Medicine could make recommendations regarding effective and ethical T trials. It has even been suggested that men who only have a family history of PCa to not undergo TTh [6].

However, with the increased interest in TTh over the last decade, the relationship of T to PCa has come under greater scrutiny. Surprisingly, multiple reviews have failed to find any compelling evidence supporting the decades-old assumption that higher T causes PCa growth [7–12]. And there is now a growing population of otherwise healthy men who have survived definitive treatment for PCa and who happen to have symptomatic hypogonadism and are requesting treatment. These events have conspired to create a new environment regarding the use of TTh in men with PCa or at risk for it.

A dramatic reassessment of this issue has been precipitated by reassessment of historical literature [7, 10, 12], a shift in understanding of the relationship of PCa to androgens [13, 14], and by the appearance of a number of studies that have reported no ill-effects from TTh in men who have undergone definitive treatment for PCa [15–18].

Historical Experience with Testosterone and Prostate Cancer

The Original Report: Huggins and Hodges

In 1941, Charles Huggins and Clarence Hodges reported that men with metastatic PCa demonstrated significant reductions in serum acid phosphatase when T was severely reduced by castration or with estrogen treatment [4]. In the same publication, acid phosphatase levels were reported to rise with T administration, leading the authors to conclude that T caused "enhanced growth" of PCa. This paper established the hormonal dependence of PCa and forms the basis for current treatment with the use of LHRH agonists in men with advanced PCa. Huggins was awarded the Nobel Prize in 1966.

Although today there is no doubt that androgen deprivation does indeed cause PCa regression, the conclusions of Huggins and Hodges regarding the effects of raising T have not stood up as well over time. A close review of the original publication reveals that results of T administration were provided for only two men, and one of these men had been previously castrated [3]. Today we know from the experience of intermittent androgen deprivation therapy that allowing normalization of T in a previously androgen-deprived individual routinely causes markers such as PSA to increase, even in men without PCa [19], and so a rise in acid phosphatase in the previously castrated individual would today be an expected outcome. However, the key question is whether raising T in an otherwise untreated individual with PCa will cause cancer progression. In retrospect, the original assertion that T administration causes "enhanced growth" of PCa was based on a blood test result in only a single patient [3, 7]!

Historical Experience with T Administration in Men with PCa

Other investigators in the pre-PSA era also explored the results of T administration in men with advanced or metastatic PCa. Prout and Brewer [20] found that T administration caused progression or death within several weeks in five of ten men with recurrent PCa after castration. However, no progression was noted with T administration in a separate group of 26 men, consisting of 20 without castration and 6 who had just recently been castrated. Several of these men experienced subjective improvements, such as increased appetite, decreased bone pain, and an improved sense of well-being. The improvement in bone pain reported by these investigators is in contrast to the conventional modern wisdom that higher T routinely causes worse bone pain among men with bone metastases. The critical observation is that men who had been androgen deprived prior to T administration did poorly,

whereas men who were hormonally intact had benign outcomes.

The Memorial-Sloan Kettering Experience

Fowler and Whitmore reported on the experience of T administration in men with a history of bone metastases from PCa treated at the Memorial Sloan-Kettering Cancer Center over a period of 18 years [21]. Of 52 men, 45 were reported to have experienced an "unfavorable response," a broad category that included clinical progression, increased bone pain, or a rise in acid phosphatase. This report is often cited as proof that T administration is dangerous for men with PCa.

However, of these 52 men all but four had already undergone castration or were being treated with estrogens. Of the four previously untreated men, one had an early "unfavorable" response, not otherwise specified, one had a beneficial subjective response, and the remaining two had "unfavorable" responses at 56 and 310 days of T administration. The authors concluded from this experience that endogenous levels of T may be enough to provide "near-maximal stimulation" of PCa growth [21]. This conclusion was an early articulation of the concept that there is a limit to the ability of androgen to stimulate PCa growth, but most clinicians were unaware of this minority view until the more recent re-assessment of the risks of TTh.

Modern Evidence Regarding Testosterone and the Risk of PCa

Natural History

The belief that higher T represents a risk for PCa growth or subsequent development has been a touchstone of uro-oncology, but evidence to support this belief has been elusive. Indeed, this belief defies the epidemiology of PCa, rarely occurring during the peak T years of the twenties and thirties, and instead becoming highly prevalent when men are older and T levels have declined substantially. Moreover, it is known from autopsy studies that a significant percentage of men in their twenties already harbor microfoci of PCa [22]. If high T caused "enhanced" or more rapid PCa growth, one would expect to find a much greater number of PCa cases in young men, but this is not the case.

Longitudinal Studies of Serum Testosterone and Subsequent Risk of Prostate Cancer

There are at least 23 English-language longitudinal studies investigating the relationship of endogenous levels of multiple hormones and the subsequent risk of PCa [23–29]. In these studies, blood is obtained at baseline, men are followed for periods of up to 20 years or longer, and a group of men is identified who has developed PCa in the interim. A control group of an equal or greater number of age-matched individuals who did not develop PCa is then identified. Samples frozen from study entry are then thawed and tested for various hormone levels. Not one has shown an association between total testosterone and subsequent risk of PCa. A few have shown weak associations with minor androgens or ratios of T to other hormones, but those findings have not been reproducible. The largest of these studies, from Scandinavia, actually reported an association between PCa and *low* serum testosterone [25].

In 2008, the investigators from 18 of these studies pooled data from their studies to form one very large dataset in order to achieve the statistical power necessary to detect even small differences in PCa risk due to variation in endogenous sex hormone concentrations [30]. This global analysis included 3,886 men with PCa and 6,448 age-matched controls, making it one of the largest published studies regarding PCa. Analysis was performed for several androgens, including

total T, free T, and dihydrotestosterone (DHT). The results of this highly powered study found no relationship between endogenous androgen concentrations and PCa [30].

Clinical TTh Trials

No large-scale, long-term TTh trials have yet been performed. Although no definitive assurances of safety may be possible until such a trial is completed, there have been a modest number of smaller trials that do provide valuable information regarding PCa risk. In TTh trials of 6–36 month duration, the cancer detection rate was approximately 1% [1]. These studies have included regular PSA tests and DREs, with biopsy triggered by development of abnormalities. This rate of cancer is similar to that found in prostate screening studies [1].

A meta-analysis of 19 controlled TTh studies revealed no increased risk of PCa in men who received T compared with those who received placebo [31]. The T-treatment population also demonstrated no increase in the number of men whose PSA rose above 4.0 ng/mL, and no increase in voiding symptoms.

TTh in Men with Prostatic Intraepithelial Neoplasia

A group of 20 hypogonadal men with high-grade PIN and 55 hypogonadal men with benign prostate biopsies underwent 12 months of TTh [32]. One of the men in the PIN group was found to have cancer, with biopsy triggered by development of an abnormal DRE. This represents a 5% cancer rate in this population and a 1.3% cancer rate for the group as a whole. Since development of frank cancer has been reported to occur within several years in 25% or more of men with PIN [33], these data suggest that TTh did not cause any precipitous progression of cancer in these at-risk men.

Prostate Biopsy in Men with Low Testosterone

The notion that higher T causes increased PCa growth should also mean that men with lower T should be relatively protected against the growth of PCa. However, this also appears to not be the case. Sextant prostate biopsy in untreated hypogonadal men with PSA of 4.0 or less revealed cancer in 11 of 77 men, or 14% [34]. This rate is not dissimilar to the cancer rate of 15% in men with PSA of 4.0 or less noted in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) [35]; however, the mean age of men in the hypogonadal series was approximately 10 years younger than men in the PCPT. In a recent report of 345 men with low T and PSA ≤ 4.0 ng/mL, men with more severe reductions in T had a significantly greater risk of cancer than men with milder reduction in T [36]. This suggests the possibility of an important association between *low* T and PCa. Two additional studies have reported that a low ratio of T to PSA is predictive of a positive prostate biopsy. One of these was in a group of men with PSA of 3.0–10.0 ng/mL [37], and the second was in a group of T-deficient men with PSA of 4.0 ng/mL or less [38].

Testosterone Flare and PSA

Testosterone flare refers to the transient rise in T that occurs within 7–10 days of administration of LHRH agonists, before T levels drop to castrate levels. Several publications have reported that the T flare is associated with increased bone pain, cancer progression, urinary retention, or vertebral collapse with spinal cord compression [39]. However, in two studies that measured PSA acutely during the flare interval mean PSA levels did not increase during the T flare despite the presence of metastatic disease in all individuals [40, 41]. Since PSA is the best available indicator of PCa progression and volume, these results fail to support the concept that a rise in T causes growth of PCa. Reports of negative effects seen

in association with the T flare were uncontrolled and occurred in men with advanced disease. One must consider the possibility that the reported negative clinical effects seen during the period of testosterone flare may have been due to the natural history of the disease itself, or possibly, via direct effects of T on bone.

Testosterone Treatment in Men with Prostate Cancer

Rationale

Treatment of PCa with LHRH agonists or radiation treatment may cause testosterone deficiency and cause symptoms of erectile dysfunction, diminished libido, difficulty achieving orgasm, and fatigue. With severely depressed T levels, men may also experience hot flushes. Even when LHRH therapy is discontinued, there may be long-lasting suppressive effects on serum T, and in some cases T levels never return to normal. Men who are symptomatic from testosterone deficiency, particularly if they appear stable with regard to PCa, may request treatment for their hypogonadal symptoms (Table 47.2). If there is little evidence that higher T causes PCa growth, then why withhold treatment that may be symptomatically beneficial?

Table 47.2 Evidence regarding safety of testosterone therapy in men with prostate cancer

Worrisome
Castration causes decline in serum acid phosphatase and PSA in men with metastatic PCa
T administration in castrated men causes increase in serum acid phosphatase and PSA
Intermittent LHRH agonist therapy associated with rise in serum PSA concurrent with rise in serum T
Prostate cancer cell lines demonstrate dose–response growth curve with increasing androgen concentrations
Reassuring
T administration in noncastrated men with metastatic PCa was associated with unchanged acid phosphatase and benign clinical course
Elevation of serum T into supraphysiologic range in healthy volunteers for up to 40 weeks associated with no increase in serum PSA or prostate volume
In prostate cancer cell lines, even logarithmic increases in androgen concentrations cause no increased growth once growth plateau is reached
The androgen receptor in human prostate becomes maximally bound to androgen at the relatively low concentration of approximately 120 ng/dL
Large, longitudinal studies reveal no association between endogenous serum sex hormone concentrations and PCa risk
Risk of biochemical recurrence after radical prostatectomy associated with *low* serum T but not high serum T
Intraprostatic T and DHT concentrations were unchanged after 6 months of T therapy despite large increases in serum T
Studies of T therapy in men following definitive treatment of PCa have shown very low cancer recurrence rates

Testosterone Following Radical Prostatectomy

The most straightforward population in whom to consider TTh following treatment of PCa is the group of men with undetectable PSA several years following radical prostatectomy. If no cancer cells are evident, as suggested by undetectable PSA, then there should be no concern that T administration would cause them to grow. If the concern is that dormant cells might become stimulated to grow by the presence of higher T, causing cancer progression, then why are men with high endogenous T concentrations at no greater risk of PCa recurrence? Indeed, in one study of T concentration and risk of biochemical recurrence following radical prostatectomy, the presence of *low* serum T was associated with greater risk of recurrence [42].

Three small studies [15–17], in a total of 74 men, have been published reporting the use of TTh in men following radical prostatectomy and with undetectable PSA. No PSA recurrence was noted in any of the men, with the longest follow-up being 12 years. In an additional series presented as a meeting abstract, a single recurrence was noted in a group of men who received TTh

following radical prostatectomy. However, these men were at high risk for recurrence due to Gleason 8 disease [43].

Testosterone Following Other Treatments for PCa

In theory, TTh in men following nonsurgical treatment of PCa may pose a greater risk of PCa progression or recurrence if higher serum T truly caused greater PCa growth, since the possibility exists of untreated foci of cancer remaining in situ following brachytherapy, external beam radiation therapy, or cryotherapy. Sarosdy reported the results of 4.5 years of TTh in 31 men who had previously undergone brachytherapy for PCa [18]. With a mean follow-up of 5 years, all men had final PSA values less than 1.0 ng/mL, suggesting lack of biochemical recurrence. A small study in five men who received TTh following external beam radiation therapy for PCa also reported no recurrences [44].

TTh in Men with Untreated or Recurrent PCa

There is little modern experience of administering TTh to men with known PCa who have not otherwise undergone treatment or with recurrent PCa. Historical papers, described previously, were uncontrolled and accurate measures of progression, i.e., PSA, were unavailable. It is therefore impossible to state with any certainty what the effect TTh might be in men with active, untreated PCa. However, a recent case report described the effects of TTh in an 84-year-old T-deficient man who elected to undergo no treatment for his Gleason 6 score PCa but desired TTh for symptoms of sexual dysfunction [45]. PSA values declined over a 2-year period, suggesting that higher serum T does not necessarily cause PCa growth even in men with untreated PCa.

Current Understanding of the Relationship of PCa and T

The relationship of T and PCa seems paradoxical because androgen deprivation causes rapid and dramatic decreases in PSA, yet the available data suggest that PCa is unaffected by serum T values in men who have not undergone androgen deprivation. The paradox is resolved by the Saturation Model, which acknowledges that prostate tissue (malignant and benign) is exquisitely sensitive to fluctuations in androgen concentrations at very low values, but appears to be indifferent to changes in serum androgens above the near-castrate range [13, 14]. The Saturation Model resolves the paradox by recognizing that there appears to be a limit to the ability of androgens to stimulate PCa growth based on multiple lines of evidence from studies in humans, animals, and PCa cell lines [14].

In animal models and PCa cell lines, there is a clear dose–response curve for prostate cell growth as androgen levels are increased, however in all studied cases a plateau is reached, following which further increases in androgen concentrations fail to cause additional growth [14].

At least two mechanisms may contribute to this phenomenon in humans. One is the finite ability of the AR to bind androgen. In benign human prostate tissue, maximal androgen-AR binding occurs at approximately120 ng/dL [46]. Since it is the AR-androgen complex that binds to the androgen response elements of relevant genes, maximal AR-androgen binding represents a significant rate-limiting step for androgen-mediated effects on prostate tissue.

Another mechanism is suggested by the study of Marks et al. [47], in which 40 hypogonadal men were randomized to 6 months of placebo or T injections. Prostate biopsies were obtained at the beginning and end of the trial, and assayed also for hormone levels and gene markers of interest. Serum T and DHT increased significantly in men receiving TTh, as expected, yet intraprostatic concentrations of T and DHT were unchanged. Genetic markers of cell proliferation were also unchanged. These results suggest that

the intraprostatic hormonal milieu differs in important ways from serum, with as-yet-undetermined mechanisms that appear to promote androgen homeostasis.

Conclusions

Over the last several years there has been a gradual reassessment of the relationship of T and PCa. Although traditionally, it has been considered taboo to offer TTh to any man with a history of PCa, regardless of disease status, many clinicians have begun to offer treatment to selected patients. The most common clinical scenario is for the symptomatically hypogonadal man with undetectable PSA following radical prostatectomy; however, new evidence suggests that men who have undergone other forms of definitive treatment for localized PCa with favorable prognosis may also be considered for treatment [48].

It is difficult to discard old ideas, particularly when they conjure up concerns regarding progression or recurrence of cancer. However, in this age of evidence-based medicine, it is imperative that we examine the basis for risk-related concerns as carefully as we do other parameters of health care. With regard to TTh and PCa, it is important to acknowledge that the putative risk of TTh causing PCa progression was based on historical data that do not stand up to scientific scrutiny. It is hoped that one day we may have definitive data regarding the safety and risks of TTh in men with PCa, but until then clinicians have no choice but to act based on existing data and an understanding of the biology of T and PCa. For many health care providers, it may be reasonable to offer TTh to selected men with PCa who are symptomatic from T-deficiency following discussion of the relevant information [48].

Discussions with patients should include information that there are no large-scale, long-term studies, and there is therefore an unknown degree of risk of cancer progression or recurrence. It is prudent to document this discussion in the medical record. Nonetheless, as a clinician one must balance the demonstrated benefits of TTh in T-deficient men against the theoretical risk of negative PCa outcomes. Once the patient has been educated with regard to the issues, many of these men will choose TTh, and a majority of these will experience symptomatic benefits and improved quality of life. However, particular care should be exercised when offering TTh to men with severe T-deficiency in the near-castrate range, because these men may still have ample potential for androgen-mediated PCa growth.

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Chapter 48
Sex Therapy in Male Sexual Dysfunction

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Keywords Sex therapy • Counseling • Cognitive behavioral therapy • Psychotherapy

Introduction

Now more than ever, cancer treatment can be viewed from a standpoint of survivorship medicine, which involves processes of cancer prevention, health promotion, side effect mitigation, and enhancement of quality of life (QOL) and relationships [1]. Advances in early detection of prostate cancer due to PSA screening coupled with advances in surgical technique and treatment options have resulted in men being diagnosed earlier in life and surviving for longer periods of time. The focus has thus changed from simply surviving cancer to enhancing or maintaining the patient's lifestyle and overall QOL posttreatment.

One salient aspect of QOL for cancer survivors is sexual health or the ability for cancer survivors to maintain physiologically and psychologically healthy sexual relationships or experiences after cancer treatment. Erectile dysfunction (ED) is a common and enduring outcome of prostate cancer treatment. It is often psychologically devastating to men, especially young men without prior ED. Prevalence of ED following prostate cancer treatment is reported to range between 25 and 86% for bilateral nerve sparring radical prostatectomy, 8 and 85% for external beam radiation, 14 and 61% for interstitial radiation, and 71% following short-term neoadjuvant hormonal therapy [2–5]. Frustration, shame, depression, and sexual bother often accompany the ED, while partners suffer from distress, not infrequently more distress than the cancer survivor, as well as depression and anxiety [6, 7].

Clinicians should be aware that it is not only erectile function that is damaged by prostate cancer treatment, but also orgasmic function and sexual desire. Reporting on men's orgasmic experiences postprostatectomy, Barnas et al. [8] noted that 37% of men had a complete absence of orgasm. Diminished orgasmic intensity was experienced by 37% while 14% reported pain with orgasm. Decreased sexual interest was noted by 45% of men who underwent either radical prostatectomy or radiotherapy [3]. The precipitating and maintaining factors for the men's low sexual desire is likely an amalgam of both physiological and psychological factors. Adding insult to injury, 68% of men postprostatectomy also report penile shortening [9].

A negative progression of physical, psychological, and sexual consequences ensue after treatment for prostate cancer. Men tend to delay enrolling in sexual rehabilitation programs leading to further damage to the penile tissues lessening the likelihood that conventional treatment will be successful. Psychologically, men's sexual

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failures generate increasing disappointment, preoccupation, and dysthymia. These psychological responses lead men to further delay enrolling in rehabilitation programs, drop out prematurely, and ultimately retire from sexual life [10].

Only recently have health professionals begun to establish sexual rehabilitation programs [11–13]. These programs utilize several medical erectogenic treatments including PDE5 inhibitors, intercavernosal injections (ICI), transurethral therapy, vacuum pump therapy, and penile prosthesis, used alone, or sometimes in combination with one another. Dr. Tal's and Mulhall's chapter (Chap. 43) will address these options in greater detail. However, the majority of these programs do not include psychosocial components.

This chapter will review the psychological impact of prostate cancer treatment on men and their female partners. This chapter reports on the different forms of psychological interventions available and review the results of published psychosocial interventions with this population. We will focus on sexual rehabilitation by emphasizing the role of sexual education, therapy, and counseling in the psychological treatment of this population. We will conclude with suggestions for future combined physical and psychological rehabilitation programs.

Psychological and Sexual Impact on Men and Their Partners

The Men

It goes without saying that the majority of men place great value on their ability to function sexually. QOL and outcomes research in prostate cancer emphasizes the primacy of sexual function as an essential component of overall well-being [5]. The level of sexual distress experienced by men who have lost their sexual function is high while sexual satisfaction is extremely low. Unfortunately, these variables do not significantly improve over time [6, 10].

Loss permeates the cancer survivor's sense of self. Psychologically, men equate loss of sexual function with loss of masculinity, self-esteem, manhood, sexual responsivity to sexual cues, penile length, bodily control (incontinence worries) and the meaning of life [5, 14–17]. Men feel old before their time and are nostalgic for their past sexual life. Some feel that they are letting their partners down. Finally, for men with incontinence, their negative sense of self is even further heightened.

All these multiple potential losses are experienced as grief, distress, worry, anxiety, and dysthymia. Some men cope with their loss by focusing on their competencies (e.g., work) or finding other forms of nonsexual intimacies to share with their partner (e.g., nature walks) [18]. However, the majority of men struggle with their emotions focused on their negatively altered sense of self, fear of the future (progression of the disease), loss of control, and sexual dysfunctions [5, 10, 14, 19].

The Partners

Female partners of prostate cancer survivors are not immune from distress, anxiety, dysthmia, and sexual dysfunction. Couper et al. [7] reviews the impact on prostate cancer survivors' partners and found the rates of depression, distress, and anxiety were higher than those of a community sample. Interestingly, women partners judge their male partner to be more distressed; however, objective measurement reveals the women to be in fact more distressed [20]. Men's psychological distress focuses on sexual function while their partner's distress tends to be more directed at decision making, and the man's potential pain and physical limitations arising from treatment [19]. As the man's physical functioning improves, the women's distress diminishes. There are two specific points in time where her distress is heightened, i.e., after the initial diagnosis and as the patient is failing.

The manner in which the woman copes affects her psychological well-being. Women who employ active problem-solving strategies, believe they can help their partner, and seek social support tend to fare better than women who are avoidant or impulsive [7].

Additionally, a high percentage of female partners of prostate cancer survivors develop sexual dysfunctions. Althof et al. [21] have discussed the dynamic and reciprocal relationship of one partner's sexual function, sexual satisfaction, and physical and mental health to the other partner's sexual health and satisfaction. The partner's role as a precipitating or maintaining factor has been overshadowed by focusing on individual medical or psychological factors or the impact of the quality of the relationship upon sexual function.

Schover et al. [3] interviewed male prostate cancer survivors about their partner's sexual function. Based on the men's observations, 66% of female partners had at least one sexual dysfunction. A total of 42% of female partners had diminished sexual desire, 13% had vaginal dryness or pain with sex, and 14% had difficulty achieving orgasm. It is not clear if their dysfunctions preceded or were precipitated and maintained by the cancer diagnosis and treatment. However, the development of female sexual dysfunction following onset of her partner's ED is not uncommon [22].

Women must negotiate a fine balance between reassuring the cancer survivor that sex is really not that important to them versus expressing their sexual dissatisfaction and needs. They anticipate that they might lose the sexual availability of the partner; however, some give up on sex prematurely [23]. The women consistently describe how devastating the loss of sex was for their husbands and feel that it is their role to reassure their husbands and build-up his self-esteem [7]. This self-denial and lack of communication has the potential to find negative expression in other areas (e.g., arguments over household chores).

The Relationship

Although the survival rate for prostate cancer is generally quite high, nonetheless, a "brush with death" has the ability to transform the relationship. Communication regarding the disease, treatment decisions, and sharing of emotions is compromised. Partners' avoid discussing their emotions, worries, and fears. Ptacek et al. describe the infrequent spousal communication regarding the implications of prostate cancer on their lives [24, 25]. Avoidance of sharing thoughts and feelings in relationships is a risk factor for couples' poor adjustment to prostate cancer.

Wittmann et al. [5] points out that men and women report different needs for intimacy and guidance about recovery from treatment. Similarly, men and women may demonstrate different styles of coping and their trajectory of emotional recovery may be different for survivors and partners.

All of the available literature on partners is directed at heterosexual dyads. Research is sorely needed examining the impact of prostate cancer on gay men and their partners and devising sensitive interventions for this population.

Psychosocial Interventions

There are several forms of psychosocial interventions differing in intensity, duration, format, and focus. Their objectives may include one or more of the following: supplying information/education; sexually rehabilitating the man or couple; teaching constructive coping strategies; facilitating communication within the dyadic relationship; decreasing interpersonal sensitivity; and diminishing dysthymia, preoccupation, and anxiety.

The most basic psychosocial intervention provides men and their partners with information/education concerning their disease state, treatment options, and potential benefits and limitations of each choice. This can be done in a face-to-face meeting, group meeting, by dissemination of pamphlets, or link to a website designed to answer patient's and partner's concerns. The goal of such educational interventions is to supply information, respond to questions, and to create a sense of normalcy and universality of the patient's and partner's emotional experiences (e.g., many patients and partners experience distress that can linger for significant periods of time).

There are also several prostate cancer support groups, which can be of value, including Man-to-Man, Franktalk, Innerman Angels, MaleCare, and US TOO! International [26]. These support groups may typically meet monthly in a group setting with a designated leader, pair veteran cancer patients with recent survivors for one-on-one meetings, discuss issues online, and provide patients/partners with a periodic newsletter. Such groups tend to offer education and as the name implies, support.

Role of Sex Therapy and Psychotherapy

A more intensive intervention, sexual therapy, seeks to enhance or restore sexual function, including erectile function. Ideally, sexual rehabilitation would involve both medical and psychological interventions. Sex therapy is a specialized form of psychotherapy that draws upon an array of technical interventions known to effectively treat male and female sexual dysfunctions. Treatment generally follows the principles of short-term psychotherapy with the therapist and patient(s) electing specific issues to focus on in an individual, couples, or group format. While employing traditional psychotherapeutic techniques such as support, interpretation, confrontation, cognitive reframing, and homework to name a few, sex therapy incorporates specific technical interventions such as sensate focus (i.e., to diminish performance anxiety and introduce nongenital pleasuring) or insertion of dilators paired with relaxation for sexual pain disorders [27].

Individual psychotherapy or couples therapy can be short-term or long-term and has a broader focus than sexual rehabilitation. It is an ideal venue for helping men or their partners manage concerns with distress, worry, fear, anxiety, preoccupation, communication problems, marital discord, and mood disturbances. Psychotherapy is the most intensive of all interventions and is conducted by a trained therapist.

Alternatively, programs might consider supplementing face-to-face office visits with web meetings. There are published reports of the utility of Internet psychotherapy for sexual problems [28].

Review of Existing Psychosocial Programs

There are relatively few published reports describing the rationale, format, and outcome of psychosocial interventions for men and their partners following treatment for prostate cancer.

All focus on sexual rehabilitation, although they employ different methodologies, number of sessions, and durations of follow-up [16, 17, 29, 30].

Canada et al. [16] examined the impact of treating men alone versus treating them conjointly with their partners in a four session group counseling program. The treatment protocol was manualized and consisted of cognitive-behavioral techniques targeted to diminish negative beliefs regarding cancer and sexuality, education about prostate cancer and sexual function, options for treating ED, and sexual communication and stimulation skills. Standardized assessments were completed at 3- and 6-months and focused on sexual function, marital adjustment, distress, and utilization of treatments for ED. After four group meetings, over a period of 3 months, the authors concluded that there were no significant differences between the two groups (men alone versus with partners) on the sexual functioning or other outcome measures. At the end of 3- and 6-months, both groups had a higher frequency of using ED treatments compared to baseline. Erectile function demonstrated some improvement at 3-months but this improvement was not sustained at 6-months.

Molton et al. [17, 31, 32] have a series of publications that describe their work with prostate cancer survivors. They devised a ten session cognitive-behavioral therapy (CBT) stress-management group intervention focused on men's interpersonal sensitivity and sexual function. The authors believed that the men's ED

caused them to feel less masculine, more rejected, abandoned, and more distressed. At the end of the treatment period, the men's sexual function had improved.

Weber et al. [33] reported on the impact of peer support. Long-term prostate cancer survivors met with men who recently underwent radical prostatectomy for eight 1-h peer support sessions. These men were compared to 15 men who were not offered the peer counseling. There were no differences in sexual functioning between the groups, indicating that time, attention, and support alone do not impact sexual functioning.

Titta et al. [30] reported on a group of non-nerve sparring radical retropubic prostatectomy and cystectomy patients who were using ICI to restore erections postsurgery. The authors randomized patients into two groups. The first group received ICI plus sexual counseling, while the second group received only ICI. The sexual counseling consisted of enhanced injection monitoring and management of technical difficulties related to injections, enhanced dose titration of injection medication, and psychodynamically oriented short-term sex therapy. Patients were followed for 18 months after initiating ICI. Over the course of the 18 months, all men also received a trial of sildenafil. In these patients, there were no differences between the groups on baseline IIEF or postsurgery scores. At the 3- and 18-month follow-up, compared to the ICI only group, the counseling plus ICI group achieved significantly better erectile function, desire, orgasm, and satisfaction scores. Additionally, the counseling plus ICI group manifested a lower discontinuation rate and were able to achieve good quality erections with lower doses of medication. Finally, more men in the sexual counseling group responded to sildenafil than subjects in the ICI-only group.

Finally, Davison et al. [29] reported results of a pilot project in which men were seen for individual counseling appointments. Some partners participated in these meetings too. The aim of the counseling appointments was to perform a detailed sexual evaluation, provide information regarding options for restoring erectile function, facilitate patients making a decision regarding which option was best for them, provide detailed instructions on how to use the selected treatment(s), and counseling subjects regarding techniques to broaden their sexual repertoire and to enhance their sexual experiences. Patients were encouraged to be seen for follow-up. They also had the option to telephone or e-mail clinicians with questions or concerns.

It is difficult to evaluate the overall effectiveness of the interventions described in these studies as they employed different formats, outcome measures, and durations of follow-up. Additionally, the subjects in three of the five studies had, on average, received prostate cancer surgery 1–2 years prior to beginning the psychosocial interventions. By the time 24 months had passed, many patients have failed and/or become discouraged with outcomes of ED treatments, and may be more frustrated and disheartened than patients who have only recently undergone treatment. Both Titta's and Weber's studies recruited patients who recently underwent prostate cancer treatment; Canada's, Davision's, and Mouton's sample consisted of patients who underwent treatment, on average, 31, 24, and 13 months prior to beginning the intervention. Additionally, some of these studies suffered from the methodological limitation of not utilizing control groups and being underpowered to demonstrate efficacy.

Other Suggestions Regarding Content and Timing of Interventions

Clearly both men and their partners experience different forms of psychosocial distress following treatment for prostate cancer. Men are generally reluctant to seek help, especially from mental health professionals and are more hesitant overall to participate in groups. However, with the consistent prompting and encouragement from their health providers, some men are able to overcome their reluctance. Women are more willing to seek help for themselves and their spouses, and tend to welcome group support.

Couper et al. [7] advise us to carefully consider the timing of the intervention and the thematic areas included in the program. Based on our experience, we believe that psychosocial intervention should begin prior to prostate cancer treatment. From the sexual rehabilitation clinician's perspective, it is important to impart information concerning the usefulness of early physical intervention rather than having patients wait 6–12 months before seeking treatment. During the waiting period, the vascular supply to the penis and tissues in the penile corpora may be further compromised. Additionally, intervention prior to treatment may help predict and normalize the patient's and partner's course of recovery.

Clearly, the program must focus on restoring men's overall sexual function and not be limited in focus to erectile function only. Careful monitoring of patient's use of PDE5s and ICI may enhance the efficacy of the treatments. It is important to be aware of psychosocial barriers to the use of these interventions such as restarting a sexual life after an extended period of abstinence, partner resistance, partner concerns or dysfunction, lack of confidence, performance anxiety, depression, relationship issues, and unrealistic expectations [34]. These psychosocial issues need to be explored and resolved in order for the patient to effectively use any of the medical intervention. Doing so will also increase patient's and partner's sexual satisfaction.

Nonsexual expression, including hugging, kissing, hand-holding, or other forms of nongenital touching can also be emphasized. Finally, sensate focus exercises can reintroduce or minimize difficulties in posttreatment sexual expression between partners through staged, progressively intimate activities. Sensate-focus touching does not emphasize intercourse or orgasm, which can minimize pressure on male survivors to achieve erections or perform with unrealistic levels of sexual vigor. Finally, it is important to include components within the intervention that would enhance the woman's sexual pleasure and desire, target negative beliefs that interfere with help-seeking for ED, and teach the partners skills in sexual communication and stimulation that would allow them to better integrate treatments for ED into their sexual life [1].

Psychosocial interventions should also address the negative impact of patient's/partner's reluctance to disclose news of the cancer to family and friends who are potential sources of support for the them. Depression increases social isolation leading to further despair and feelings of abandonment. Of course, patients and partners will only disclose when they are ready to do so. Including this information in a psychosocial intervention is meant to encourage patients and should not be perceived as a mandate that disclosure must be made.

It is difficult to design a program that fits all cultures and ethnicities. Nonetheless, clinicians need to inform themselves about, and be sensitive to the cultural nuances regarding self-expression, sexuality, and use of medical interventions to restore sexual function. For instance, African American males may report greater loss of desire, but more positive attitudes toward help seeking. They also put greater emphasis on erectile function as a necessary and essential component of sexual dysfunction treatment because other sexual activities were not valued or not utilized [35]. African Americans also show better sexual recovery than Whites and Hispanics, according to this study.

Psychosocial intervention programs should also include a module on communication [3]. The National Cancer Institute promotes communication strategies for encouraging openness in communication and to foster open-minded dialog about sexual difficulties. Some of their dialog strategies include focusing on partner comments, instead of planning a response; reiterating partner's comments in one's own words; asking direct questions to clarify and understand partner's concerns; and acknowledging partner's views as relevant and important to the other partner. Such exercises are designed specifically to make talking about sexual difficulties easier following a diagnosis or treatment for cancer.

Conclusion

There appears to be a large void in providing quality psychosocial intervention for men and their partners following prostate cancer treatment.

We have documented the significant psychosocial impact on men and their partners and discussed the importance of including dialog and communication about these issues. Unfortunately, there is a dearth of controlled studies on these interventions to date. It is surprising that few academic medical centers are involved in state-of-the-art prostate cancer treatments and have not implemented psychosocial interventions as the standard of care. Hopefully, it will become part of the routine treatment of men with prostate cancer and their partners in the future.

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Chapter 49
Restoring Intimacy in Relationships Affected by Cancer

Sharon Manne

Keywords Intimacy • Relationship • Communication • Psychological intervention

Introduction

Existing medical treatments for men diagnosed with prostate cancer have a number of distressing side effects, which can include erectile dysfunction, leakage of urine with orgasm, dry ejaculation, penile shrinkage, loss of libido and responsiveness to sexual visual cues, urinary incontinence, bowel dysfunction and rectal bleeding, hot flashes, weight gain, fatigue, loss of muscle mass, pain, and physical impairment [1, 2]. Symptoms can occur immediately after treatment or may not develop until 2–5 years following treatment [3]. These symptoms can be troubling for men because they can compromise masculinity, self-esteem, sexual confidence, responsivity to sexual cues, sexual fantasies, sexual desire, the ability to engage in sexual activity, and subsequently increase psychological distress [2, 4–7]. Sexual dysfunction can be a particularly difficult stressor. Although approximately half of men diagnosed and treated for prostate cancer use erectile aids to partially or completely restore erectile functioning [8, 9], the majority of men do not continue to use and/or are not satisfied with these aids [9–11]. Ultimately, many men never achieve the same level of or satisfaction with sexual activity as they experienced before the cancer [6], and the disruptions to sexual activity compromise men's quality of life [7, 12].

The diagnosis and treatment of prostate cancer also affects partners. Partners typically play an important role in treatment decision making [13, 14], are active participants in medical treatment [15], have an important role as assisting the patient in managing distress, and facilitate both their own and their partners' acceptance of the loss of sexual function [16]. Studies suggest that partners report increased psychological distress [17–20]. Specific concerns about the patient's side effects (Manne et al. unpublished data) [19], changes in relationship roles [21], changes in relationship satisfaction (Manne et al. unpublished data), sexual satisfaction [21–23], sexual dysfunction [24], and impairment in patients' quality of life associated with sexual and urinary problems [25, 26] significantly contribute to partners' distress.

Prostate Cancer, Intimacy, and the Marital Relationship

The myriad stressors placed upon the prostate cancer patient and his partner can stress the relationship and ultimately compromise relationship intimacy. Indeed, recent studies have suggested that marital quality can decline after diagnosis, particularly among female partners [18]. Stressors on the relationship include managing practical

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problems such as financial issues and difficulties completing medical care, changes in personal (e.g., health) and relationship (e.g., leisure time) priorities that may come about as a result of the diagnosis, managing their own and their partner's emotional distress, managing treatment side effects (pain), and attempting to maintain a sense of "normalcy" in the relationship.

Before discussing the impact of prostate cancer on the marital relationship, clarifying the definition of relationship intimacy may be helpful. Intimacy has been defined in many ways, sometimes as a property of an individual and sometimes as a property of relationships [27]. Conceptualizations of this construct have ranged from the willingness to disclose information about private topics to another person [28] to an interaction that is physically proximate or nonverbally engaging [29]. Since these early conceptualizations, the operational definition of intimacy has been broadened to include a range of interpersonal processes. For example, Prager [27] has characterized intimacy as self-disclosure, attentive listening by one or both partners, and positive affect between partners, and Reis and Shaver [30] have defined intimacy as the disclosure of feelings and information that results in feeling cared for, understood, and validated. Measures assessing relationship intimacy typically evaluate feelings of being listened to, cared for, and understood [31]. In the literature evaluating the impact of prostate cancer on relationships, the evaluation of intimacy has typically not been separated out from other relationship outcomes and processes. For example, global assessments of marital quality, which assess the outcome of intimate interactions, have been used as an indicator of relationship intimacy (e.g., [23, 32]). In addition, it has also been defined more narrowly by evaluating sexual functioning and/or sexual satisfaction as the key indicator of the relational impact of both prostate cancer and psychological interventions designed to address intimacy issues (e.g., [33]).

A stressor that can particularly challenge the relationship is the loss of sexual functioning and a possible reduction in sexual intimacy. Sexual interactions are an important part of the majority of marital relationships and a key way that couples establish and maintain relational intimacy. In addition, sexuality is one of the basic aspects of life, an important aspect of one's identity and self-esteem, and a way to affirm body functioning. Many couples use sexual activity as a primary way to express physical affection and love to one another. Sexual activity continues to serve the same functions among older individuals. For couples who had an active sex life prior to the diagnosis, the loss of sexual functioning, the loss of the ability to have spontaneous intercourse, and/or a decrease in sexual interest on the part of the patient have implications both for the patient as well as the partner. Partners may have a number of different reactions, ranging from feeling rejected and unattractive to feeling relieved due to their lack of personal sexual desire or ability to function. The degree of interest in continuing an active sexual relationship may be compatible or not: both partners may no longer desire sexual interaction, the male partner may wish to continue sexual activity and the female partner may not, or vice versa. How couples redefine the way that they express affection and sexual intimacy in their relationship can be a significant challenge [34].

These practical and emotional challenges, particularly the stress imposed by the loss of sexual functioning, can compromise relationship quality if not handled effectively. Communication between partners is critical to manage these stressors and maintain or improve relationship quality. Indeed, empirical research has suggested that the amount and quality of communication that couples engage in can influence both partners' emotional distress and quality of life. For example, Kershaw et al. [35] reported that spouses reported higher quality of life when they reported communicating more frequently about prostate cancer with the patient because it reduced their level of uncertainty about the illness. Similarly, patients reported higher quality of life when they communicated more with their spouse because it reduced their level of hopelessness about the illness. However, when spouses reported communicating more about the illness, patients subsequently reported more

hopelessness. Obviously, not all communication is viewed or intended to be supportive or constructive.

There are a number of other studies which have evaluated the role of relationship communication in the psychological and relational functioning of men with prostate cancer and their partners. Lepore and Helgeson [36] reported that social constraints, defined as the avoidance of discussion regarding cancer or discomfort talking about prostate cancer with one's partner and others, on the association between intrusive thoughts and distress as rated by men diagnosed with early stage prostate cancer. Intrusive thoughts about prostate cancer (e.g., dreams, not being able to stop thinking about it) were more strongly associated with greater psychological distress among men perceiving more constraints in sharing their worries and concerns about cancer with their spouses than among men perceiving low levels of constraints. These findings suggest that feeling constrained in one's ability to share thoughts and feelings results in greater distress.

Banthia et al. [37] studied the role of marital satisfaction in psychological distress among men diagnosed with prostate cancer. They found that higher relationship quality predicted lower patient distress and that relationship qualityt moderated the association between avoidance and intrusions on distress. Among men in more satisfactory marriages, both avoidance and intrusions were not significantly associated with distress. Among men in less satisfactory marriages, avoidance and intrusions were associated with greater distress. Marital quality did not moderate the role of coping among wives. The authors concluded that marital quality was important for both partners but that the marital relationship may play a more important role for patients. Although relationship communication was not directly assessed, it is assumed that higher frequency of communication regarding the patients' intrusive thoughts and worries about cancer was one mechanism whereby a higher quality marriage affords a reduction in patients' distress.

Communication about prostate cancer may also impact distress by influencing the level of emotional intimacy each partner experiences. The Relationship Intimacy Model of Cancer Adaptation [38] proposes that relationship communication influences couples' psychological adaptation by its effects on relational intimacy. According to this model, communication can be either "relationship enhancing" or "relationship compromising." Relationship-enhancing communication improves closeness and includes greater cancer-related disclosure and mutual constructive communication (e.g., mutual discussion and expression of feelings about cancer-related concerns). Relationship-compromising behaviors such as holding back concerns, actively avoiding cancer-related discussions, and one partner pressuring the other to discuss concerns while the other partner withdraws (demand-withdraw communication) can reduce relationship closeness. We examined whether relationship intimacy mediated the association between communication and couples' distress by studying 75 couples coping with early stage prostate cancer [39]. Multilevel models with the couple as unit of analyses indicated that the association between mutual constructive communication, mutual avoidance, and patient demand-partner withdraw and distress could be accounted for by their influence on relationship intimacy. Self-disclosure, holding back sharing concerns, and partner demand-patient withdraw did not mediate the associations between communication and distress.

Collaborative coping, defined as the proportion of strategies in which a couple works together on dealing with the most bothersome event related to prostate cancer that occurred each day over a 2-week period, has also been shown to be associated with higher positive affect and lower negative affect among and partners [40]. For men, collaborative coping leads to greater positive mood and reductions in negative mood by improving coping effectiveness. For partners, collaborative coping leads directly to improvements in positive mood and reductions in negative mood. Collaborative coping was used more frequently when relationship quality was high. These findings suggest that collaboration between partners in facing issues results in improved mood for both partners.

Relationship communication also can play an important role in how much sexual dysfunction affects marital quality. Badr and Taylor [24] found that open communication alleviated the effects of sexual dysfunction on marital quality. Specifically, prostate cancer patients and their partners who reported greater mutual constructive communication reported higher levels of marital adjustment regardless of their own levels of sexual satisfaction after treatment. Couples were more likely to avoid communicating when the patient had more severe ED. Mutual avoidance of communicating was, in turn, associated with lower levels of marital adjustment among female partners. In summary, open communication may alleviate some of the detrimental impact of sexual dysfunction on the marital relationship, particularly among female partners.

Despite the importance of communication in maintaining relationship quality, available research suggests that it can be challenging for couples to discuss prostate cancer-related problems and concerns. Boehmer and Clark [13] interviewed a small sample of men diagnosed with prostate cancer and their wives in order to identify how couples communicate about the impact of prostate cancer. Interviews revealed that there was little direct communication between partners about the disease. Men had a difficult time adjusting to physical changes, particularly ED, but were not comfortable disclosing their feelings about these changes to their wives. Holding back fears and concerns was common among men. Wives expressed a wish to share their emotional reactions to the cancer with their spouses but described a similar tendency to hold back discussing their worries and concerns. Couples did not discuss the loss of sexual intercourse with one another. Similar results have been recently published by Badr and Taylor [24] who reported that levels of couples' constructive communication were lower, and levels of mutual avoidance were higher, among patients with greater levels of ED as compared with patients with lower levels of ED. *In other words*, *communication was less constructive among couples coping with ED.*

In sum, the diagnosis of prostate cancer and its treatment can disrupt relationship closeness and ultimately increase the psychological distress for both patient and partner. Detrimental effects on sexual functioning contribute to lack of intimacy or relationship closeness and associated distress, and the way that couples communicate or do not communicate about the concerns they encounter during the experience also contribute to couples' coping and adaptation.

Psychosocial Interventions Addressing Relationship Intimacy Needs

Although bolstering relationship intimacy may be an important therapeutic goal, the majority of studies evaluating methods of addressing intimacy concerns have evaluated pharmacological and other medical approaches to improve erectile function, such as PDE5 inhibitors, self-injection therapy, and penile prostheses. These interventions significantly improve erectile function and sexual quality of life among both patients (see Miles et al. [41] for a review of this topic) and partners [42] and have been shown to have significant effects upon relationship satisfaction (e.g., [7, 43]).

There is very little known about the utility of psychological interventions used in conjunction with medical treatments. Titta et al. [44] evaluated the effects of sexual counseling provided in conjunction with injection therapy (ICI) for treatment of ED after nonnerve sparing prostate cancer surgery as compared with injection therapy alone. The six sessions of sexual counseling were utilized to motivate couples, to improve sexual intercourse, and to correct mistakes in ICI administration. Assessments were made at 3 and 6 months posttherapy. Results indicated that significantly more participants receiving sexual counseling successfully used injection therapy. Both patients and partners receiving counseling along with injection therapy reported higher satisfaction with the treatment. With the exception of erectile function at 18 months which was

significantly improved in the group of male patients who had sexual counseling, for all outcomes there was no significant difference between those who received counseling and those who did not: EF domain scores at 3 months, sexual satisfaction, and sexual desire. Average injection therapy doses were higher however in the sexual counseling group. The authors hypothesize that ICI assisted couples in correcting errors in injection administration and facilitated couples continuing the use of injections and reduced the likelihood of discontinuation of injections. At the end of follow-up, satisfaction with treatment was higher in the sexual counseling group. In summary, sexual counseling in conjunction with injection therapy increased the efficacy of treatment, compliance with treatment, and sildenafil responder rate, and decreased the dropout rate.

The main focus of the remainder of this review will be on psychological interventions. We will divide our review of the literature into interventions focusing on patients only, on partners only, and on the couple. Only interventions that address relationship issues and/or communication following cancer diagnosis and treatment will be described.

Patient-Focused Psychological Interventions

Several studies targeting patients only have included material focusing on intimacy and sexuality. Lepore et al. [45] compared a group education intervention to a group education plus discussion group intervention and a control group receiving no psychological intervention, in a large sample size (n = 250) of men who had been treated for localized cancer in the past month. The group education intervention consisted of hour-long lectures on prostate cancer biology and epidemiology, control of physical side effects of treatment, nutrition and cancer, stress and coping, relationships and sexuality, and follow-up care and future health concerns. No time for peer interaction was provided. The education plus peer discussion intervention consisted of the 6 weekly 1-h lectures described previously as well as a 45-min discussion focusing on the lecture topic. Patients were encouraged to attend the meetings with a family or friend. During group discussions, female family members met separately with a female oncology nurse. Results indicated that the education alone and the education plus group discussion interventions improved disease knowledge and physical functioning significantly more than the control group, but did not differ from one another in their effects. The education plus peer discussion intervention resulted in greater improvements in health behavior and were more likely to be employed full or part-time than the control condition but no differences were noted between this group and the education alone intervention. Treatment fidelity was not reported, but follow-up survey return rates were reported and were high (90%). Relationship outcomes were not included in the analyses nor were effects on spouses or family and session attendance was not reported.

Molton et al. [33] evaluated the effect of group cognitive-behavioral stress management intervention (CBSM) on sexual functioning among men who recently underwent prostatectomy. The ten-session group provided practical information on treatment options for ED, provided a safe and supportive environment to address their concerns about sexuality and sexual function, broaden definitions of sexuality to include options other than intercourse, train participants in skills necessary to discuss sexual issues with partners, and teach participants ways to address distorted cognitions about sexual functioning. Results indicated that CBSM had a greater effect upon sexual functioning than a 1-day seminar. Effects were stronger among men who began the group with higher levels of interpersonal sensitivity. The authors hypothesize that men who reported higher interpersonal sensitivity viewed ED as a greater threat to their masculinity and that the group helped them to face their anxiety and fear, learn good partner communication, and reframe the experience as less threatening to their identity. No data were collected from partners.

Weber et al. [46] evaluated the effectiveness of a supportive male peer partner intervention in men who had ED following a radical prostatectomy compared to a control group who received usual care. The supportive male peer partners were ten long-term survivors of prostate cancer who previously had a prostatectomy that had resulted in ED. During the eight sessions, the men discussed problems encountered after surgery including erectile dysfunction and incontinence. It is not known whether relationship communication and intimacy were discussed during the eight intervention sessions. Comparisons between the intervention and control groups found significant reductions in depressive symptoms, sexual bother, and improved self-efficacy in the intervention group compared to controls. However, there were no significant group differences between the groups in regard to urinary and sexual function. Thus, this intervention had beneficial effects on mood and self-confidence.

Partner-Focused Psychological Interventions

There have been only two randomized clinical trials evaluating an intervention targeted to partners, and both have focused on wives. Giarelli et al. [47] randomly assigned partners to receive usual care or an intervention. Eight sessions were provided by an advanced practice nurse (APN) with specialized training in the care of patients with cancer and postprostatectomy. The APN had 16 meetings over an 8-week period of time. For 8 weeks, the APN received one telephone call and one home visit to the patient and spouse. The four components were assessment of wound and incision pain and other physical symptoms postsurgery, stress management, assistance with role adaptation, and assistance with tasks provided by the spouse. During the first ten sessions, basic physical symptom management was assessed. In addition, the APN addressed communication issues and gave the couple the booklet "Sexuality and Cancer" [48]. Baseline intimacy issues were assessed and areas for to work on with regard to open communication were discussed (e.g., expectations about future intimacy). Psychosocial issues such as changes in the marital relationship and sexuality were addressed in sessions 10–16. Spouse-specific content areas addressed by the APN during the home visits were common myths and misconceptions about surgery, how to manage the recovery as a team, the impact of the illness on the spouse, the impact of caregiving on the spouse, ways to communicate love and support, intimacy strategies to promote closeness and pleasure, future concerns about intimacy and sexuality, and future concerns about disease progression. There were no between-group differences on the any of the subscales of the primary outcome measure, Preparedness for caregiving [49] at the 3- or 6-month follow-ups. Treatment integrity as well as formal statistical analyses was not reported.

Manne et al. [50] conducted a randomized clinical trial comparing a 6-session psychoeducational intervention for wives of prostate cancer survivors with usual care ($n = 60$). One of the group sessions focused on relationship communication and was led by a psychologist. The other sessions focused on medical side effects of prostate cancer (lead by a radiation oncologist), nutrition and prostate cancer (led by a nutritionist), stress and coping, sexuality, and survivorship issues (all lead by a psychologist). Female partners completed measures of global and cancer-related distress, coping, posttraumatic growth, and cancer-related marital communication. Relationship satisfaction and intimacy were not included as outcomes. No differences were found with regard to psychological distress at 1-month follow-up assessment. However, wives participating in the group reported more posttraumatic growth (in particular, increased personal strength, spiritual growth, and appreciation for life), more positive reappraisal coping, and lower denial coping than wives in the control group.

Couple-Focused Psychological Interventions

Four studies have adopted couples' focus. Mishel et al. [51] evaluated an uncertainty and symptom management intervention that included spouses. A total of 239 patients diagnosed with localized prostate cancer who underwent prostatectomy or had recently begun radiation therapy participated. Participants were randomly assigned to receive 8 weekly telephone counseling sessions alone (alone), 8 weekly telephone counseling sessions with a family member (family supplemented), or a control group (control) that received no psychosocial intervention. Trained nurses matched with regard to ethnicity and the family member's gender (in the family supplemented arm) identified possible problems from a standardized list, use cognitive restructuring to frame challenges in a more positive light and develop strategies to manage the problem. Strategies included learning ways to manage incontinence and ED, how to express intimacy in other ways than sexual intercourse, ways of working on patient-provider communication, and problem solving, and ways of working on patient-provider communication. Materials relevant to problems discussed were mailed to individual patients after each session. In the family supplemented arm, the spouse or designated family member also received a weekly call (separate from the patient) from a nurse who was matched in ethnicity and gender who evaluated the family member's concerns about the patient and used the same approach to assisting the family member. The most commonly addressed problems were leaking urine, ED, communication with health care providers, and general treatment side effects. Information about family members' concerns was not described and outcome measures from family members were not collected. It is also not known how many family member participants were spouses or life partners. Information about session attendance and treatment fidelity was not provided and the impact on family members was not assessed. Results showed a lack of statistical differences between study groups with regard to patients' levels of illness uncertainty. However, there were significant treatment effects in favor of the two intervention groups (alone and supplemented) at the 4-month follow-up time point with regard to two illness uncertainty management strategy use, cognitive reframing and problem solving. Unfortunately, these group differences were no longer significant at the 7-month follow-up. Control over incontinence was also significantly higher among men in the two intervention groups as compared with men in usual care, although the effects were no longer significant at the 7-month follow-up. A similar pattern of results as was reported for incontinence was reported for satisfaction with sexual functioning among the African American men in the sample. There were no between-group differences for patient-provider communication. Treatment adherence was not reported. Overall, this study suggests some short-term improvements in patients' abilities to use cognitive reframing and problem solving coping, as well as perceived control over urinary incontinence and sexual satisfaction. However, inclusion of family members did not appear to enhance the effects of the intervention.

Canada and colleagues [32] evaluated the feasibility and impact of a four session sex therapy intervention for prostate cancer survivors with ED. Participants (n=84) were randomized to receive the intervention alone or with their partner. Primary outcomes were distress, marital quality, sexual desire, erectile and orgasmic function, intercourse satisfaction, and overall sexual satisfaction (with arousal, lubrication, orgasm, pain, and satisfaction for wives). Intervention sessions focused on medical treatments for ED, how to talk about ED and cancer-related emotions, sexual communication skills, coping with incontinence, coping with menopausal dryness, planning for better sexual encounters, viewing cancer as a positive change, and enhancing passion and play during sex. 61% of couples completed all four sessions. Treatment drop outs reported discomfort with the sexual content. Treatment fidelity was not reported. Analyses of treatment completers indicated no between group differences on

psychological, marital, or sexual outcomes for either partner. Analyses combining the treatment arms and evaluating pre-post changes indicated that there were significant improvements in men's distress and sexual satisfaction immediately post-treatment. However, changes were not maintained at the six month follow-up.

Northouse et al. [52] developed a three-session education and supportive intervention for men with prostate cancer and their spouses. The intervention encouraged the couple to work as a team and communicate openly about the illness, maintain hope and focus on achieving short-term goals, learn techniques to reduce distress and maintain an active lifestyle, how to live with uncertainty, and learning self-care strategies to manage symptoms. Sessions were conducted by nurses. Assessments were administered preintervention and 4-, 8-, and 1-year postintervention. The control group received standard clinic care. At the 4-month follow-up, intervention group patients reported less uncertainty about their illness and more communication about the illness with their partner. Importantly, there were no differences reported on patients' quality of life or on the appraisal of the illness, hopelessness, self-efficacy, active coping, avoidant coping, and symptom distress. There were no significant group differences noted at the 8-month and 1-year follow-up. At the 8-month and 1-year follow-up, intervention group spouses reported better physical QOL than control spouses. Intervention spouses reported higher mental QOL and overall QOL than control spouses at the 4-month follow-up but not at the 8-month or 1-year follow-ups. Intervention group spouses also reported lower negative appraisal of caregiving, significantly less illness uncertainty, and less hopelessness than control spouses at 4 months. Uncertainty continued to be lower for the intervention group subjects at the 8-month follow-up. Intervention group spouses reported higher self-efficacy at 4 and 12 months and reported more communication with the patient at all three assessments. Overall, the intervention had more effects on spouses than patients. There were few relationship level outcomes included in this study and the emphasis was not specifically on communication and intimacy.

Manne et al. [53] developed an intimacy-enhancing intervention for patients diagnosed with early stage prostate cancer and their partners. *Seventy-one* couples were randomly assigned to receive either five sessions of intimacy-enhancing therapy (IET) or usual care. The five 90-min sessions focused on communication strategies to assist couples in learning ways to more comfortably share their concerns about prostate cancer, to improve mutual understanding and support regarding their own and one another's cancer experience, to facilitate constructive and empathic communication regarding concerns about the loss of sexual functioning, to find methods of talking about feelings of shame, embarrassment, and any perceived loss of masculinity in a sensitive manner, and to promote ways to maintain and promote emotional and sexual intimacy despite restrictions in sexuality. The primary outcomes were global distress and well-being, cancer-specific distress and concerns, global relationship satisfaction, and relationship intimacy. Secondary outcomes were relationship intimacy and relationship communication (self-disclosure, perceived partner disclosure, mutual constructive communication, mutual avoidance, perceived partner responsiveness, and demand-withdraw communication). Participants completed measures preintervention and immediately posttreatment (IET) or 2 months later (UC). Overall, IET holds promise as an effective intervention for couples with greater distress and fewer relationship resources. Chambers et al. [54] developed a couple-focused intervention (ProsCan for Couples) consisting of eight telephone sessions provided by a nurse accompanied by an educational DVD, which they are presently evaluating by comparing it with usual care and a peer-delivered telephone counseling accompanied by the same educational DVD. Telephone sessions focused on education about prostate cancer; its effects on sexuality; assisting couples in expressing affection and nonintercourse sexual touch; challenging negative thoughts about prostate cancer, aging, and sexuality; and helping the couple select a

medical treatment for ED that is acceptable to them and integrating this treatment into their sexual relationship. The DVD reviews this material and contains actors speaking about ways to communicate with one's partner about sexuality and intimacy. The peer support intervention was provided by prostate cancer survivors who offered support and empathy and education. Partners are invited to all eight phone sessions, and calls begin before surgery and continue biweekly until 22 weeks postsurgery. Results are not yet available.

Future Directions

There have been few well-controlled studies to evaluate psychological interventions designed to assist couples in dealing with the many challenges and obstacles to relationship intimacy encountered during the diagnosis and subsequent treatment of prostate cancer. The majority of studies have shown beneficial effects on one or more quality of life measures and several interventions have shown significant effects on psychological distress. However, there are a number of design flaws and methodological problems that have limited conclusions regarding the efficacy of the interventions tested to date.

The first concern is that the majority of psychological interventions subjected to empirical evaluation thus far have been targeted to either the patient or the partner alone (and not the couple). Several interventions targeted to the couple have not included partners in the same session (e.g., separate sessions), thereby missing the opportunity to directly address relationship concerns and communication. Second, the emphasis of interventions has varied widely, with content ranging from information about symptom management (e.g., managing incontinence) to cognitive-behavioral interventions addressing cognitions about sexual dysfunction and stress management. It is encouraging that improving relationship communication about sexual concerns and enhancing communication skills have been a component of most interventions. However, when topics vary widely and are not targeted towards sexuality, intimacy, and communication about concerns, it is not clear what content is responsible for changes in relationship outcomes.

Third, the primary outcomes evaluated have ranged broadly across studies and have not consistently included relationship outcomes. Although global relationship satisfaction has been included as an outcome in many studies, relationship intimacy is rarely included as an outcome. It will be necessary to include relationship outcomes to evaluate whether intimacy-focused interventions are effective. Fourth, with the exception of two interventions [51] (Manne et al. unpublished data), the majority of interventions have not been based on theory and meta-analyses have suggested that theory-based interventions may have greater effect sizes [55, 56].

Fifth, the majority of studies do not report adherence to the intervention or the degree to which the treatment was manualized/standardized. Low treatment fidelity is a serious threat to the external validity of the findings. Sixth, with the exception of two intervention studies [33, 51] minority representation has been low, which is problematic because prostate cancer is more prevalent among African American men. Cultural influences on relationships and communication styles may result in different treatment foci than interventions for Caucasian couples. Same sex couples have also not been included in studies.

Seventh, it is unfortunate that patients diagnosed with advanced prostate cancer have not been studied. Couples' concerns may differ. Pain and symptom management, dealing with the feminizing side effects of androgen deprivation therapy, coping with existential issues related to the end of life, and opening communication about grief are each important and not typically relevant to couples dealing with localized disease. Demands on the relationship and challenges to intimacy are likely to differ. Therefore, it is important that this population of couples be studied. Eighth, other than the level

of patient education [45], we do not know whether treatments are more or less effective for particular types of patients, partners, or couples. It is possible that intimacy-enhancing therapies may be most effective for couples who have lower marital satisfaction before the cancer or for individuals, among couples who have higher levels of emotional distress, or among men who have stronger traditional masculinity. Finally, there has been no evaluation of the reasons why treatments are not successful. A greater understanding of treatment mechanisms will be key as this literature develops. The identification of active and inactive therapeutic ingredients can result in refinements to enhance treatment efficacy [57, 58] and inform theoretical underpinnings of psychological treatments and thereby provide refinements to underlying theory [57]. It may also be important to evaluate outcomes at the dyadic level as well as the individual level. Evaluating the couple as a unit may more accurately reflect relationship outcomes.

In terms of future directions, intervention studies might benefit from attempting to incorporate a common set of psychological and sexual outcomes. Couples and patients at risk for intimacy-related problems as well as couples coping with advanced cancer may benefit from specialized approaches to addressing intimacy concerns.

Conclusion

The diagnosis and subsequent treatment of prostate cancer has the potential to both damage and enhance close relationships. Fear about cancer recurrence, progression, and death may fuel increased emotional intimacy needs at the same time that interest and/ or ability to use sexual activity as a way to express love and affection decline. Helping couples negotiate their intimacy needs and concerns together has the potential to facilitate and maintain close relationship ties and ultimately lower distress on the part of both patient and partner. Couple-focused interventions have the potential to improve the quality of life, but have not received sufficient empirical attention. If shown to be effective, these treatments should be integrated into the oncology setting.

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Chapter 50
Dating and Disclosure for Cancer Survivors

Rachel Hamilton and Brad Zebrack

Self-disclosure follows an attitude of love and trust. If I love someone, not only do I strive to know him; I also display my love by letting him know me... Loving is scary, because when you permit yourself to be known, you expose yourself not only to your lover's balm, but also to a hater's bombs! [1] (p. 4).

Sidney Jourard, pioneer in self-disclosure research and theory.

Keywords Disclosure • Dating • Culture • Age • Gender • Religion

Introduction

Forming intimate emotional and sexual relationships is a highly meaningful aspect of human life. In the process of creating such relationships, individuals inevitably reveal themselves – their personal histories, identities, emotions, thoughts, and bodies. Yet for cancer patients and survivors, such disclosures are complicated by the effects of cancer. For cancer survivors not involved in established committed relationships, the process of dating and disclosure becomes new and uncharted territory marked by uncertainty. Negative feelings about their bodies and sexuality, discomfort in communicating about cancer, and fear of negative reactions to their cancer may lead some survivors to avoid relationships or remain in unsatisfying ones rather than risk telling new potential partners about their cancer. Such issues may lead survivors to feel deprived of fulfilling companionship, support, and intimate relations with a partner.

Health providers working with cancer patients and survivors require an understanding of how cancer impacts relationships. In this chapter, we focus specifically on how cancer may affect the process and outcomes of dating. How do those with cancer or a cancer history decide what, how, and when to tell dating or intimate partners about their cancer? What resources exist to assist cancer patients and survivors in navigating the dating world?

This chapter addresses these questions and provides a framework by which health care providers can consider issues of dating, intimate relationships, and disclosure for cancer patients and survivors. First, we define disclosure and provide an overview of theoretical frameworks that have been used to understand whether, how and when people decide to disclose private information. We then provide an in-depth discussion of dating and disclosure for cancer survivors, drawing from limited research and patient education materials. We also discuss how experiences of cancer, dating, and disclosure may be affected by survivors' developmental stage, age, gender, race/ethnicity, religion, socioeconomic status, sexual orientation and gender identity. In the final section, we review available resources and offer advice for survivors navigating dilemmas of dating and disclosure. We conclude by identifying potential areas for continued development of clinical care, programs and services, and research.

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Theoretical Perspectives on Disclosure

Self-disclosure refers to the act of voluntarily communicating something authentic about oneself to another when such information is not readily available [2]. By exposing private aspects of oneself to another, self-disclosure creates the possibility for one to be known, to know oneself more deeply, and to feel close with others; however, it also raises risks of rejection or negative perceptions of oneself by others. Thus, self-disclosure decisions fundamentally revolve around tensions between open expression and privacy, intimacy and distance, and potential risks and benefits of being known by another [3]. Unfortunately, no theoretical literature exists that pertains specifically to the disclosure decisions of cancer patients or survivors to dating partners. However, theory related to disclosure of stigma, persons with physical disabilities, and persons with chronic illness is informative in conceptualizing disclosure issues that may be relevant to cancer patients and survivors.

According to Goffman, "stigma" was originally used by the Greeks to refer to bodily signs that marked something unusual or disgraceful about the person and signified to others that the person should be avoided. In its contemporary usage, stigma no longer refers only to these physical markers, but rather to the condition of social inferiority and "undesired differentness" [4] associated with belonging to particular social categories. Individuals with cancer may experience stigma in both the ancient and modern senses of the word. Cancer may result in physical changes such as hair loss, amputation, or scars; yet even when it does not leave observable bodily signs, cancer serves as a reminder to society of our human frailties, vulnerability, and mortality. Because thinking about such issues may evoke discomfiting feelings, people may physically or psychologically distance themselves from individuals with cancer. According to Goffman [4], the main problem for stigmatized individuals is acceptance; they find that many "normal" persons do not accept them on the basis of their stigma, and in turn, may conclude that there is something unacceptable or shameful about themselves. Thus, a central concern for stigmatized individuals is managing their social lives in order to limit, or where possible, avoid the impact of stigma on their social interactions and feelings about themselves [4]. The ways in which they do this will differ according to the degree to which their stigma is evident to others.

Goffman [4] refers to a central difference between "discredited" individuals – those whose stigma is immediately apparent to others – and "discreditable" individuals – those whose stigma is not apparent, but who will become discredited if their stigma is revealed. Discredited individuals need not verbally disclose their stigma for it to be known by others, as their stigma is unavoidably communicated through public signs (hair loss, extreme weight loss, presence of prostheses, or other medical devices, etc.). Conversely, discreditable individuals are often perceived by others as "normal" and treated accordingly unless they verbally disclose their stigma, or until they enter a situation in which their stigma becomes apparent (revealing scars or amputations normally covered by clothing, infertility, etc.). As a result of these differences, discredited and discreditable individuals face very different social conditions for disclosure.

Braithwaite [5] highlights the situation of discredited individuals through her study of individuals with observable physical disabilities. She found that such individuals commonly experienced incidents in which able-bodied strangers and casual acquaintances would request – and expect them to reveal – normally private information about their health, bodies, sexuality, and disability. In other situations, able-bodied persons would stare at the disability or appear exceedingly uncomfortable with the disabled person until the disability was discussed. Based on these experiences, Braithwaite concludes that individuals with visible disabilities "live in a world of reduced privacy" [5] that raises decisions about whether, when, and how to disclose their disability. Under these conditions, individuals disclosed in order to reduce discomfort and uncertainty in the interaction, to communicate to the other person that they were willing to talk

about their disability, and to address the disability so that they could "move on" to focus on other aspects of the relationship. However, participants were also sensitive to the risk that by disclosing they might be perceived as helpless, or the disability might become the main focus of the relationship.

Charmaz [6] addresses the situation of discreditable individuals through her study of individuals with invisible chronic illnesses. In this work, Charmaz emphasizes that disclosure of invisible illness offers the potential for both significant benefits (receipt of support, accurate understanding of one's limitations) and significant risks (loss of autonomy, rejection, pity, being seen primarily in terms of one's illness, being perceived as a complainer). She makes the important point that disclosure can result in a loss of control over one's information, emotions, identity, and life – the same areas in which individuals may have already experienced a loss of control due to illness. Accordingly, when individuals with chronic illness choose to disclose their illness, they often plan disclosures in ways aimed to maintain a sense of control and protect themselves, others, and relationships from harm.

Goffman [4], Braithwaite [5], and Charmaz [6] each suggest that decisions about disclosure can influence how individuals with stigma feel about their identity, self-esteem, and autonomy, as well as how they experience relationships with others. They also suggest that disclosure decisions always involve a tension between perceived risks and benefits. The work of all three authors has relevance to cancer survivors because the effects of cancer may be immediately apparent, nonobservable, and/or apparent to others only in certain situations, such as in close or sexually intimate relationships. The degree to which the effects of cancer are visible to others will influence how, when, and why survivors disclose to potential partners.

Goffman's work specifically addresses the intersection between stigma and dating. Goffman [4] notes that intimate relationships introduce particular pressures on discreditable individuals to disclose their stigma. Social expectations dictate that individuals should share their vulnerabilities in intimate relationships as proof of mutual trust and commitment. For this reason, individuals may feel guilty or inauthentic if they do not disclose their stigma once a relationship becomes seriously intimate; furthermore, spouses, partners or intimate others may feel betrayed or misled if a person does not disclose his/her stigma, or does not disclose it early enough in the relationship [4]. As individuals have greater interaction across different domains of life (work, school, and social circles), it also becomes more difficult to keep one's stigma from becoming known [4]. As relationships deepen, the potential risks and benefits of disclosure increase. Thus, dating and intimate relationships are particularly likely to evoke concerns about disclosure for cancer patients and survivors.

Dating and Disclosure in the Context of Cancer

Across all age groups, a substantial number of cancer patients and survivors will be single at some point post-diagnosis, and many will be interested in forming intimate relationships. For instance, in a study of 864 breast cancer survivors (aged 31–88 years), 31% did not have a partner at the time of study [7]. Of those without a partner, 77% were interested in a relationship, with interest decreasing with age (95% for those under age 50, 84% aged 50–59 years, and 65% aged 60 or older) [7]. Thus, issues of dating and disclosure may arise at any age.

Extant evidence suggests that single cancer survivors commonly experience worry or problems surrounding dating. Heinrich and Schag [8] found that among 23 single survivors of various cancers (mean age 60 years), 44% reported that they experienced "somewhat" of a problem with dating, and another 44% reported that they experienced "severe" problems. Studies of adult survivors of breast cancer [9–11] and of lung, colon, and prostate cancer [12] detail specific challenges, including difficulties meeting or initiating contact with potential dating partners,

fear of meeting dates, fear of initiating a sexual relationship, and difficulties telling a date about cancer. Rates of survivors who experience difficulties disclosing a cancer diagnosis to dating partners range from 10% to 68% in the literature [9, 10, 12]. These estimates appear to vary partly as a function of type of cancer and time since the completion of treatment.

The most common concerns of cancer survivors regarding disclosure appear to be when, how, and how much to tell a dating partner about their cancer history, as well as whether they will be rejected for revealing this information. Research suggests that cancer survivors often experience negative feelings about their own attractiveness and sexuality, pessimism about their future relationship possibilities, uncertainty regarding disclosure of their cancer history to partners, and fears or actual experiences of rejection by partners [13–15]. Some survivors report feeling that their prior identity has been lost and replaced with a primary identity as "cancer patient." [14] Such feelings may result in difficulties in knowing how to talk with others without disclosing one's cancer. In contrast, some cancer survivors establish and maintain a positive identification with being a cancer survivor in that they feel they are a better or stronger person for having overcome adversity [16]. Some indicate that cancer has become a part of who they are, which often is shared with new friends and associates in early stages of new relationships. Unfortunately, this can also create problems for survivors when others hold different understandings of the meaning of cancer and react negatively to this valued part of their identities.

Patient education literature, including online materials at cancer websites [17–29] and book guides [15, 30–32] offer further detail regarding specific dating and relationship problems faced by cancer survivors. These works suggest that a primary obstacle for single patients and survivors is the fear that others will perceive them as undesirable or unacceptable dating partners [24–29, 32]. Several articles note that cancer survivors may perceive themselves as "damaged goods." [23, 32] Some cancer survivors worry that a partner will no longer find them attractive once they see a scar or amputation, and are very uncomfortable allowing a partner to see them naked [21, 22]. When survivors have an altered sense of their body or sexuality after treatment, they may believe that they cannot satisfy a partner sexually or experience sexual pleasure themselves [15, 32]. Patients and survivors may be convinced that no one will be interested in a relationship with them once they know about their cancer history, due to changes in physical appearance or functioning, infertility, the possibility of passing genetic risk to offspring, and the possibility of future recurrence and/or early death [13–15, 29]. Such perceptions may lead survivors to avoid dating and sexual contact, or to remain in unsatisfying relationships because they believe that other options do not exist [13, 15, 24–27]. It is important to note that for some, these beliefs have been reinforced by actual experiences of rejection or negative responses from partners when they learned about the survivor's cancer [13, 17]. However, it is also important to note that many of these beliefs may also reflect survivors' negative perceptions of themselves, failure to consider alternative options or interpretations, and fears of possible rather than inevitable outcomes. Such beliefs may render dating and disclosure highly anxiety-provoking and may result in cancer survivors avoiding attempts to enter into meaningful and satisfying intimate relationships.

When they choose to communicate with partners about their cancer, patients and survivors may struggle with managing dating partners' reactions as well as their own feelings about their cancer [18, 19, 33]. When dating partners respond with distress or discomfort, this is often upsetting to survivors and may preclude them from talking about cancer in the future. Partners also sometimes respond in some ways that are unhelpful, such as mentioning someone they know who did not survive cancer, telling the patient or survivor how he/she should cope or feel about cancer, implying that the patient or survivor is responsible for his/her cancer (especially in lung or skin cancer), minimizing the importance of cancer, or being overly protective [32, 34].

Such reactions may reflect the partner's desire to contain his/her own fears about cancer and death, or simply a lack of knowing what to say [32]. Fear of negative responses and difficulty knowing how to cope with these reactions may lead survivors to avoid or delay disclosure of their cancer diagnosis or history [33].

Cancer can require individuals to communicate with dating and intimate partners about topics that they are often unaccustomed to talking explicitly about, such as health and illness, the possibility of cancer recurrence in the future, physical limitations and changes to one's body, sex, losses (of one's job, friends, fertility, hopes, dreams, and life plans), limitations in one's ability to perform expected social roles, needs for practical or emotional support, financial difficulties, and death [18]. Many people are not equipped with the levels of comfort and esteem required to engage these topics in meaningful ways in the context of their relationships. For example, sex is a difficult enough topic to address explicitly in an intimate relationship without also having to address cancer and its effects on sexual intimacy, behavior, function, and relationships. Failures in communication may lead to misinterpretations, lack of intimacy, or inability of each partner to meet their needs in the relationship.

Patients and survivors may also experience difficulties with dating relationships due to a lack of information or misinformation. Both survivors and their dating partners may be uninformed about common physical, psychological, and sexual effects of treatment. Particularly when cancer occurs in childhood or adolescence, survivors may not fully understand their treatment or potential late effects. Some survivors may be unclear about their fertility status, their risk of recurrence, and options for managing fertility and health [35]. They may also be unaware that sexual problems can often be improved through counseling, education, emotional support, and adopting supplemental sexual practices [36]. Furthermore, both partners and survivors may have mistaken beliefs about cancer. For instance, they may believe that cancer is contagious or can be sexually transmitted [15, 28], may perceive cancer as a death sentence [33], or may be unaware that treatment advances have lead to great improvements in long-term survival. Both misinformation and lack of information can increase both partners' anxiety and can make it difficult to realistically address the impact of cancer on the relationship.

Culture as Context

Cancer, dating, and disclosure derive their meaning from individuals' social and cultural context. Accordingly, we now discuss how dating and disclosure challenges may be experienced differently depending upon a person's age/stage in life, gender, race/ethnicity, socioeconomic status, religious or spiritual beliefs, sexual orientation, and gender identity.

Age and Developmental Stage

Different stages in life present different tasks, challenges and concerns, and people experience cancer in the context of their roles and expectations of what life is supposed to be like at a given age or life stage. For instance, adolescents and young adult survivors have reported being especially upset by the effects of cancer on their appearance, self-concept, and sexuality [37–42]. This is expectable, as persons at this age are typically concerned with developing a sense of identity, positive body image, and initiating meaningful relationships [41, 42]. Cancer may interfere with these tasks [41, 42]. Research also consistently finds that adolescent and young adult survivors worry about their future health, their ability to have children, and the risk of their children getting cancer [43, 44]. Such concerns may be less prevalent among older individuals who are now reviewing their lives and may already have had children or passed childbearing age.

The meanings individuals attribute to cancer, and their expectations of how dating partners may respond to their disclosure of cancer, also

will be shaped by cultural expectations for their age group. For instance, young survivors may perceive themselves and be perceived by others as "too young" to have had cancer, and may experience stigma as a result of this difference [45]. In contrast, older adults are more likely to experience health problems as a function of aging, and therefore may be more accepting of cancer or other health conditions in themselves and in a potential partner (Tolbert, 2009, personal communication).

Individuals whose cancer occurs during childhood, adolescence, or young adulthood may face additional issues due to the ways cancer may impact the normative course of development [41]. Research suggests that ill young people tend to feel isolated and dependent on their parents at a time in life at which socializing and establishing independence and a personal sense of responsibility are critical for healthy psychological and emotional well-being [40]. Due to fatigue and isolation from peers during treatment, young patients may miss important opportunities to hone social and emotional skills that are commonly developed at this stage in life [23]. Perhaps as a result of these constraints, survivors of childhood cancer may initiate dating and sexuality later than healthy peers [46] and may have fewer romantic relationships [47]. Gray et al. [48] found that survivors of childhood cancer were both more desirous of relationships and less satisfied with important relationships than their healthy peers. Because a childhood cancer diagnosis may lead to highly emotional and intense relationships with health care providers, parents and others early in life, young survivors may develop greater expectations for relationships than their healthy peers, and that this may lead to disappointment in dating and subsequent relationships [48].

Gender

Gender plays a central role in individuals' perceptions of appropriate communication and relationship roles with dating partners. Traditional gender roles in relationships reinforce greater disclosure and emotional expression by women than by men [49, 50]. Because traditional gender role norms for men also emphasize characteristics such as independence, power, and strength [50], men may face particular difficulties in disclosing information about cancer or cancer-related vulnerabilities. Gray et al. [51] and Hilton et al. [49] both report that men with cancer often avoid or limit their disclosure to friends and family in order to limit the impact of cancer on their lives and maintain a sense of normalcy, avoid burdening others, and avoid stigma. They also note that men may also refrain from disclosing because they feel they do not need or want support from others.

Disclosure of sexual or reproductive organ-related cancers (breast, prostate, and gynecological) and sexual side effects may differ by gender because male and female anatomy and sexuality are assigned different cultural meanings. For instance, women may experience particular social pressures related to their physical appearance and ability to be caregivers, whereas men may face enhanced pressure to perform sexually [52]. Due to the importance of such conceptions to individuals' sense of femininity or masculinity, it may be particularly upsetting for individuals when cancer disrupts these areas [14, 15]. In a recent study of sexual dysfunction in childhood cancer survivors, females reported more sexual symptoms than did male survivors; however, male survivors were more distressed by sexual symptoms than were females [53]. Topics bearing upon individuals' sexuality or sense of femininity or masculinity may be particularly anxiety-provoking for cancer survivors to disclose to their dating partners.

Race/Ethnicity, Socioeconomic Status, and Religion

Race/ethnicity and degree of acculturation may affect communication norms, health beliefs, and expectations regarding dating relationships. For example, studies of breast cancer survivors suggest

that non-White women were more likely than White women to report that others in their communities had misconceptions, elevated fears, and taboos surrounding cancer and its discussion [33, 54]. Non-White survivors also were more likely to report that they continuously needed to educate others that cancer is not a death sentence and that it is "treatable and beatable." [33] Research suggests that differences exist between racial/ethnic groups in their beliefs about the origins of cancer, specific fears regarding cancer, body image, beliefs about their family role, and experiences in intimate relationships [54]. In one qualitative study comprising individuals from several ethnic groups, concerns about dating and disclosure were most frequently expressed by African-American, Latina, and Asian-American survivors [54].

Acceptance of cancer survivors as relational partners may differ not only across racial/ethnic groups, but also across socioeconomic status and religious groups. For instance, within some cultures, female fertility is considered a prerequisite for marriage [55]. Thus, given the uncertainty associated with cancer treatment and infertility risks, this cultural norm stigmatizes some cancer survivors and precludes them from full participation in life. Other cultural groups may view cancer as contagious or as a punishment by God [54]. Cancer survivors in such communities are likely to have enhanced concerns about their relationship possibilities, stigma, and the impact of disclosure on establishing meaningful and intimate relationships.

Sexual Orientation and Gender Identity

Gay, lesbian, bisexual, and transgender (GLBT) persons face dual stigmas of cancer and a sexual orientation or gender identity not fully embraced or tolerated by society. GLBT persons may also encounter discrimination or lack of knowledge by health care providers about their lives and specific concerns [15, 56]. As a result, GLBT persons may receive less routine health care and may be at special risk for delayed diagnosis of cancer [24, 25]. It is important to note that health risks, sexual/reproductive concerns, relationship norms, and forms of sexual expression within GLBT communities may differ from those within heterosexual communities [15], with corresponding differences for GLBT survivors in terms of their cancer experience and relationships. Unfortunately, information about disclosure of cancer, dating, and GLBT persons is severely lacking. We do not know whether disclosure of cancer to a same-gender partner raises different issues than disclosure to an opposite-gender partner; however, this is a possibility due to gender differences in communication norms and patterns. Furthermore, GLBT persons commonly encounter decisions about whether, when, and how to disclose their sexual orientation/gender identity to others. It is unknown how such experiences making decisions about disclosing another stigmatized identity might impact their disclosure of cancer.

Patient Information and Resources

As cancer patients and survivors experience challenges around dating and disclosure, they often require guidance in how to navigate this unknown world. Unfortunately, relatively little empirical literature exists regarding the dating experiences of cancer survivors, and around what supportive services or programmatic interventions will best support their (re)-integration into the dating scene. This lack of data, however, has not precluded health care professionals, as well as cancer patients and survivors themselves, from developing programs and services that promote social connection and offer support for the challenges associated with disclosure of one's cancer experience (Table 50.1).

A range of psychoeducational resources exist to help patients and survivors address their concerns about dating, disclosure, and sexuality. Several popular cancer websites offer helpful and user-friendly discussions of these topics. Additionally, many books are available to serve

Table 50.1 Selected resources

Books

Nessim S, Ellis J. Can survive: reclaiming your life after cancer. Boston, MA: Houghton Mifflin Company; 2000.

Rosenthal K. Everything changes: the insiders' guide to cancer in your 20s and 30s. Hoboken, NJ: Wiley; 2009.

Schover LR. Sexuality and fertility after cancer. New York, NY: Wiley. 1997.

Tolbert P, Damaskos P. 100 Questions and answers about life after cancer: a survivor's guide. Sudbury, MA: Jones and Bartlett; 2008.

Grinyer A. Life after cancer in adolescence and young adulthood: the experience of survivorship. Oxford, UK: Taylor & Francis (Routledge); 2009.

Websites

Alere Cancerpage.com

Zmuda RA. Being single, sexual, and a cancer survivor. 2000; http://www.cancerpage.com/news/article.asp?id=1497. Accessed 10 Jul 2009.

American Cancer Society

The single man and cancer. 2009; http://www.cancer.org/docroot/MIT/content/MIT_7_2X_The_Single_Man_and_Cancer.asp?sitearea=MIT. Accessed 10 Jul 2009.

The single woman with cancer. 2008; http://www.cancer.org/docroot/MIT/content/MIT_7_2X_The_Single_Woman_and_Cancer.asp?sitearea=MIT Accessed 10 Jul 2009.

Cancer Support Community

Support for those affected by cancer. 2009; http://www.thewellnesscommunity.org/. Accessed 17 Feb 2010.

Cancer.Net

Being single with cancer. 2009; http://www.cancer.net/patient/Coping/Relationships+and+Cancer/Being+Single+With+Cancer. Accessed 10 Jul 2009.

Body image and sexuality. 2005; http://www.cancer.net/patient/All+About+Cancer/Treating+Cancer/Sexual+and+Reproductive+Health/Body+Image+and+Sexuality/Body+Image+and+Sexuality. Accessed 10 Jul 2009.

Cancer and being single. 2006; http://www.cancer.net/patient/Coping/Age-Specific+Information/Cancer+in+Young+Adults/Family%2C+Friends%2C+and+Relationships/Cancer+and+Being+Single Accessed 10 Jul 2009.

Cancermatch.com

CancerMatch. http://www.cancermatch.com. Accessed 10 Jul 2009.

Cancer Network

Hara R, Blum D. Social well-being and cancer survivorship. Oncology Nurse Edition. 2009; http://www.cancernetwork.com/display/article/10165/1374232. Accessed 10 Jul 2009.

Cisforcupid.com

C is for Cupid: Online dating for people affected by cancer. 2007; http://www.cisforcupid.com. Accessed 10 Jul 2009.

I'm too young for this! Cancer Foundation

i[2]y. 2009; http://i2y.com/. Accessed 11 Aug 2009.

Lance Armstrong Foundation

Planet Cancer. 2010; http://myplanet.planetcancer.org/. Accessed 10 Jul 2009.

Communicating with your partner. http://www.livestrong.org/site/c.khLXK1PxHmF/b.2660643/k.E784/Emotional_Effects_Communicating_With_Your_Partner.htm. Accessed 10 Jul 2009.

Dating and new relationships. http://www.livestrong.org/site/c.khLXK1PxHmF/b.2660623/k.55D0/Emotional_Effects_Dating_and_New_Relationships.htm. Accessed 10 Jul 2009.

Telling others you are a survivor. http://www.livestrong.org/site/c.khLXK1PxHmF/b.2660635/k.E13D/Emotional_Effects_Telling_Others_You_are_a_Survivor.htm. Accessed 10 Jul 2009.

Macmillan Cancer Support Community

We all support each other. 2009; http://community.macmillan.org.uk/whatsnew/default.aspx. Accessed 10 Aug 2009.

How roles and relationships can be affected by cancer. 2007; http://www.macmillan.org.uk/Cancerinformation/Livingwithandaftercancer/Relationshipscommunication/Sexuality/Rolesrelationships.aspx. Accessed 10 Jul 2009.

Talking about your cancer. 2006; http://www.cancerbackup.org.uk/Resourcessupport/Relationshipscommunication/Talkingaboutyourcancer. Accessed 10 Jul 2009.

Memorial Sloan-Kettering Cancer Center Post-Treatment Resource Program

Educational support groups. 2008; http://www.mskcc.org/mskcc/html/12140.cfm. Accessed 11 Aug 2009

National Cancer Institute

Body changes and intimacy. *Facing forward series: Life after cancer treatment.* 2006; http://www.cancer.gov/cancertopics/life-after-treatment/page5. Accessed 10 Jul 2009.

Prescription4love

Prescription4Love. http://prescription4love.com. Accessed 10 Jul 2009

as resources to patients. *100 Questions and Answers about Life After Cancer: A Survivor's Guide* [32] provides guidance regarding many of the questions survivors have about their health and relationships after cancer. *Can Survive: Reclaiming Your Life After Cancer* [31] includes sections on relationships, dating, sexuality, and fertility, as well as other survivor concerns. *Everything Changes: The Insider's Guide to Cancer in Your 20s and 30s* [30] provides guidance, resources, as well as personal accounts of young adult cancer survivors. *Sexuality and Fertility after Cancer* [15] is a comprehensive resource that provides clinical information about cancer and treatment side effects, treatments for these effects, and advice for managing sex and intimate relationships after cancer. This book includes chapters addressing specific issues for women, men, breast cancer, prostate cancer, survivors of childhood cancer, gay and lesbian survivors, and single survivors. Sharing emergent research examining young women's personal experiences of identity, body image, and sexuality during and after cancer may also be useful for patients in order to help normalize their experiences [14]. Additionally, Memorial Sloan-Kettering Cancer Center in New York periodically offers a workshop called "*Dating and Disclosure*" through its Post-Treatment Resource Program [57]. This workshop combines discussion and didactic techniques to help normalize the experiences of survivors and address their practical concerns about dating in a group setting.

Perhaps a more direct source of advice and support are survivors themselves. Many young patients and survivors participate in support groups where discussions of dating, sexuality, and survivorship occur with others their same age [27, 29, 58]. Community support groups are offered in many cities through the Cancer Support Community [59] (formerly Gilda's Club and The Wellness Community), and other support groups may be found through contacting national cancer organizations. Survivors can also access online support communities (Planet Cancer [60]) and an emerging group of social networking sites, such as I'm Too Young for This [61] and MacMillan Cancer Support Community [62]. These organizations offer online discussion forums dedicated to dating, relationships, and sexuality, and MacMillan Cancer Support Community offers a discussion forum for partners of cancer patients and survivors.

A few websites exist to help cancer patients and survivors meet and connect with potential partners. These websites allow survivors to bypass some of the difficulties associated with disclosing illness to dating partners by being geared specifically toward individuals with cancer or other health conditions, and by allowing individuals to control how much health information they present to others on their profiles. C is for Cupid [63] is a free online dating website founded by cancer survivors for individuals affected by cancer. CancerMatch [64] is a free social networking site for individuals with cancer to help them find friendships and dating partners. Prescription4Love [65] is a free dating service for individuals with various health conditions (e.g., cancer, diabetes, STDs, disabilities, etc.). These websites permit individuals "to be honest in advance [about their health condition] and progress to the next stages of friendships and relationships." [65] In this way, the Internet appears to be offering additional ways to address dilemmas associated with dating and disclosure.

Clinical and Research Implications

Health care providers provide a key point of contact for individuals affected by cancer, and can serve as a resource for anticipating and addressing potential concerns. Medical practitioners can assist patients through providing information about common psychosocial concerns and side effects, inviting discussion of sexuality and disclosure with patients, and helping refer patients to appropriate resources. Social workers and other practitioners of psychosocial care are well positioned to provide information and support to patients and survivors, their partners, and their families. These practitioners can help patients and survivors to integrate and address the impact of cancer on their identity, body image, and sexuality.

Psychosocial care providers can also help individuals or couples to develop strategies that allow them to be more comfortable in communicating and navigating relationship issues. Finally, both medical and psychosocial care providers can reach out to patients and survivors by offering to serve as a guest speaker at cancer support groups or by facilitating informational workshops.

As we have noted, many patient education materials offer advice to cancer patients around dating and disclosure. Based on common themes within this literature, we offer the following as kernels of information or advice that health providers can offer to cancer patients and survivors:

- You are more than your cancer experience; it is only one part of your identity.
- There is no one "right" way or time to disclose. You have the choice of whether, when, how, and what you tell others about your cancer.
- While you cannot control another person's reaction to your having had cancer, you may be able to increase the chances of receiving a supportive reaction by considering the time, setting, and way that you disclose. Others may react more positively if you establish a relationship with them prior to disclosing your cancer history, rather than disclosing upon meeting someone.
- You will be able to date after cancer if you choose. Some people may reject you for your cancer history, but many others will accept and love you for who you are.
- Intimate relationships may be different after cancer. While some people experience greater challenges, others find that their relationships are deeper or more meaningful.
- Practice communicating about cancer and sexuality, so that you feel prepared for and are comfortable navigating these issues in a relationship. For example, write in a journal, role-play with a friend, talk with other cancer survivors, or seek professional counseling.
- Get involved in social activities. These offer a way to meet others and will allow you to practice interacting with others after cancer.

While such advice appears clinically sound, as of yet there is no research to empirically support the utility of these suggestions. Indeed, virtually no research focuses on disclosure of cancer to potential dating or sexual partners. This represents a surprising gap given the frequency with which issues of disclosure and dating are mentioned in the patient education literature. Research is urgently needed to better understand how cancer patients and survivors make decisions about disclosing cancer to dating or intimate partners, as well as the effects of these decisions on survivors and their relationships. Future research on strategies that patients and survivors adopt when disclosing cancer to potential partners, outcomes of these strategies, and ways that culture affects disclosure strategies and outcomes could assist health providers in providing practical and culturally sensitive counsel to cancer patients and survivors.

Conclusion

Dating, intimacy, and sexuality are important components of a cancer survivor's quality of life, impacted by the diagnosis and consequential treatments. Unfortunately, many of these treatments and side effects are not likely to resolve themselves in the short-term, and some may be permanent, requiring cancer survivors to redefine a "new normal" for intimacy patterns, dating, sexual behavior, and self-concept. Part of this redefinition involves making decisions about disclosing cancer to potential dating or intimate partners, as well as dealing with potential negative reactions and stigma. By acknowledging these challenges, oncology professionals can be effective change agents in promoting healthy social involvement, sexuality, and intimacy for cancer patients and survivors throughout a continuum of care that initiates at the time of diagnosis and continues on through phases of treatment and, for many, post-treatment survival.

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