Mira Harrison-Woolrych
Editor

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Chapter 1
Medicines for Women: Medicines for Half the World

Mira Harrison-Woolrych

Introduction

Medicines for women are not a minority issue: women represent half our worldwide population and at all ages women take more medicines than men (Kaufman et al. 2002). A population survey conducted in the United States (USA) showed that 89 % of women aged 45–64 years took at least one medication – including prescription and non-prescription medicines – and 43 % in this age group took five or more medicines (Kaufman et al. 2002). Women primarily take responsibility for contraception (Ringheim 1993) and mothers are responsible for administering medicines to babies – both before and after delivery – and to children too. The health of women determines the health of families and of wider communities, so we all have a vested interest in the medicines women take throughout their lifetimes.

In this book many issues concerning medicines for women are brought together for the first time in one volume. There have of course been other texts on specific groups of medicines for women (for example, contraception, medicines in pregnancy) and thousands of research publications on individual medicines, but my aim in editing this book was to construct a work which pulled the focus onto the subject of women's medicines: to recognise women as important – and often vulnerable – consumers of medicines and address some of the issues which prescribers, healthcare workers, patients and their families face on a daily basis around the world.

In this opening chapter, I begin with some historical and social perspectives which provide the backdrop for the setting in which medicines for women are prescribed. I then present an overview of the following 18 chapters of this book, in which I summarise and comment on some of the most significant issues associated

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with the medicines, vaccines and devices available for women today. Amongst the technical evidence-based information presented in each chapter, there are many fascinating stories – some familiar and some less so – and important themes emerge throughout this book.

In the latter part of this chapter we discuss some general principles about prescribing medicines to women, again drawing on the valuable information provided in each of the other chapters. Finally, I present some conclusions from this book and how we might move forward from here.

Historical and Social Perspectives

Women have been using medicinal products for at least 2,000 years. Soranus was a Greek physician who practised medicine in Alexandria, Egypt and later in Rome during the first part of the second century A.D. He wrote a four-volume work on gynaecology which included the following advice on contraception (Shelton 1998):

> It is safer to prevent conception from occurring than to destroy the fetus through abortion. . ..therefore one must avoid intercourse at those times which we said were favourable for conception. . .It also helps, in preventing conception, to smear the entrance to the uterus with old olive oil or honey or sap from a cedar or balsam tree, alone or mixed with white lead. . ..One might also add a clump of finespun wool. . .

The first part of this statement is very enlightened for its time, but it is sensible (perhaps even obvious) advice which remains true today. The latter part of Soranus' text above, reveals some of the contraceptive products which women were advised to use in the second century AD. It is difficult to know whether women actually used these methods and if they did, how effective and safe they were. But this text shows that medicines for women have been a feature of gynaecological practice for the duration of the speciality itself.

It is also likely that women before this time were using their own treatments for female disorders and for prevention of pregnancy. A tutor at a family planning course in the UK told us that women have known for centuries that half a lemon could be inserted into the vagina for use as a cervical cap. She would not be drawn on the details of how effective or safe (or comfortable) this was, but advised that one advantage of the lemon method was that the other half could be used in a gin and tonic, either before or after coitus!

The history of medicines and devices for women to use as birth control is closely linked to the history of women's development in many socio-cultural and economic respects. It has been a key component in movements for gender equality and women's rights, as the ability to limit family size is an important factor in determining not only women's and children's health, but also in determining women's opportunities (van der Gaag 2008). The broader aspects of women's lives are the backdrop against which medicines for women are prescribed, researched and

monitored. Throughout this book we will learn that the environment in which women live is a key factor determining how medicines are used and how effective and safe they are in real life use.

Marketing Medicines for Women: Early Tragedies for Women and Their Babies

The history of medicines for women has been central to the history of pharmacovigilance – the specialty which monitors the safety of medicines worldwide. This theme is developed further in Chap. 15 on medicines regulation and is well illustrated in Fig. 15.2 of that chapter (p. 437). Pharmacovigilance in many countries began in the wake of the tragic story of thalidomide, when women and their babies became the innocent victims of a medicine designed to relieve morning sickness of pregnancy. Dr WG McBride, an obstetrician and gynaecologist from New South Wales, Australia was the first to report the shocking limb deformities he noticed in babies born to women who had taken thalidomide (Distival®). His short but effective letter to the Lancet in 1961 is shown in Box 1.1:

Box 1.1: Text of Dr WG McBride's Letter to the Lancet, 1961
Thalidomide and Congenital Abnormalities

"Sir – congenital abnormalities are present in approximately 1.5 % of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ("Distival") during pregnancy, as an antiemetic or as a sedative, to be almost 20 %.

These abnormalities are present in the structures developed from mesenchyme – i.e. the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?"

WG Mc Bride, Hurstville, New South Wales

Lancet Editor's note – *in our issue of December 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide (Distival) with harmful effects on the fetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all preparations containing thalidomide.*

Fig. 1.1 1950s advertisement for desPlex (diethylstilboestrol)

In addition to thalidomide, there have been other lesser-known tragedies relating to medicines for women. From the late 1940s onwards, diethylstilboestrol (DES) was widely prescribed to pregnant women for prevention of miscarriage and desPlex® was advertised for prophylactic use in all pregnancies (see Fig. 1.1).

In the following decades, cases of a rare clear-cell adenocarcinoma (CCA) of the vagina were reported in young women whose mothers had taken DES during pregnancy. This type of vaginal cancer had previously occurred mainly in post-menopausal women and the new cases (with a median age of 19 years, range 15–29 years) alerted researchers to an association with DES, although exposure to the medicine had occurred many years prior to diagnosis of the adverse event (Goodman et al. 2011). The full story of DES was reviewed in the New England Journal of Medicine in 2011, 40 years after the issue was first reported in this journal (Goodman et al. 2011).

In Box 1.2 I have included a powerful personal testimony from Elizabeth Claire Hooper who discovered she was a "DES baby". It is a humbling and instructive story, which I hope will place women at the centre of all our efforts to prevent such tragedies happening again.

Box 1.2

It was my birthday and the phone was ringing. I expected it to be birthday greetings from a friend; instead, it was a nurse from the university health clinic. In an indifferent voice, she informed me that I had advanced cervical cancer and needed to seek treatment immediately. I quickly scheduled an appointment with a gynecologist for a second opinion; the second opinion was dire. The doctor flatly said I had both breast and cervical cancer. I desperately sought a third opinion from another OB/GYN. He examined me and told me that I did not have cancer, but I was a "DES Baby." Fortunately, I had found a gynecologist who is an expert in DES exposure. I was relieved to not have cancer, but the ramifications of being a DES Baby didn't fully sink into my consciousness at that moment.

Diethylstilbestrol (DES) is a synthetic form of estrogen that was prescribed to pregnant women in the United States from the 1940s through the early 1970s to prevent premature labor, miscarriage, and other potential complications of pregnancy; it was also used to "dry up" a mother's lactation during the time in which American women were inculcated with the idea that "formula" was superior to breast milk. DES was still being used in Europe into the late 1970s. By one estimate, DES was prescribed to six million women worldwide, even though a clinical study done in 1953 concluded the drug did not prevent miscarriages.

DES is a potent carcinogen. Pregnant or nursing women who took the drug have higher risks of certain cancers; this carcinogen passes from generation to generation with no end in sight at present. As a DES Baby, it would be difficult for me to have biological children; and if I did so, that child and all my descendants would still suffer from the increased risks of cancers and of DES-related deformities.

(continued)

Box 1.2 (continued)

I am lucky that I have not yet developed any DES-related cancers. I am lucky that my DES-related deformities are internal, not external. However, I'm not so fortunate in that this has been a "pre-existing condition," and that I have had to pay "out of pocket" for all the required, extra cancer screenings. Ironically, miscarriages (and infertility) are common among those women who were the progeny of mothers exposed to DES.

Few class action lawsuits against the pharmaceutical companies that created and supplied this drug have been successful. To paraphrase one judge, when ruling against a "DES Baby" class action lawsuit, we wouldn't want to stymie the pharmaceutical industry's right to innovation.

Elizabeth Claire Hooper **May 2014**

Overview of This Book

In this section I will summarise key points from each chapter and identify some important matters for further consideration. One aim is to highlight issues to compel you to read more in each of the 18 chapters, which have been written by expert authors from around the world. I have also added my own comments on specific issues – some of which may be viewed as controversial, but one purpose of this book is to provoke discussion on some of the more difficult issues associated with medicines for women. A further aim of this summary is to consolidate the huge amount of information provided – to bring the book together as a whole and to highlight the important themes.

Medicines for Women is divided into three parts: first, issues relating to women's exposure to medicines and considerations for particular subgroups of women are discussed; second, specific groups of medicines for women are reviewed; and in the third part different perspectives on women's medicines are presented. I have also identified some interesting (and often alarming) facts and figures from the 18 chapters and these are presented in Table 1.1.

Part I: Women's Exposure to Medicines and Consideration of Special Sub-populations

Examination of the effect of sex differences on the phases of drug disposition is an appropriate way to begin to understand how women's exposure to medicines may differ from men's. In Chap. 2, Drs Emmanuel Fadiran and Lei Zhang from the US Food and Drug Administration (FDA) examine sex differences in pharmacokinetics and consider how these may impact on the safety of medicines in women.

Compared with men, women generally have a lower total body weight, a higher proportion of body fat, a lower body surface area, lower muscle mass, smaller organ size, a lower glomerular filtration rate, and also gastrointestinal differences (e.g. lower gastric acid secretion, longer bowel transit times) – all of which may influence how medicines are processed.

Fadiran and Zhang carefully explore sex differences in all four phases of drug disposition: absorption, distribution, metabolism and excretion. Understanding these differences will enable us to consider how exposure to medicines may differ in women and the authors of this chapter conclude this is '*critical for optimal dosing in both sexes*'. They also consider how female sex hormones and changes during physiological processes (e.g. throughout the menstrual cycle or during pregnancy) and molecular differences (e.g. differences in metabolizing enzymes and transporter proteins) may affect these pathways. However, Fadiran and Zhang also point out that sex-based differences in pharmacokinetics do not apply to all medicines and when these do occur, the magnitude of any differences may be small.

In the second part of Chap. 2, the authors present some interesting examples of medicines for which there are known sex differences in pharmacokinetics. These include ondansetron, olanzapine, amlodipine and zolpidem. For each of these examples, information is presented which demonstrates how sex differences in drug disposition can result in exposure differences which may affect the efficacy and safety of the medicine. These differences also underline the need for dose adjustment in women. Moving to the future, Fadiran and Zhang suggest routine evaluation of potential sex differences in pharmacokinetic studies. Sex is among the factors that can affect a medicine's pharmacokinetics and in turn, affect its safety and efficacy.

Whilst the US FDA has been collecting routine data on women in clinical trials for several decades, we learn elsewhere that it was not mandatory to include women in government funded clinical research protocols until after the 1993 US National Institute of Health (NIH) Revitalization Act (Chap. 16, political and religious perspectives, p. 487). Therefore, older medicines may have been approved without specific pharmacokinetic or other clinical data from women. Collection and analysis of more data from women in clinical trials will allow more accurate dosing regimens to be determined, which will hopefully improve the effectiveness and safety of medicines for women in due course.

Having considered differences between women and men in terms of how medicines are processed, we move on to consider some sub-groups of women and evaluate prescribing in these special populations. In Chap. 3, Dr Sue Bagshaw – a specialist in youth health in New Zealand – considers a group of patients who may fall between the two stools of girlhood and womanhood. Adolescent or young women require special consideration: some insightful comments, relating to the development of the brain during this time, show us why there may be challenges in prescribing to and advising young people. (This chapter is particularly interesting if you are the parent/caregiver of teenagers at the time of reading this book!) Bagshaw also covers the legal and medical issues of patient consent in this age group and

concludes that assessment of a patient's ability to consent to medical treatment should be based on competency, not absolute age.

To demonstrate the complexities of advising and prescribing to adolescent women, Bagshaw discusses two commonly prescribed medicine groups: contraceptive medicines and medicines used for mental health issues, in particular depression. The focus on management of depression is an important inclusion in this book as women suffer from mental health disorders more frequently than men (also discussed in Chap. 14, perspectives on primary care) and take more psychotropic medicines than men (Hausken et al. 2007). Bagshaw shows us useful models of care for common clinical scenarios and encourages the use of simple diagrams to assist in communication with young women. Some examples included will be helpful aids for clinical practice. Bagshaw concludes that whilst the prescribing of medicines to young women may be similar to that for older women, the key difference is in the nature of the communication needed. The importance of good communication is a recurring theme of this book: the ability to listen to patients, relate what we know and assist women in their treatment decisions are all vital in our research and clinical practice.

The safety of medicines during pregnancy is a key concern to many women and their families and in Chap. 4 – by Dr Yifat Gadot and Professor Gideon Koren from the Canadian Motherisk programme – we learn that up to 90 % of pregnant women are reported to take at least one medicine during pregnancy. This remains a cause of anxiety for doctors and other prescribers: whilst knowing pregnant women should not be denied treatment with medicines, we are still haunted by the thalidomide and diethylstilboestrol tragedies. Gadot and Koren argue that perhaps prescribers have become too cautious and that pregnant women – many of whom have important medical conditions requiring treatment – have become therapeutic orphans.

In their masterly overview, Gadot and Koren first present us with summary information on medicines which are considered safe during pregnancy. Readers may be surprised by the number medicines which are considered safe (presented in Table 4.1, Chap. 4, p. 99). The authors of Chap. 4 then review the medicines for which there are safety concerns if taken during pregnancy or breast feeding. This list includes: antibiotics, biological therapies, angiotensin-converting enzyme inhibitors, antidepressants, lithium, anticonvulsants, codeine, corticosteroids, leflunomide, isotretinoin, methotrexate, misoprostol, mycophenolate mofetil, thiopurines, warfarin and also the rubella vaccine. This is an extensive list too and one which includes commonly prescribed medicines, both for acute illness and for women with long term conditions.

Many women face difficult choices about medicines during pregnancy and lactation, especially women with chronic diseases, whose condition may present significant risks if untreated. The example of women with epilepsy is discussed further in Chap. 19 on risk communication (p. 593) in which Bruce Hugman comments that good information is sometimes hard to find, especially for women themselves. For prescribers, information on risks of medicines during pregnancy may be presented in drug formularies and on product data sheets: in an attempt to standardise this, the FDA has assigned pregnancy categories which are summarised

in Chap. 4. The value of these categories may be debated – some information is better than none and use of standardised categories should help prescribers and pharmacists around the world, but so often we read "there are no adequate and well-controlled studies in pregnant women" – for example in FDA category B or C (see Chap. 4, p. 122) and are still unsure how to advise patients.

What do we do in the face of uncertainty? We may look for pregnancy registries or post-marketing data on risks of particular medicines in pregnancy (but these are often lacking too) or turn to expert centres for advice. In this respect, most countries are not as fortunate as Canada which has the excellent Motherisk programme. If a global version of Motherisk could be developed, this would improve the available information on pregnancy and lactation drug exposure and reduce the anxiety associated with this area of medicines for women.

Part II: Specific Medicines for Women

In the second part of this book we move to the specific medicines, devices and vaccines commonly used by women.

Oral contraceptives

Oral contraceptive medicines are widely prescribed across the world and in Chap. 5 this group of products is expertly reviewed by Ms Julie Craik and Dr Louise Melvin from the Clinical Effectiveness Unit (CEU) of the UK Faculty of Sexual and Reproductive Healthcare. Oral contraceptives (OCs) are very effective in preventing pregnancy, but their effectiveness in real life use is dependent on accurate compliant use. Missed pills are an important concern for all women using OCs, but more so for users of traditional (i.e. non-desogestrel) progestogen-only pills (POPs) where the margins for late pills are shorter, due to different mechanisms of action. These issues are discussed in Chap. 5, which also includes review of the efficacy and safety of both types of OC.

An extensive amount of research over more than 50 years has identified and aimed to quantify the risks associated with oral contraceptive medicines, including breast cancer, cervical cancer, myocardial infarction and stroke, and venous thromboembolism (VTE). Craik and Melvin discuss these serious concerns in some detail (with VTE covered by Susan Jick in Chap. 6) and also cover other potential safety issues including bone health, glaucoma and gastrointestinal conditions – for which the evidence is currently less certain and more research is required. Whilst the results of most studies to date suggest an increased risk of cervical cancer and possibly a small increased risk of breast cancer in women taking combined oral contraceptives (COCs), Craik and Melvin also present evidence which demonstrates that COCs protect women against ovarian and endometrial cancer. This benefit lasts for several decades after stopping the pill and raises the question

Table 1.1 Editor's selection of interesting facts from this book

Summary of statement	Chapter title (abbreviated)	Chapter number
Several mechanisms relevant to drug absorption and disposition have been shown to exert sex-specific activity differences, and for some drugs these have the potential to result in clinically relevant differences in pharmacological response	Pharmacokinetics	2
Girls start their cognitive development earlier than boys and may be more advanced than boys in terms of their chronological age	Adolescent women	3
During the last 50 years the gap between biological and social adulthood has widened considerably		
Twelve million prescriptions for potentially teratogenic medications are prescribed annually to women of reproductive age in the USA	Medication use in pregnancy	4
Less than 50 % women prescribed potentially terato genic medicines receive contraceptive counselling		
Clinical trials show a gross one year cumulative failure rate of the COC between 0.2 and 2.3 per 100 women, but data from real life use suggest 9 % of women using oral contraceptives (COCs and POPs) will experience an unintended pregnancy in the first year	Oral contraceptives	5
Data largely support the view that use of oral contraceptives does not increase a woman's risk of death as compared with non-use		
The rate of VTE in women using a COC containing levonorgestrel, norethisterone or norgestimate (second generation COCs) is approximately 5–7 per 10,000 women age <35 years	Oral contraceptives and the risk of VTE	6
In the USA one million teenage girls become pregnant each year	Emergency contraception	7
If the emergency contraceptive pill is used within 12 h of unprotected intercourse, the risk of pregnancy is less than 1 %		
Etonogestrel and levonorgestrel implants are reported to have pregnancy rates of 0.13 and 0 per 100 women respectively	Contraceptive devices	8
In the first 20 days following insertion of an intra-uterine device, the risk of PID is increased six fold but remains low thereafter		
HPV vaccines in women and girls who are not already infected prevent >98 % of HPV16/18 caused pre-cancers (e.g. CIN)	HPV vaccine	9
The most commonly reported vaccine related adverse events are injection site reactions including pain, swelling and erythema		

(continued)

Table 1.1 (continued)

Summary of statement	Chapter title (abbreviated)	Chapter number
Chronic pelvic pain accounts for 10 % of referrals to a gynaecologist, 12 % hysterectomies and 40 % diagnostic laparoscopies. Prevalence in the community is estimated at 24 %	Chronic pelvic pain	10
Typical pharmacologic treatments for neuropathic pain achieve only partial relief in 40–60 % of individuals		
In the late 1990s about 50 % of UK women aged 50–64 years had ever used MHT	Menopausal Hormone Therapy (MHT)	11
5 years use of oestrogen-progestagen MHT results in a net excess of potentially life threatening events affecting 14 per 1,000 users aged 50–59 or 22 per 1,000 users aged 60–69 in women with a uterus		
The relative risk of clinical vertebral fractures was 0.23 (95 % CI 0.14–0.37) in zoledronic acid treated patients when compared with placebo. Corresponding values for non-vertebral, non-hip fractures were 0.75 (0.64–0.87) and for hip fractures were 0.59 (0.42–0.83)	Bisphosphonates	12
In 2000, about 16 % of the US population used herbal medicines: this increased to about 30 % by 2013	Herbal medicines	13
In 2009, about 45 % of pregnant women used a herbal medicine		
In the USA, 18 women die every day from an overdose of prescription medicines (five-fold higher than 10 years ago)	Primary care	14
If all women were of normal weight, exercised daily and ate a healthy diet, the number of women with hypertension could be reduced by 50 %		
Animal studies conducted with thalidomide prior to marketing were only conducted in rodents, species which turned out to be incapable of identifying thalidomide embryopathy	Medicines regulation	15
For reports submitted by patients in the UK MHRA Yellow Card database, the proportion of ADRs reported for females is 64 %, compared with 35 % for males (with 1 % unknown gender)		
In Russia, a tremendous unmet need for contraception exists with abortion still remaining the main method of birth control	Political and religious perspectives	16
In Judaism at least a sixth of the Oral Tradition's volume is dedicated to women, with a substantial amount dealing with female health and fertility		

(continued)

Table 1.1 (continued)

Summary of statement	Chapter title (abbreviated)	Chapter number
Fifteen percentage of the world's population utilises 91 % of pharmaceutical products available worldwide	Developing countries	17
Only one third of lower to middle income countries have access to essential drugs		
A national survey of physicians found that >65 % of respondents were unaware of gender differences in the symptoms and tests used to diagnose heart disease	Risk communication and gender issues	18
In Tibet women prefer to learn pregnancy-related health messages from their close family, especially their mothers, rather than group teaching, television/ radio programs, and health professionals visiting patients' homes as health communication modalities		
In his book "Risk Savvy" Gigerenzer proposes that free access to the Cochrane Library, to journal articles and to medical records are amongst the reforms necessary to support literate patients in their pursuit of the best possible information and decisions	Risk communication and specific medicines for women	19
Risk communication must take account of multiple variables intrinsic within patients and in the total context of their lives; it must also take account of the fact that many patients and many health professionals are seriously deficient in risk literacy		

whether COCs should be prescribed for cancer prevention. However, the evidence is currently insufficient to allow such recommendations to be made at this time.

Other benefits of COCs, including the management of menstrual dysfunction (for example, dysmenorrhoea, menorrhagia and irregular bleeding) acne, polycystic ovarian syndrome and endometriosis, are also discussed in Chap. 5. Consideration of these benefits may be overshadowed by concerns women have about the risks of OCs, both serious and minor. Weight gain associated with the pill is an issue which has become almost an urban myth – according to colleagues in general practice, this is a commonly cited reason that younger women give for not wanting to take an OC. Craik and Melvin discuss the evidence on the weight issue, including two Cochrane reviews which did not find evidence supporting a causal association between OCs and weight change (Lopez et al. 2013, Gallo et al. 2014). However, the authors of these reviews also concluded that the available evidence was insufficient and further research on weight change with OCs is still needed.

There are fewer contra-indications to prescribing POPs and research to date suggests the 'mini pill' does not carry the same serious (but rare) risks of COCs – in particular cardiovascular risks – so is there an argument to support first line

prescription of the POP to more women? Craik and Melvin present evidence which shows similar efficacy of COCs and POPs in the first year of real life use. However, most POPs need to be taken at the same time each day or effectiveness is reduced (and pregnancies may occur) and so adherence may be more difficult for women using POPs. Adverse effects may be an issue too and the higher likelihood of irregular bleeding patterns with POPs may also be a disadvantage for some women. In counselling women about the two main groups of OCs available, it is important to consider the circumstances of each individual and their socio-cultural circumstances.

Venous Thromboembolism and Oral Contraceptives

Safety concerns surrounding the risk of venous thromboembolism (VTE) with oral contraceptive pills have been a much discussed issue in pharmacovigilance of women's medicines and inclusion in this book was mandatory. Professor Susan Jick is a highly respected researcher from the Boston Collaborative Drug Surveillance Program at Boston University, who has lead several epidemiological studies investigating the risk of VTE with oral contraceptives and had advised the US FDA on this issue. In Chap. 6 Jick provides an excellent overview of the major studies which have investigated the risk of VTE from the early 1960s to the present day. Her expertise as an epidemiologist is welcome in explaining the factors we need to consider when interpreting these studies.

VTE is a potentially serious and sometimes fatal complication associated with combined oral contraceptive (COC) pills and this risk was identified early in the history of the Pill. Because the incidence of VTE is very low in women taking OCs, large epidemiological studies have been required to investigate this further. In Chap. 6 Jick summarises the evidence from these studies which has shown that, in women without other predisposing risk factors, there is an absolute risk of around seven cases of VTE per 10,000 women taking a second generation pill for a year. In the past 20 years there have been concerns about a higher risk of VTE associated with newer third generation and drosperinone-containing pills and these discussions continue today in regulatory authorities around the world. Jick concludes that the risk of VTE with these newer pills is between 1.5 and 3 times higher than the risk with the older second generation pills.

While VTE is a rare adverse event of COCs, it may be fatal: deaths of healthy young women have made headline news in some countries. The issues surrounding media coverage of this risk and pill scares in some countries are discussed further in Chap. 19. Many women requesting COCs will have heard of the risk of VTE and we need to explain the facts to them clearly and objectively, using diagrams and charts (e.g. a Paling palette as illustrated in Fig. 19.2, Chap. 19, p. 620) if necessary, to explain the size of the risk. As the contraceptive effectiveness of all COCs is very similar, my advice would be to ignore the marketing hype of certain pharmaceutical companies and for first line prescribing i would recommend a second generation COC, as these products have the lowest risk of VTE. Dr Dee Mangin concurs with

this advice in her chapter on primary care perspectives on prescribing medicines for women (Chap. 14).

Emergency Contraception

In Chap. 7, Dr Katarina Ilic reviews the topic of emergency contraception (EC). In this chapter she describes the main methods of post-coital contraception available and summarises their mechanism of action, efficacy and safety. An important reminder is that although in recent years more effective and safer emergency contraceptive pills (ECPs) have become available, the most effective method of post-coital contraception is insertion of a copper intra-uterine device (IUD). However, for most women, tablets offer a more acceptable method and ECPs may now be obtained without a prescription in many countries, with no need to see a doctor or have a physical examination and procedure, as is required for fitting an IUD. Increasing access to EC is an issue discussed in this chapter and also in Chap. 16 by Brian Edwards and Veronika Valdova in their coverage of political and religious issues which have affected the availability of EC in the USA.

Emergency contraceptive pills are safe and effective medicines for women. In most countries a single dose levonorgestrel (LNG) ECP is approved for use up to 72 hours after unprotected sexual intercourse and ulipristal acetate (UPA) is approved in some countries for use up to 5 days after unprotected sex. Women should be advised to take ECPs as soon as possible after unprotected intercourse or contraceptive failure and they also need to be informed about where and how ECPs may be obtained, including during outside clinic hours. To promote early use, we should stop referring to this method as the 'morning after pill' and start calling it the 'immediately after pill' – which also avoids the presumption that the unprotected sex happened during the evening or night!

Another incorrect presumption held by some, is that ECPs are abortifacient medicines. This is a sensitive issue which has been discussed at high level committees around the world. In Chap. 7 Ilic informs us that in 2002, a Judicial Review in the English High Court ruled that pregnancy begins at implantation, not with fertilization and as emergency contraception is a method of contraception not abortion, it can continue to be lawfully supplied. Chapter 7 also discusses studies on the mechanisms of action of ECPs and understanding the results of these studies and the science of how these medicines work will enable us to have factual, rather than emotional, discussions with women (and men) who are concerned that using ECPs may conflict with their religious or ethical beliefs.

In many countries, even where access has been widened, women's use of emergency contraception has been inexplicably low, including countries with high rates of teenage pregnancy and abortion. Some studies have suggested a gap between knowledge and actual use of EC. For example, Ilic describes an American study which reported that whilst 43 % of women who had had a termination of pregnancy knew EC was available, only 6 % of these women had ever used it (*see* p. 203). There are many issues regarding the uptake and use of EC still to be

researched, but in the meantime, it is in the interest of women's health that we promote the use of post-coital contraception – not as a regular method of contraception, but as a back-up emergency method when required. All methods of EC carry lower risks than abortion or pregnancy.

Contraceptive Devices for Women

For regular, long-acting and reversible contraception for women, in Chap. 8 Ms Julie Craik from the CEU of the UK Faculty of Sexual and Reproductive Healthcare and Dr Sam Rowlands, Chair of the Clinical Effectiveness Committee – describe a range of devices available. Contraceptive devices have been included in this book, not only because of the valuable options they provide to women, but also because most major medicines authorities worldwide now evaluate and regulate medical devices with the same rigour as for pharmaceutical products (FDA 2014). This is appropriate, because the efficacy and safety of devices for women is equally as important as for medicines.

Some contraceptive devices covered in Chap. 8 have been used by millions of women worldwide for many years, for example intrauterine contraceptive devices (IUDs). Craik and Rowlands provide a detailed yet concise review of the efficacy and safety of non-hormonal and hormonal IUDs. They conclude that IUDs are highly effective and present an objective assessment of the safety concerns. In some countries IUDs are still very under-utilised, despite evidence which, as discussed in Chap. 8, supports the effectiveness, safety and cost-effectiveness of this method.

While IUDs are effective and safe methods of contraception, continuing post-marketing monitoring is needed – as for other medicines for women. For many years, the NZ Intensive Medicines Monitoring Programme (IMMP) independently monitored the utilization and safety of IUDs (Zhou et al. 2003) and published the results of nationwide cohort studies of women using these devices (Harrison-Woolrych et al. 2002, 2003). Data from IMMP studies were shared with regulators and clinicians and for many years the IMMP was the only unit worldwide performing such cohort event monitoring studies of IUDs. However, from 2010 onwards, funding to continue these studies (or to initiate monitoring of new devices or medicines) could not be found from either the NZ Ministry of Health (Medsafe) nor from pharmaceutical companies or other sponsors. In December 2013 the IMMP closed due to insufficient funding. Now, the only type of post-marketing surveillance for IUDs (and other contraceptive products) in NZ and most other countries are spontaneous reporting programmes, which do not collect denominator data and are therefore unable to calculate frequency rates of adverse events (Harrison-Woolrych 2014).

Chapter 8 also includes a review of progestogen implants and other contraceptive devices for women. Again, Craik and Rowlands give an excellent summary of the evidence for effectiveness and safety of these products. Contraceptive implants are highly effective, at least partly because adherence with daily tablet taking is not required. However, there have been some concerns with implants, for example

insertion problems with the etonogestrel implant Implanon®. This issue was first reported in 2005 (Harrison-Woolrych and Hill 2005) after more than 200 cases of unintended pregnancy were reported to the Australian Therapeutic Goods Administration (TGA). This led to training initiatives for Australian inserters, but in the UK, it took another 6 years for the Medical Defence Union to publish advice on this issue (MDU 2011). Craik and Rowlands document that by November 2013, 1,334 pregnancies associated with Implanon® had been reported to the UK Medicines and Healthcare products Regulatory Agency (MHRA), 1,076 of which were listed specifically under the heading Unintended Pregnancies (see Chap. 8, p. 4). Might some of these contraceptive failures in the UK have been prevented if earlier action had been taken following the Australian experience? This example underlines the need for collaborative global pharmacovigilance and effective systems of communication, where issues raised on one side of the world are relayed and acted upon in the rest of the world within the shortest possible time frame, in order to minimise risk to patients.

Newer contraceptive devices – including the combined hormonal patch and the vaginal ring are also included in Chap. 8. Craik and Rowlands conclude that "*contraceptive devices releasing estrogen and progestogen directly through skin or mucous membrane are considered to have similar risk and benefit profiles as combined oral contraceptives*". This statement is based on data available to date (e.g. from clinical trials and epidemiological studies) but for newer products – such as the contraceptive patch and vaginal ring – this is much less information than has been collected for oral contraceptives over many years. Usually pre-licensing clinical trials do not include a sufficient number of patients to quantify the risk of rare adverse events, for example, VTE associated with combined hormonal contraceptives. Regulatory authority assessments of new medicines/devices are based on the information available at the time a licence application is submitted and it would be unrealistic to suggest that new products should not be approved until studies including thousands of women had been completed. NuvaRing® has been approved in the USA and other major markets as '*adequate information was submitted to demonstrate the product was safe and effective for use*' (CDER 2001) but cases of VTE have been reported in the post-marketing period (DrugWatch 2014). In June 2014 Drugwatch.com (a website which offers women a 'free case review' if they have suffered a VTE whilst using NuvaRing®) reported:

> More than 1,500 people have filed federal lawsuits against Merck, the product's manufacturer, claiming the company created a defective product, failed to adequately test the product, engaged in deceptive marketing and failed to properly alert consumers to the dangers associated with NuvaRing. (DrugWatch 2014)

As NuvaRing® contains similar active ingredients to oral contraceptives, the occurrence of cases of VTE is not unexpected, as covered in Chap. 6. The number of lawsuits relating to the vaginal ring may well increase, but it will require collection of high quality post-marketing data to properly evaluate this risk further.

Sometimes pre-licensing clinical trials contain safety data which raise concerns about a product at the time of assessment of the licensing application. This was the

case in 2007, when the NZ medicines regulatory body (Medsafe) declined an application to licence the Evra® contraceptive patch. Following assessment of data submitted with the licensing application, the NZ Medicines Assessment Advisory Committee advised that "*the application for EVRA 150/20 (norelgestromin/oestradiol) be declined under section 21 of the Medicines Act 1981 for female contraception. This decline is because of an unfavourable risk: benefit ratio. The Committee remained concerned about the high incidence of oestrogenic side effects associated with EVRA*" (information obtained in June 2014 via a request under the Official Information Act 1982). The decision not to approve the Evra® contraceptive patch in NZ could be seen as denying NZ women an alternative method of combined hormonal contraception which has since become available in other countries. Or, it could be seen as protecting NZ women from exposure to a product which appears to carry higher risks than other equally effective methods of combined hormonal contraception.

HPV Vaccines

Millions of girls and women worldwide have now been vaccinated against human papilloma virus (HPV) induced disease. Professor Margaret Stanley, from the University of Cambridge, concludes her excellent chapter on HPV vaccines (Chap. 9) by stating that this is a major public health achievement. It certainly is, and the story of development of a vaccine to prevent cervical cancer is perhaps the most positive account of a medical product in this book. The story began long before HPV was cloned from cervical cancer biopsies (confirming the link between these viruses and this cancer) in 1983 (see Chap. 9, p. 283). Early epidemiologists observed that nuns almost never developed cancer of the cervix (and this was shown in a study of 13,000 nuns performed in 1952) and that the incidence was highest in women with multiple sexual partners. This suggested that the cause of cervical cancer may be a sexually transmitted infection, but it was not until the 1970s that the link with HPV was recognised, leading to cloning of the virus from cancer biopsies in the 1980s. Stanley documents how this rapidly led to the development in the 1990s of two vaccines to target infection by the oncogenic HPV 16 and 18 and also one to target HPV 6 and 11 which cause genital warts. These vaccines were first licensed in 2006 which she believes is '*a remarkable story of scientific achievement, entrepreneurial drive and commercial and scientific interaction*'.

The HPV vaccines chapter provides a comprehensive account of the science of these vaccines and a review of their efficacy and safety. Both vaccines have been shown to be more than 94 % effective against HPV 16/18 induced high grade cervical intraepithelial neoplasia (CIN 2 and 3) – which is the ethically acceptable proxy endpoint for the efficacy of these vaccines against cervical cancer. Safety data are available from randomised controlled trials (RCTs), spontaneous reporting programmes worldwide, active surveillance schemes and some large post-licensing studies sponsored by the manufacturers and/or national regulatory authorities. The safety profile of the HPV vaccines in 2014 – after distribution of more than

160 million doses worldwide – is very reassuring, with the most common adverse event being a sore arm after the injection.

In view of the large amount of efficacy and safety data now available for HPV vaccines, Stanley writes that the focus and discussion has now moved to implementation, access and affordability. The key issue for implementation is the need to vaccinate young women before the age of sexual debut and schemes should aim to target girls aged 9–14 years. She describes highly successful school programmes in Australia which achieved coverage rates – for the full three dose regime – of about 75 %. The Australian programmes produced some striking effectiveness data: the incidence of genital warts fell by 93 % in women under 21 years and the vaccine was also effective in reducing CIN 2 and 3 by about 48 % (see Chap. 9, pp. 277–278). The story of the HPV vaccine gives hope that in years to come we will describe to our daughters (and sons) the 250,000 deaths per year from cervical cancer in historical terms. These vaccines will save women's lives and will also reduce the significant morbidity associated with HPV infection, including genital warts and invasive procedures for high grade CIN and cancer.

Chronic Pelvic Pain

Sadly, the story for women with chronic pelvic pain (CPP) is not yet predicted to have such a positive outcome. In Chap. 10, Professor Wayne Gillett and Dr David Jones inform us that the prevalence of CPP – defined as non-menstrual pain of at least 6 months duration – is approximately 25 % in women aged 18–50 years. There are other worrying statistics in this chapter, especially for women needing surgical procedures. Gillett and Jones report that persistent post-surgical pain occurs in 12–18 % of women after Caesarean section and 32 % of women after hysterectomy: they comment that it is a largely unrecognised problem in clinical practice. This is important information for obstetricians and gynaecologists, when considering the benefits and risks of procedures for their patients – we should inform women having a hysterectomy that almost a third may experience chronic pelvic pain afterwards. This also adds to the ongoing debates about whether Caesarean section rates are too high in some countries (Robson 2001) and the need to consider medical alternatives to hysterectomy (Banu and Manyonda 2005).

Gillett and Jones provide a comprehensive overview of the mechanisms and causes of chronic pelvic pain. As experienced practitioners in this field, they offer insightful comments on how understanding pain mechanisms can assist in assessment and treatment of women with CPP. They include a review of the commonly used pharmacological treatments for CPP, but describe the evidence for effective treatment as '*weak at best*' with only single studies representing much of the available evidence. Gillett and Jones report that of 2,000 citations on CPP, only 21 were identified as controlled trials or prospective cohort studies including 50 or more women, or cross sectional or case series studies with 100 women.

Traditional treatments for CPP have been directed at disease-based pathology and in Chap. 10 the authors suggest that this may be too simplistic. In presenting a

'biopsychosocial model' of pain Gillett and Jones emphasise the need to understand all the factors which may contribute to a woman's experience of chronic pain. They observe "*it is not surprising that failure to recognize a mechanism for pain leaves many women incorrectly labelled or dismissed under the guise of psychological problems*" and note that an important issue for women suffering from chronic pain is communication. Chapter 10 includes discussion of a study which examined the attitudes of women with pelvic pain to the gynaecological consultation (Price et al. 2006). This showed that women want their pain to be taken seriously, they want an explanation as much as a cure, and that this in itself may be all that is required for them to manage better with their pain. Throughout this book we learn that women want to be treated as individuals, not just as vessels for medication, and that listening and understanding are essential components of communication in all areas of women's health.

Menopausal Hormone Therapy

In Chaps. 11 and 12 we move to medicines which have been commonly prescribed to older women, particularly in the developed world. Professor Emily Banks (Head of Chronic Disease Epidemiology at the National Centre for Epidemiology and Population Health in Canberra, Australia) begins her excellent summary of Menopausal Hormone Therapy (MHT) by explaining this term is preferable to Hormone Replacement Therapy (HRT) because it avoids the implicit assumption that postmenopausal women have a hormone deficiency that requires replacement. MHT has been available in some countries since the 1930s, with use rapidly increasing in the 1980s and 1990s. Banks informs us that by the end of the 1990s, in the UK approximately one third of women aged 50–64 years were current users of MHT.

The rise and subsequent fall in use of MHT, is perhaps one of the best examples in pharmacoepidemiology of how utilization of a medicine can be affected by analysis of data from appropriately designed and suitably powered RCTs, the judicious interpretation of appropriate observational data and the prompt and informed actions of medicines regulators. Prior to analyses of data from the Women's Health Initiative (WHI) and the Million Women Study (as discussed in Chap. 11), results from observational studies were interpreted as suggesting that MHT reduced the risk of coronary heart disease and it was undoubtedly this expectation which led to the intensive marketing, prescribing and consumption of MHT in many countries during the 1980s and 1990s.

However, as Banks explains in Chap. 11, results from the WHI study did not show reductions in coronary heart disease in women randomised to take MHT. In fact, the evidence of global harm with combined MHT led to the cessation of that arm of the trial. Further, in 2003 the writing group for the Million Women Study published results showing details of the increased risk of breast cancer in current users of MHT compared with women who had never used these medicines (Collaborators 2003). The results from these very large and well-designed studies gave prescribers, researchers, regulators, the pharmaceutical industry and women

themselves more reliable data on the benefits and risks of MHT. More informed prescribing, including advice from regulators that MHT should be used for the short-term treatment of menopausal symptoms, rather than the prevention of disease, led to a significant fall in the use of MHT in many countries including the USA, UK and Australia.

The issues which arose with MHT demonstrate that observational studies are not necessarily the best tool for assessing an outcome such as coronary heart disease, because MHT tends to be prescribed preferentially to women at lower risk of the disease. Many of the factors influencing the risk of coronary heart disease, including silent pre-existing disease, are not fully accounted for in observational studies. When women were randomised to treatment groups in large well designed studies, a benefit of MHT in reducing coronary heart disease was not seen. Moreover, a significant increase in the risk of stroke and venous thromboembolism was observed.

In 2007 the UK Medicines and Healthcare products Regulatory Agency (MHRA) published an excellent Public Assessment Report on MHT and Banks summarises the key findings and recommendations from this independent and quantitative review in Chap. 11. The report describes the key benefits and risks of MHT, in particular with regard to serious disease. It states the absolute risks of breast cancer, endometrial cancer, ovarian cancer, stroke, coronary heart disease, VTE, hip fractures and other conditions in women with and without a uterus and for both 5 and 10 years use of MHT. The MHRA report – and Banks' summary of it – are very clear, stating the number of additional cases of each disease which would be expected with use of MHT. They include strategies to minimise risk in women requesting MHT, the main advice being that these medicines should only be prescribed for moderate to severe menopausal symptoms and not for prevention of disease.

In the MHRA Public Assessment report it is gratifying to see results from work by British regulators and their advisory committees to help protect women from the risks of medicines. In the late 1990s, as a medical assessor at the MHRA, I was involved with formation of the first HRT sub-committee of the Committee on Safety of Medicines (CSM), which later developed into the body which produced the Public Assessment Report. However, it is disappointing to note that, 7 years after publication of the MHRA report, in many countries there are no independent and current guidelines for prescription of MHT.

Bisphosphonates for Osteoporosis

Bisphosphonates are amongst the most widely prescribed medicines for women, especially for the prevention and treatment of osteoporosis in older women. Utilisation of bisphosphonates has increased in many countries in recent years and this may be partly due to declining use of MHT since the early 2000s and the increased proportion of older women in the population of the developed world. In Chap. 12 Professor Stuart Ralston – a rheumatologist and specialist in metabolic

bone disease from the University of Edinburgh in Scotland – provides a clear description of the mechanism of action of bisphosphonates and summarises the efficacy and safety of the currently marketed products including etidronate, alendronic acid, risedronate, ibandronate and zoledronic acid.

For women with osteoporosis, Ralston concludes that bisphosphonates reduce the risk of non-vertebral fractures by 20–25 %, hip fracture by 40 % and vertebral fractures by 50–70 %. He makes the interesting observation that there have been no direct comparative studies of bisphosphonates against other anti-osteoporosis medicines and few comparisons between different members of the class and so it is difficult to draw conclusions about comparative efficacy in fracture prevention. Indirect comparison of results from different studies suggest bisphosphonates have similar efficacy to MHT and denosumab and probably superior efficacy to strontium ranelate.

Upper gastro-intestinal (GI) adverse effects – for example dyspepsia and epigastric pain – are common with oral bisphosphonates and there have been cases of oesophageal perforation, thought to be due to tablets sticking in the oesophagus. For these reasons and the somewhat complicated administration instructions (patients need to take oral bisphosphonates on an empty stomach and remain upright for at least 30 minutes afterwards) non-oral formulations have been developed in recent years. These include zoledronic acid which can be administered intravenously (IV) once a year and in some countries – for example NZ – this is funded for administration in the primary care setting. Ralston describes the safety issues with IV formulations, the most common issue being a transient flu-like illness. More serious safety concerns with all bisphosphonate medicines include atypical sub-trochanteric fractures and osteonecrosis of the jaw (ONJ). ONJ is thought to be a rare adverse event, but more research is needed into the frequency of this potentially devastating condition in real life use of bisphosphonate medicines.

A further interesting issue with bisphosphonate medicines is duration of use. Bisphosphonates inhibit osteoclastic bone resorption and have a long duration of action, but it currently not fully understood for how long they should be taken and for IV formulations, how often they should be re-administered. Ralston describes the results of one study which showed that the relative risk reduction for fractures with a single infusion of zoledronic acid was similar to that in patients who had received three infusions (see Chap. 12, pp. 360–361). Although this was based on a post-hoc analysis, it raises the question as to whether zoledronic acid could be given less frequently: to reduce the risk of adverse reactions to medicines, it is pragmatic to prescribe the lowest effective dose for the shortest possible duration. Whilst Ralston concludes that the overall benefit to risk is very positive for bisphosphonates, it would seem more research is needed to further reduce potential harm to patients taking these medicines long term.

Herbal Medicines for Women

In Chap. 13, Dr Sheila Wicks and Dr Gail Mahady provide a fascinating overview of herbal medicines used by women. Whilst the focus of this book is mainly on prescription medicines, there has been increasing use of alternative or complementary treatments in recent years and prescribers should have some knowledge of these medicines. Wicks and Mahady start by defining terms such as 'dietary supplement', 'traditional medicine' and 'herbal medicine' and we begin to understand the enormous number of products available (usually without a prescription) throughout the world. In some countries – for example, China – traditional practitioners have used herbal products for centuries. In the western world of major pharmaceutical markets, the last 15–20 years has seen a steep increase in use of herbal medicines. Wicks and Mahady describe how this market in the USA is now worth about half a billion dollars per year.

In 2013 herbal medicines were used by approximately one third of the USA population. In Chap. 13 we learn that women are the primary consumers of these products, using them to treat a wide spectrum of ailments including anxiety and depression, dysmenorrhoea and other menstrual disorders, symptoms of menopause, fatigue and the common cold. (Note that in other chapters of this book, authors have argued that some of these female 'ailments' (e.g. menopause) are not illnesses and treatment of female physiological processes represents medicalization of women's problems, often for commercial profit). Wicks and Mahady detail the use of five herbal products commonly used by women: black cohosh, cranberry, dang gui, green tea and panax ginseng. For each of these, they describe the common uses in women's health and review the evidence for efficacy and safety of these products. A rather alarming conclusion of this chapter is that whilst for some herbal medicines there is evidence of efficacy and safety, Wicks and Mahady state that for many herbal medicines used worldwide *'there is little in the way of information on quality, efficacy and safety*.' It should also be added that most of these products are available over the counter and most do not have an approved product licence, meaning they have not be subjected to the rigours of assessment by a medicines regulatory body.

Use of herbal medicines during pregnancy and labour is another concern. Chapter 13 includes an interesting section on this aspect of use of herbal medicines by women. Wicks and Mahady describe how use of herbal medicines during pregnancy is widespread in many countries: in Malaysia, they report that 73 % of women used a herbal medicine during labour. Another study showed that use of herbal products in the first trimester was associated with an increase in perinatal mortality (p. 378). Again, these authors report that evidence on efficacy and safety is lacking. They call for better regulation and increased funding of international independent groups – for example the World Health Organisation – to review all herbal medicines.

Part III: Perspectives on Medicines for Women

For the final part of this book, I invited selected authors to give wider perspectives on women's medicines. There are many different influences affecting how we care for and prescribe to female patients – some of these factors may seem obvious, others may not easily be discussed in the environment in which we work and there are others of which we may not even be aware. I encouraged the authors of these chapters to stand back from the individual medicines (although some products are discussed to illustrate particular issues) and look more broadly at the issues which may determine availability, utilisation and safety of women's medicines worldwide.

Primary Care

Dr Dee Mangin begins Chap. 14 with an important observation: most prescribing occurs within the environment of primary care, but the vast majority of evidence for the safety and efficacy of medicines in obtained from secondary care settings. With years of experience as a general practitioner in New Zealand, as director of a primary care research unit and as a Chair in Family Medicine in Canada, Dr Mangin is well qualified to explain the 'complex prescribing landscape of primary care' which doctors and other primary health care workers navigate through when treating women in this environment. In many countries, this is where women are seen for the majority of their health care and where most medicines for women are prescribed.

In Chap. 14, Mangin discusses assessment of risks and benefits in women in primary care, illustrating her points with some interesting examples of commonly prescribed medicines. She informs us that for statin medicines "*an analysis across all major prevention trials showed the absolute risk of benefit was less for women than for men, with no demonstrated statistically significant advantage in all-cause mortality, no clinically significant benefit in primary prevention and less absolute benefit (and therefore a higher number needed to treat) than men in secondary prevention* (Roberts and Redberg 2013)". This highlights the need to regularly re-evaluate the benefits (and risks) of continuing long term medication in primary care. Mangin suggests that computer software in general practice could assist with highlighting dates for review to ensure we consider stopping or reducing medicines as often as we consider starting them.

There are several other important issues relating to prescribing medicines to women which are covered in Chap. 14 including: polypharmacy (especially in older women), over-prescribing, medicalization of women's health issues (medicines for healthy women) and 'legacy drugs' (medicines for which efficacy data suggest should have a time limited prescription duration, but are often carried on indefinitely in primary care). Mangin also discusses some of the pressures doctors and women face from advertising and promotion of new medicines. When prescribing

for women in primary care, she suggests a '*super-precautionary principle*' which might mean, in prescribing medications for chronic conditions, that dosing could start at the lowest possible dose – lower than the standard dose recommendation – and be titrated upwards according to effect where possible.

General practitioners are usually the healthcare providers who manage the long term medical well-being of women and they face many challenges. Chapter 14 includes depressing figures on prescription drug abuse and prescribed medicines overdose (see Table 1.1), both of which are increasing in women in recent years. Understanding how we may help women in desperate situations requires not just and understanding of the prescriptions we have given them, but (as we keep returning to throughout this book) a deeper understanding of the socio-cultural environment in which women live. For many problems, including those for which 'lifestyle medicines' may be requested, Mangin suggests we go even further than stopping a patient's medicines and consider supporting women in using non-pharmacological treatments, which have lower rates of adverse reactions and other benefits. When assessing any treatment for women (or indeed any patient) our perspective should include comparative safety as much as comparative efficacy.

Medicines Regulation

The discipline of regulation of medicines may seem somewhat remote and complex to many practitioners, but in Chap. 15 we have an expert and experienced perspective from Dr June Raine and Dr Janet Nooney of the UK Medicines and Healthcare products Regulatory Agency (MHRA). Dr Raine is Director of Vigilance and Risk Management of Medicines Division of the MHRA and also Chair of the European Pharmacovigilance Risk Assessment Committee (PRAC) and Dr Nooney is Principal Assessor of the Medicines for Women's Health Expert Advisory Group of the UK Commission on Human Medicines (CHM). Throughout this chapter we learn that the discipline of medicines regulation has been profoundly shaped and influenced by women's medicines and many interesting examples are discussed, from the early thalidomide tragedy (in the 1960s thalidomide was widely available without prescription in the UK and Germany) through to very recent examples of regulatory action which have affected access to – and use of – medicines for women.

Chapter 15 includes an outline of the processes of product development and of regulatory assessment which lead to approval (or refusal) of a medicine. Whilst these processes are applicable for all medicines, Raine and Nooney highlight the special issues relating to medicines for women, for example, data are generally missing on safety during pregnancy. The authors then move on to cover the multiple roles of the regulator during the post-marketing period. A key function is monitoring the safety of medicines in 'real life' use by collection and analysis of post-marketing data. It is interesting to note that the assessment of safety issues in clinical use is now broadening to include consideration of the efficacy of medicines. In the European Union in recent years there has been a shift in the regulatory

approach, from the progressive addition of safety information to product information to an overall assessment of both benefit and risk: this is reflected by the renaming of Periodic Safety Update Reports to Periodic Benefit Risk Evaluation Reports.

Another important public health role of regulators is to make decisions about access to medicines and this is especially relevant to medicines for women. Raine and Nooney discuss some examples of medicines which have been reclassified from prescription-only to pharmacy availability in the UK, including topical imidazole antifungals for vaginal candidiasis (reclassified in 1992), emergency contraception (reclassified in the UK in 2000) and tranexamic acid for menorrhagia (reclassified in 2007). There remain some interesting examples of other women's medicines not yet reclassified from prescription-only in the UK, including oral contraceptive medicines. Access issues for new medicines are also discussed and Raine and Nooney describe some new initiatives to improve access to innovative medicines, which they believe *"may have the potential not only to facilitate access to new treatments for patients with unmet medical need, but also to change the face of medicines' regulation"*.

Communication is discussed again in this chapter and European Union (EU) regulators continue to evaluate how to communicate the conclusions of their risk: benefit assessments, both to healthcare providers and to women themselves. There is evidence that in some situations Direct Healthcare Professional Letters have failed to make an impact, but Raine and Nooney inform us that there is now an EU requirement for companies to test patient information leaflets and that the European Commission has taken further steps to address the shortcomings of product information. However at this time, the impact of regulation of women's medicines has not been systematically assessed. To learn for the future, this would seem the logical next step. At the heart of regulation of women's medicines should be the need to involve women in the decisions about their medicines. This should include inviting women to contribute at all stages in the regulatory process: both as consumers of medicines and professional women as experts on medicines assessment advisory committees around the world.

Political and Religious Perspectives

Politics and religion are known to be contentious issues and Dr Brian Edwards and Ms Veronika Valdova conclude Chap. 16 with a key reason for including this fascinating chapter in a book about medicines for women: in some environments political and religious issues may determine aspects of medical practice and are not easily discussed. In some parts of the world, women may be scared to raise such issues, for fear of discrimination, fear of being denied treatment, or fear of mistreatment in the clinic and/or at home. Doctors may be frightened too, perhaps afraid of practising outside their own belief systems, or of not fully understanding the religious or political environments which influence female patients.

In Chap. 16, Edwards and Valdova summarise the political and religious issues surrounding several different aspects of women's healthcare and the provision of medicines to women. The availability of the emergency contraceptive pill in the USA is one example. It is an intriguing story and there was significant fall-out, not just for women needing to access EC in the USA, but for some of the doctors involved too. In 2005 Dr Susan Wood, Director of the Office of Women's Health at the FDA resigned from her position in protest over political interference in the availability of this medicine for women (Kaufman 2005). She wrote in an email to her staff and FDA colleagues: "*I can no longer serve as staff when scientific and clinical evidence, fully evaluated and recommended for approval by the professional staff here, has been overruled*".

Although not discussed in Chap. 16, other doctors have paid an even higher price for providing treatment to women: in 2009 Dr George Tiller was murdered (in the foyer of his long-time church) for providing therapeutic abortions in a community where some thought this was wrong (Stumpe 2009). In many parts of the world, doctors providing medicines and other treatment for women live in fear of personal harm – as do the women themselves – and this is not acceptable.

Despite of, and because of our fears, we need to discuss political and religious issues openly and with respect to gain a better understanding. Edwards and Valdova believe the fundamental issue for women's health is one of gender inequality on a global level. For most of recorded history, human societies have been largely paternalistically driven with women relegated to a secondary, even distant, second-class status. The male of any hierarchal structure determined what was best for, and what the woman would be *allowed* to have. We see this most glaringly today in the developing world and in Chap. 17 Nighat Khan documents how women are seen and treated in Pakistan. It could be argued that this historical gender inequality can be reduced to an anthropological issue, with how it manifests secondarily in all the social, political, religious, cultural and biological spheres, impacting collectively on women's health.

Edwards and Valdova remind us that the right to control fertility, influence sexual behaviour and other key indications for women's medicines, are some of the most delicate issues we will face and that a sensitive approach is required. In their comprehensive chapter they cover issues relating to women's healthcare in many different countries including China, the Czech Republic, Cuba, the Middle East, North Africa, Romania, Russia and the USA. They give us examples of how religious, political and moral objections have affected the availability of women's medicines and point out that formal legal availability of a medicine (for example contraception) does not necessarily guarantee access for women. Edwards and Valdova believe that despite the 1994 International Conference on Population and Development (ICPD) historic milestone resulting in four tenets under its Program of Action being a platform for 179 signatory governments and the United Nations (UN) and WHO follow-on actions furthering these tenets, we are still left dealing with little real movement in achieving gender health equality. Another important conclusion relating directly to medicines for women is that approaches to risk management should involve adapting plans in line with social, religious and

cultural variation. Edwards and Valdova call for a more holistic approach which should take into account the social, political and religious environment in which a woman lives.

Women's Medicines in Developing Countries

The influences of environment on women's medicines, are discussed further in Chap. 17 in which Dr Nighat Khan gives her perspective on women's health and women's medicines in developing countries. Dr Khan lives and works in Pakistan and presents us with critical insights into the systems in which women seek healthcare and medicines in this country. She reports that these systems are '*weak and fractured*' and explains how many women have no access to a skilled or qualified health professional in this patriarchal society. The figures for maternal mortality and other devastating outcomes for women and their families reflect the poor standard of care, limited access issues and the urban rural divide in many developing countries. Dr Khan explains how poverty is also driving many disturbing medical tourism practices in India, where Surat city in Gujrat State has become the 'surrogacy capital' of the world.

Access to and availability of essential medicines for women is extremely poor in developing countries like Pakistan. Adding to these problems are the issues of counterfeit medicines and poor legislative control over the regulation, marketing and sales of medicines. Dr Khan is concerned by the lack of accountability and lack of cohesion in the Pakistani systems and describes the tragedy which occurred at the Punjab Institute of Cardiology in 2012 (see Chap. 17, p. 508) as an example of the failure of systems to protect patients. There are also virtually no post-marketing systems to monitor the safety of medicines in Pakistan and there is no culture – amongst doctors, other health professional or patients – of reporting adverse reactions to medicines. Women, with their essential requirements for safe and effective medicines to control fertility and survive childbirth, are particularly vulnerable especially during their reproductive years. This enlightening chapter also includes discussion of some of the main contraceptive and obstetric medicines available to women in developing countries and the issues surrounding their use. Chapter 17 presents a very different perspective from that of the developed world and I suggest it as essential reading for all who work in women's health. Many of the issues we face are global and therefore the solutions must be global too.

Communication

How we communicate with patients should be central to our practice of medicine, whatever area we work in. This is particularly true in women's health and in prescribing medicines for women, where our discussions are often about major life decisions. In pharmacovigilance in recent years there has been increasing interest in risk communication and in 2012 Priya Bahri and I edited a theme edition

of Drug Safety on this subject (Bahri and Harrison-Woolrych 2012). For this book, I invited Bruce Hugman – a communications expert whose credentials include advising the WHO and writing books on managing risk – to contribute two chapters on risk communication. It seems appropriate to conclude *Medicines for Women* in this way as almost every other chapter of the book mentions communication. But in reading Chaps. 18 and 19, don't expect a tidy wrap up of all the issues already discussed – prepare to be challenged and to challenge yourself!

Chapter 18 is presented in two parts: first, Hugman guides us through the basics of risk communication. He begins by exploring how women differ from men and how '*one size does not fit all*' when it comes to discussions of risk or the provision of information. Then we move on to a key issue when discussing the safety of medicines: how is risk expressed? This is essential reading for anyone in clinical practice and for researchers, regulators and pharmaceutical companies who need to explain study findings to a general audience. Hugman reviews issues such as absolute versus relative risk; causality assessment and the challenges of risk: benefit assessment, or 'Trade Offs', to use language which patients might understand. Throughout this section – and throughout his two chapters – Hugman presents thought-provoking examples and challenges us to reform how we communicate.

The second part of Chap. 18 covers gender specific issues in risk communication for women. Even broadly scoping these issues is a huge task, but a worthwhile one as we believe that this is the first time this subject has been included in a published book. Hugman explores the evidence for women's preferences and needs in several areas of their healthcare and in several different parts of the world, including preferred sources of information, degree of decision-making participation, preferences during pregnancy and choices regarding the gender of their healthcare provider. Of course, in many health care systems – often those in developing countries – women do not have the luxury of choice for many things (they may not have access to any health care provider at all) but this does not mean their views and preferences should not be considered. Even in resource poor environments, under great pressure of time, we can still apply Hugman's advice and communicate with empathy, sympathy, altruism and compassion.

A range of issues of profound importance to women are also covered in Chap. 18. These include discussions of gender bias, issues relating to young people (also discussed in Chap. 3), body image and physical threats to women. Whilst some of these issues may not seem to be directly related to medicines for women, this would be too narrow a view to take when considering how we communicate with women about risk. Hugman concludes this chapter with several important questions including: (1) What are the unique personal, social, cultural characteristics of this woman that will influence her response and behaviour as a patient? (2) Are there high priority risk factors influencing this woman's life, e.g. poverty, stress, male oppression, striving for ideal beauty?

In the final chapter – Chap. 19 – Hugman continues to develop the theme of how personal, social and cultural factors may influence how women take medicines and how we communicate information about these medicines. The chapter begins with review of some of the basic information and skills of understanding and

communicating the risks of medicines; some of these points will be discussed further in the section '*How to Prescribe Medicines for Women*' below. Hugman suggests an approach which is '*based on credible evidence and shaped by the perceptions and priorities of the patient*'. This apparently simple and sensible sentence raises more questions explored further in Chap. 19, for example: what is credible evidence and how does a woman seeking information on her medicines know it is credible? The internet is a primary source of information for many people in today's world and Hugman includes an interesting note about websites and the difficulties of assessing the quality and validity of information provided if you are not an expert with training in evidence-based medicine. The issues surrounding regulation of information provided about medicines on the internet are too broad and complex for this book, but it is worth remembering that patients may be obtaining inaccurate information from various sources which they believe are credible.

Four interesting examples of risk communication for specific medicines for women are discussed in Chap. 19. First, the dilemmas for women with epilepsy are explored, in particular the issues surrounding anticonvulsant medicines in pregnancy and how women may obtain good information on the benefits and risks of treatment. Next, Hugman discusses communication regarding the risks of oral contraceptives and provides an analytical commentary on media-generated 'pill scares' which have occurred in some countries. The third issue covered is risk communication in relation to HPV vaccines, which (as covered in Chap. 9) are highly effective and safe products which have now been administered to millions of women worldwide. In Chap. 19 Hugman describes how HPV programmes in Romania and India were abandoned and examines the reasons for this and how public concerns regarding vaccination programmes emerge and may be managed.

In the final example included, Hugman explores the socio-cultural aspects of menopause and some of the major narratives on this subject are summarised (see Chap. 19, p. 585). It is essential to understand the different socio-cultural beliefs which may be behind a women's request for hormone therapy, although it is not always necessary to over-complicate a simple request for relief of menopausal symptoms. The benefits and risks of MHT are covered in Chap. 11 (as discussed above) and in the final chapter of this book we are encouraged to consider the menopausal woman's situation more broadly. In his conclusions to this chapter Hugman writes *"Women, in all their immense and remarkable variety, need a synthesis of risk information that matches the profile of their individual needs, presented in ways that leave them free to make a decision that is best for them"*.

In summarising the key principles of risk communication and re-enforcing Hugman's passionate promotion of empathy, I also offer the advice of the Chinese philosopher Lao Tzu who wrote:

> I have just three things to teach: simplicity, patience, compassion. These three are your greatest treasures.

Simple, understandable explanations of complex issues are not always easy, but it is a skill worth learning in risk communication. With patience, I would include

the importance of listening and taking time to understand another person's perspective before talking and giving advice. Compassion should be a central principle of medical practice, but it is sometimes lost under the pressure of doing what we feel we need to do in the (often very limited) time available. However, if we can apply these three things to our discussions of the benefits and risks of women's medicines, we will all have learnt something.

How to Prescribe Medicines for Women

Mira Harrison-Woolrych and Jonathan Woolrych

In this section we will discuss some general principles of prescribing medicines for women. It is not our intention to provide a detailed prescribing guide for any or all of the medicines which may be prescribed to women – for this, we suggest you refer to the national formulary for your country, which should contain information for specific medicines and also country-specific information (e.g. the indications approved in that country; whether the product has a government subsidy etc.). If your country does not have a national formulary, the British National Formulary (http://www.bnf.org/bnf/index.htm) remains a very good source of prescribing information, although it is not designed to include regional information for medicines marketed in other countries.

Here we aim to challenge your current mind-set on how you consult with women about medicines and other treatment options. We understand that time is often short in the average consultation in primary care and also in hospital environments and clinics. The demands on doctors, other prescribers and healthcare workers may be enormous, particularly in resource poor countries, but that does not justify prescribing without first pausing to consider whether this is in the best interest of the woman in front of you. Prescribing should not be an automatic reflex, but rather a thoughtful process which actively engages each individual patient in the decision. In the following section we present some questions which, even if you have been prescribing for many years, we suggest you re-examine in the context of prescribing for women.

1. **Is the medicine really necessary?**

Writing a prescription is the most common outcome for most clinical consultations, especially in general practice. In some situations, it is the obvious thing to do – for example in consulting with a woman requesting contraception, one would usually respect her request, rather than question whether she needs it (she is the best judge of that) and we would proceed to the next steps of the consultation, as outlined below. There are other more acute situations – for example prescribing

medicines during labour or delivery, especially in emergency situations – where there may not be time to have a lengthy discussion on whether the medicine is indicated. However, even within these two examples, there may still be exceptions where it would be appropriate to first discuss if writing a prescription is really required.

Examples throughout this book demonstrate how we should first listen to our patient and then, in consultation with her, determine if prescription of a medicine is the most appropriate clinical action. In Chap. 14, Dee Mangin suggests that in primary care we should always consider a non-pharmacological alternative where possible and we concur with this advice. This is particularly true for 'lifestyle medicines' which patients may request to aid in weight reduction or smoking cessation for example. A non-pharmacological option – for example an exercise programme – does not carry the risk of adverse reactions (all medicines have some risk of these) and may offer other benefits to the patient. In Chap. 3, Sue Bagshaw notes that anti-depressant medicines are not an effective treatment for grief and in this clinical situation it may be more appropriate to refer someone for counselling. In Chap. 10, Gillett and Jones discuss that for women with chronic pelvic pain, it may be enough to acknowledge the symptoms are real and provide reassurance that there is no serious underlying cause of the pain.

Medicalization of women's physiology and sexuality is discussed in several chapters, including the classification of new conditions such as 'overactive bladder' (Chap. 14) and 'female sexual dysfunction' (Chap. 16) which are difficult to define and for which medicines are unnecessary (and also ineffectual). Another example is covered in Chap. 19, where Bruce Hugman discusses whether menopause is a clinical condition which needs treatment, or whether it should be seen as a normal physiological occurrence which may be managed in other ways. Medicalization of women's lives is not a new issue and it is likely to continue if profit can be made from it. Pharmaceutical companies have a vested interest in marketing medicines for new indications and new populations and we need to ask ourselves in every consultation, is this medicine really needed by this woman or are there alternative ways of helping her?

2. **What are the aims of treatment?**

If the prescriber and patient agree that a medicine is indicated for a particular condition, it is then important to discuss the aims of treatment. Patients may have unrealistic expectations or may not understand how medicines work. One example is that the aim of oral contraceptive medicines is primarily to prevent pregnancy and whilst these medicines have other additional benefits (as discussed in Chap. 5) these medicines do not offer protection against sexually transmitted infections. Whilst this may be obvious to health practitioners, it may not always be obvious to the woman seeking advice and we should not make presumptions about the level of patients' knowledge about medicines.

Another common example in general practice is a woman consulting for 'period problems'. In order to determine the most appropriate treatment for each patient, it

is first necessary to determine what she requires the aims of treatment to be. This should be identified by careful history taking to identify what symptoms and concerns actually need treating. Examination may also be indicated to identify any anatomical abnormalities which may need a specific treatment – for example uterine pathology which may cause abnormal bleeding. If examination is normal and the woman's main concern is that her periods are painful (she may have no need for contraception and the heaviness of her periods is not an issue) then it may be most appropriate to prescribe non-steroidal anti-inflammatory (NSAID) medicines which are effective treatments for dysmenorrhoea (Livshits and Seidman 2010). If however, she requires contraception and is also troubled by heavy periods, then these would be the two aims of the treatment and a combined oral contraceptive pill may be indicated in this situation (see Chap. 5).

3. **How effective is the medicine?**

Once we have agreed what the aims of treatment are, it is the prescriber's duty to then explain clearly what benefits the medicine can and cannot offer. In Part II of this book, almost every chapter reviews the evidence for efficacy of specific medicines for women and we learn that even the best medicines are not 100 % effective. However, our clinical experience is that most patients do not fully understand this and may expect their medicine or device to offer a much higher level of effectiveness than we know is possible.

It may come as a huge shock for a woman to discover she is pregnant with an IUD in situ – such events are life-changing. This example should alert us to the important need to discuss effectiveness of medicines and devices with women, preferably before the medicine is prescribed or the device is inserted. Another important consideration is whether the woman is taking other medicines which may reduce the efficacy of the medicine about to be prescribed. Interactions with concomitant medications are discussed in Chap. 2 (sex differences in pharmacokinetics) Chap. 5 (oral contraceptives) Chap. 14 (primary care perspectives) and Chaps. 18 and 19 (risk communication). It is always important to take a full medication history, including details of over-the counter preparations and herbal and complementary medicines, as discussed in Chap. 13.

In several other chapters authors discuss evaluation and communication of the benefits and risks of medicines for women. Here we want to stress that communication about effectiveness should be a key part of any consultation when a medicine is prescribed.

4. **How safe is the medicine?**

In our clinical practice we have found that most patients appear to know that medicines may have side effects. Reaction to this is very variable – some people are accepting of even quite large risks, whilst others may be concerned at even the small chance of a minor event. Much also depends on the nature of the condition being treated: the risk benefit assessment of a medicine for a life threatening disease

(for example, breast cancer) is very different to evaluating a medicine for treatment of a less serious condition, or for prevention of a condition in a healthy woman.

A key issue in discussing the safety of a medicine in the consulting room is which adverse effects should be discussed and how? It would seem clear that it is our responsibility to inform women taking COCs that there is a risk of VTE (which may have serious or even fatal outcomes) and we should also explain this is a rare side effect (as discussed in Chap. 6) using terms that they can understand (as discussed in Chap. 19). What is less clear is whether it is our responsibility to inform women of every possible adverse event and the frequency at which it might occur. There may not be time for a long discussion of all side effects and patients vary in their need for detailed information. We suggest briefly covering the most commonly reported adverse reactions to the prescribed medicine and also any serious (for example life-threatening) adverse effects. It is also important to advise what action the patient should take if an adverse reaction occurs.

Providing the patient with written information about their medicine is a useful tool for clinicians to use to help explain safety issues. However, patient information leaflets based on the product licence (see Chap. 15, medicines regulation) may be too complex for some patients and other sources of information available on line may not always be accurate, reliable or up to date (see Chap. 19). Some clinicians or hospital departments develop their own patient leaflets and this can be useful, as long as the information included is evidence based, accurate and objective (and preferably not sponsored by a pharmaceutical company). Patient leaflets should also be reviewed and tested for readability and understanding (Dickinson et al. 2001). A broader objective is to ensure that patients in different regions of the world have access to accurate, consistent and independent information and this is an advantage of patient information provided by national and international medicines regulatory authorities (see Chap. 15).

In Chaps. 18 and 19 Bruce Hugman discusses how a patient's concept of a 'safe' medicine may differ from our understanding and how it is important to first understand the socio-cultural environment in which the woman lives. It helps to know your patient and one advantage of working in primary care is that general practitioners, practice nurses and pharmacists often know their patients very well. However, as we have already mentioned, assumptions should not be made about what patients know and if in doubt, it is perhaps better to say something twice than not at all.

5. Compliance, cost and other considerations

There are a number of practical considerations to be made when prescribing medicines for women (as detailed in Chaps. 18 and 19) but here we will focus on just a couple of issues. Adherence with medicine is obviously important because if a woman does not take her medicine it cannot be effective. This is a crucial issue for oral contraceptives (as discussed in Chap. 5) and for any medicine where the woman may not be able to comply with the dosing regimen for various reasons. Some discussion about compliance before the medicine is prescribed is advisable.

Also consider offering alternative treatments – for example, a contraceptive implant may be preferable to a daily oral contraceptive pill, or a long acting injectable bisphosphonate may offer a better alternative than an oral bisphosphonate for some women (see Chap. 12).

Cost of the medicine prescribed (and who pays for it) is an issue which will vary greatly depending on individual countries and health systems. In some countries – for example, the UK with the National Health Service – this is less of an issue for the patient than countries like the USA where health systems are largely privatised and the patient is responsible for more costs. In New Zealand, a government agency subsidises some medicines (http://www.pharmac.health.nz/) and for prescribers and pharmacists in this country (or others with similar systems) it is important to know which medicines are subsidised, so that women can be offered the most affordable treatment. Cost may be a real barrier to accessing medicines, especially for poorer women and women in less affluent countries, and it is part of good prescribing to consider this issue.

There are numerous other matters to consider when prescribing medicines to women, many of which apply to all patients – for example, the importance of history taking to identify relevant family history, the woman's personal medical history, known allergies, alcohol and smoking history; and examination may also be indicated. Special issues to consider when prescribing medicines for women are discussed throughout this book and in summary include:

- Are there sex differences in the pharmacokinetics for this medicine which may mean the dose should be altered in women? (see Chap. 2)
- For a young woman: is she able to give consent to treatment? (see Chap. 3)
- For women of reproductive age: could she be pregnant, or is there the chance of pregnancy occurring whilst taking the medicine? (see Chap. 4)
- For women who have recently been pregnant: is she breast feeding the infant? If so, is the medicine safe in lactation? (see Chap. 4)
- For women requesting oral contraceptives: discussion of the benefits and risks of these medicines, including interacting medicines and adherence issues (see Chaps. 5 and 6)
- For women who are sexually active and of reproductive age: does she know about emergency contraception and how to access it if needed? (Chap. 7)
- For women needing long term reversible contraception: have they considered an implant or other contraceptive device? (Chap. 8)
- Has she been offered relevant vaccinations, including the HPV vaccine (most effective if given before sexual debut) for prevention of cervical cancer and genital warts? (see Chap. 9)
- For women with chronic pelvic pain: has she received a full evaluation before medication has been prescribed? (see Chap. 10)
- For women requesting MHT – is hormone treatment needed and if so, does she understand all the risks of treatment? (see Chap. 11)

- For women with osteoporosis, is treatment with bisphosphonates to prevent fractures indicated and if so, for what duration should treatment continue? (see Chap. 12)
- Is she using any herbal or alternative/complementary medicines and if so for what reason? Is she aware that herbal medicines may have risks as for conventional medicines? (see Chaps. 13 and 15)
- Is the woman's medication due for review? Is she taking more than five medicines and if so could any of these be stopped? (see Chap. 14)
- Are there socio-cultural issues which may affect adherence or other aspects of use of the medicine? (see Chaps. 16 and 17)
- Have I communicated clearly during this consultation and invited the patient to engage in the decisions about her medicine? (Chaps. 18 and 19)

Communication

As we have already discussed and will return to throughout this book, good communication is an essential part of prescribing medicines for women. Today we work in a world of information overload and one in which the information is always changing: new medicines for women continue to be developed and issues with older medicines continue to arise. As prescribers it is impossible to know everything and we must be honest about this with patients. When we don't know, or are not sure, we need to verify or obtain more information and this means getting to know which sources are reliable and trust worthy (see Chaps. 18 and 19). If the guidance needed is not available in the consulting room, there is often the option of contacting the patient again once more information has been obtained.

Professional communication and collaboration is important too: asking colleagues for advice and offering to share knowledge is part of good practice. Good communication based on the principles of honesty and integrity should also apply in all stages of medicines development, licensing, marketing and post-marketing monitoring and research. It should go without saying that research studies should be conducted ethically and honestly and there need to be systems and processes to identify and deal with fraud when it arises (Breen 2003). Findings from research on medicines should be communicated widely and published in peer reviewed journals, even when there are 'negative' findings: these data are important too (Thornton and Lee 2000). In the field of medicines regulation and post-marketing monitoring, high quality and consistent communication is needed between national and international bodies. Only in this way will patient safety be adequately protected around the world.

Conclusions

Medicines for women are used by more than half the world's population and women's use of medicines also affects their children (while in utero, during breast feeding and in later phases of motherhood), their male sexual partners (women are primarily responsible for contraception) and others, as women's health is central to community well-being. There are many important issues associated with women's medicines and more broadly women's health, which affect people all around the world. These concerns deserve to be discussed and this book is a vehicle for publishing evidence-based perspectives on selected subjects and bringing them together for the first time.

Several common themes emerge throughout the book. First is the conclusion that women themselves should be placed at the centre of discussions about their medicines. They should be invited to be involved in all stages of decision-making processes, both at an individual level and also professionally during the development, assessment, regulation and monitoring of women's medicines. If more women become leaders in these fields (and in other professional arenas) women should have more say in determining their own futures (Sandberg 2013).

While there have been improvements in the processes for obtaining and evaluating data from women in recent years (for example from clinical trials), more still needs to be done. Further research and review is needed in many areas, for example, medicines taken in pregnancy and lactation, adolescent women, treatment of chronic pelvic pain, herbal medicines and bisphosphonates. For some products, for example, HPV vaccines and oral contraceptives, there has been extensive research and regulatory review and good clinical guidance is widely available. However, for other medicines, for example MHT, whilst evidence on benefits and risks is available and regulatory review has been performed, clinical guidelines for use are still lacking in some countries.

In studies of women's medicines, comparative safety should be as important as comparative efficacy. Proactive post-marketing monitoring of medicines and devices for women (especially new products) should be conducted independently and in real life clinical settings, in addition to collecting data via national spontaneous reporting schemes. Global collaboration and communication is important in post-licensing surveillance: pharmacovigilance signals identified need to be shared in a timely manner with other national regulators and international bodies, so that prompt action can be taken to protect patients. Good communication about the benefits and risks of medicines for women is vital at all levels: in particular, drug information for women needs to be independent, high quality and consistent across different regions of the world.

Finally, prescribers, other healthcare workers, researchers and regulators must consider the socio-cultural environment in which women take medicines and how this make affect their use. In all countries of the world and in all systems in which medicines are administered and evaluated, there needs to be a more holistic approach towards women's health care. This is particularly true in places

where women are especially vulnerable due to poverty, oppression and gender inequality.

Take Home Messages

- Medicines for women are not a minority issue: this is a global matter
- More information is needed on exposure to medicines in sub-groups of women including pregnant and lactating women and adolescent women
- While there is good evidence about efficacy and safety of some products (for example, HPV vaccines; oral contraceptives), for other women's medicines more research and review is needed (for example, bisphosphonates, treatments for chronic pelvic pain)
- Better regulation of herbal medicines is required and also increased funding of international independent groups to review all herbal medicines.
- More proactive global pharmacovigilance is required to monitor the safety of medicines for women.
- There need to be more effective systems of communication in place to relay information worldwide when new issues arise
- Global initiatives are needed to provide access to accurate, consistent and independent information on medicines for women throughout the world
- Women should be given the opportunity to be involved in discussions of their medicines, both at an individual level and also professionally during the development, assessment, regulation and monitoring of women's medicines.
- A holistic approach which values women and considers their socio-cultural environment is important when prescribing medicines and in all stages of medicines regulation and monitoring.

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Chapter 2
Effects of Sex Differences in the Pharmacokinetics of Drugs and Their Impact on the Safety of Medicines in Women

Emmanuel O. Fadiran and Lei Zhang

Introduction

Inclusion of women in clinical trials and analysis of clinical trial data for sex/gender effects have been an integral component of the US FDA's consideration for approval of pharmaceutical products since the mid-1980s (FDA Guidance for Industry 1993). The study of sex differences is now a routine component of drug development because of existing data in drug exposure and response differences between men and women and the need to understand such differences for proper dosing (Harris et al. 1995; Schwartz 2003; Institute of Medicine (US) 2001; Franconi et al. 2007; Parekh et al. 2011). The resulting expanding knowledge of sex differences in the exposure and responses to drugs has led to a better understanding of the mechanisms contributing to these differences and improved pharmacotherapy for men and women.

Sex-based differences may be due to pharmacokinetics (differences in exposure in men and women following administration of the same dose of a drug) and/or pharmacodynamics (differences in the body's response to the same dose of a drug in men and women) and can manifest as differences in safety and/or efficacy of pharmacotherapy. For example, when compared to men, women are 1.5–1.7 times more likely to develop an adverse drug reaction (Rademaker 2001), which

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is defined as any unintended and undesired effect of a drug used at a dose for diagnosis, prophylaxis, or therapy (Rademaker 2001; Anderson 2005; Tran et al. 1988). This chapter will focus on sex differences in pharmacokinetics (PK) and will discuss how these differences may affect the efficacy and safety of medicines in women.

Sex and Gender

The terms sex and gender are often used interchangeably and it is important to define them (Kim and Nafziger 2000). ***Sex*** refers to the classification of living things, generally as male or female, according to their reproductive organs and functions assigned by the chromosomal complement while ***gender*** refers to a person's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation (Institute of Medicine (US) 2001). Gender is rooted in biology and shaped by environment and experience (Institute of Medicine (US) 2001). Because it is often not clear whether an observed difference in drug safety or efficacy is due to gender or sex, the U.S. Food and Drug Administration (FDA) has used the term "gender" to describe *any* difference, cultural/social or genetic/hormonal, between males and females. However, for the purpose of this chapter, we focus on the genetic/hormonal differences between males and females and will therefore use the term "sex" throughout.

Sex Differences in Pharmacokinetics

It is now well recognized that there are sex differences in the PK of many drugs (Harris et al. 1995; Schwartz 2003; Institute of Medicine (US) 2001; Franconi et al. 2007; Gandhi et al. 2004; Schwartz 2007; Soldin and Mattison 2009; Huang et al. 2007; Mattison 2013; Meibohm et al. 2002; Franconi and Campesi 2014). Examples of these differences for a selection of medicines approved in the US are summarized in Table 2.1 and some of these will be discussed further later in this chapter.

The PK of drugs may be affected by intrinsic factors such as body weight, genetic predisposition, disease, renal or hepatic function, or extrinsic factors such as smoking, concomitant medications including herbal/over-the-counter (OTC) products, alcohol use and diet. Sex differences in any of these factors can result in sex differences in the PK or exposure to a drug that could cause dissimilar responses. Observed differences in the PK of drugs between men and women are often attributed solely to body weight differences and may therefore be dismissed as not being clinically significant, once corrected for these body weight differences. Paradoxically however, most drugs are not administered on a mg/kg basis but as a

Table 2.1 Examples of drugs showing sex differences in PK parameters

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
ABILIFY (Aripiprazole)	11/15/02	6/09/14	Use in specific populations: gender	Cmax and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30–40 % higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25 %) between men and women. No dosage adjustment is recommended based on gender.
APTIVUS (Tipranavir)	6/22/05	4/07/14	Clinical pharmacology	Evaluation of steady-state plasma tipranavir trough concentrations at 10–14 h after dosing from the controlled clinical trials 1182.12 and 1182.48 demonstrated that females generally had higher tipranavir concentrations than males. After 4 weeks of APTIVUS/ritonavir 500/200 mg BID, the median plasma trough concentration of tipranavir was 43.9 mM for females and 31.1 mM for males. The difference in concentrations does not warrant a dose adjustment.
ARZERRA (Ofatumumab)	10/26/09	4/17/14	Clinical pharmacology	Gender had a modest effect on ofatumumab pharmacokinetics (14–25 % lower clearance and volume of distribution in female patients compared to male patients) in a cross-study population analysis (41 % of the patients in this analysis were male and 59 % were female). These effects are not considered clinically important, and no dosage adjustment is recommended.

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
AVASTIN (Bevacizumab)	2/26/04	12/16/13	Clinical pharmacology	The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger Vc (3.25 L vs. 2.66 L) than females.
EMEND (Aprepitant)	3/27/03	3/27/13	Clinical pharmacology	Following oral administration of a single dose of EMEND, the AUC0-24 h and Cmax are 14 % and 22 % higher in females as compared with males. The half-life of aprepitant is 25 % lower in females as compared with males and Tmax occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.
ENABLEX (Darifencin Hydrobromide)	12/22/04	3/15/12	Clinical pharmacology	PK parameters were calculated for 22 male and 25 female healthy volunteers. Darifenacin Cmax and AUC at steady-state were approximately 57–79 % and 61–73 % higher in females than in males, respectively.
FACTIVE (Gemifloxacin Mesylate)	4/4/03	8/14/13	Clinical pharmacology	There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10 % higher in healthy female patients compared to males. Males and females had mean AUC values of 7.98 μg•h/mL

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
				(range, 3.21–42.71 μg•h/mL) and 8.80 μg•h/mL (range, 3.33–47.73 μg•h/mL), respectively. No gemifloxacin dosage adjustment based on gender is necessary.
FIRAZYR (Icatibant Acetate)	8/25/11	8/30/13	Clinical pharmacology	Following single-dose administration of 30 mg subcutaneous FIRAZYR, elderly males and females showed approximately 2-fold higher AUC compared to young males and females, respectively. However, only minor differences (~12–14 %) between Cmax of gender–matched elderly and young subjects were observed. Clearance of FIRAZYR is significantly correlated with body weight with lower clearance values noted for lower bodyweights. Hence, females with typically lower body weights compared to males exhibit lower clearance values, resulting in approximately 2-fold higher systemic exposure (both AUC and Cmax) compared to males. Differences in efficacy and safety between elderly and younger patients and male and female patients have not been identified. Dose adjustment based on age and gender is not warranted.
FUZEON (Enfuvirtide)	3/13/03	10/31/13	Clinical pharmacology	Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuvirtide is 20 % lower in females than males after adjusting for body weight. Enfuvirtide clearance decreases with decreased body weight irrespective of gender. Relative to the

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
				clearance of a 70-kg male, a 40-kg male will have 20 % lower clearance and a 110-kg male will have a 26 % higher clearance. Relative to a 70-kg male, a 40-kg female will have a 36 % lower clearance and a 110-kg female will have the same clearance.
FYCOMPA (Perampanel)	10/22/12	2/24/14	Clinical pharmacology	In a population pharmacokinetic analysis of patients with partial-onset seizures receiving FYCOMPA in placebo-controlled clinical trials, perampanel apparent clearance in females (0.605 L/h) was 17 % lower than in males (0.730 L/h). No dosage adjustment is necessary based on sex.
IMAGENT (Perflexane Phospholipid Microspheres)	5/31/02	5/31/02	Clinical pharmacology	Females eliminate perflexane through the expired air more slowly than males (female terminal elimination half-life = 13 ± 4 h, N = 5; male terminal elimination half-life = 6 ± 3 h, N = 7). The clinical relevance of the gender differences observed is not known.
INTERMEZZO (Zolpidem)	11/23/11	2/6/13	Use in specific populations: gender	Women cleared zolpidem tartrate from the body after sublingual administration of a 3.5 mg dose of Intermezzo at a lower rate than men (2.7 mL/min/kg vs. 4.0 mL/min/kg). C_{max} and AUC parameters of zolpidem were approximately 45 % higher at the same dose in female subjects compared with male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended dose of Intermezzo for women is 1.75 mg,

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
				and the recommended dose for adult men is 3.5 mg.
LIVALO (Pitavastatin Calcium)	8/3/09	10/16/13	Clinical pharmacology	In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin Cmax and AUC were 60 and 54 % higher, respectively in females. This had no effect on the efficacy or safety of LIVALO in women in clinical studies.
MYCAMINE (Micafungin Sodium)	3/16/05	6/21/13	Use in specific populations: race and gender	No dose adjustment of Mycamine is required based on gender or race. After 14 daily doses of 150 mg to healthy subjects, micafungin AUC in women was greater by approximately 23 % compared with men, due to smaller body weight.
MYRBETRIQ (Mirabegron)	6/28/12	6/28/12	Clinical pharmacology (also in race and gender section)	The Cmax and AUC of mirabegron were approximately 40–50 % higher in females than in males. When corrected for differences in body weight, the mirabegron systemic exposure is 20–30 % higher in females compared to males
NAMENDA (Memantine Hydrochloride)	10/16/03	10/24/13	Clinical pharmacology	Following multiple dose administration of NAMENDA 20 mg daily, females had about 45 % higher exposure than males, but there was no difference in exposure when body weight was taken into account.
ONGLYZA (Saxagliptin)	7/31/09	5/24/13	Clinical pharmacology	No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25 % higher exposure values for the active metabolite than males, but this difference is unlikely to

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
				be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.
POTIGA (Ezogabine)	6/10/11	9/6/13	Clinical pharmacology	The impact of gender on the pharmacokinetics of ezogabine was examined following a single dose of POTIGA to healthy young (aged 21–40 years) and elderly (aged 66–82 years) subjects. The AUC values were approximately 20 % higher in young females compared to young males and approximately 30 % higher in elderly females compared to elderly males. The Cmax values were approximately 50 % higher in young females compared to young males and approximately 100 % higher in elderly females compared to elderly males. There was no gender difference in weight-normalized clearance. Overall, no adjustment of the dosage of POTIGA is recommended based on gender.
SANCTURA (Trospium Chloride)	5/28/04	7/23/12	Clinical pharmacology	Studies comparing the pharmacokinetics in different genders had conflicting results. When a single 40 mg SANCTURA dose was administered to 16 elderly subjects, exposure was 45 % lower in elderly females compared to elderly males. When 20 mg SANCTURA was dosed twice daily for 4 days to 6 elderly males and 6 elderly females (60–75

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
				years), AUC and Cmax were 26 % and 68 % higher, respectively, in females without hormone replacement therapy than in males.
SIMPONI (Golimumab)	4/24/09	12/27/13	Clinical pharmacology	Population PK analyses suggested no PK differences between male and female patients after body weight adjustment in the RA, PsA and UC trials. In the AS trial, female patients showed 13 % higher apparent clearance than male patients after body weight adjustment. Subgroup analysis based on gender showed that both female and male patients achieved clinically significant response at the proposed clinical dose. Dosage adjustment based on gender is not needed.
TEFLARO (Ceftaroline Fosamil for Injection)	10/29/10	12/16/13	Clinical pharmacology	Following administration of a single 600 mg IV dose of Teflaro to healthy elderly males (n = 10) and females (n = 6) and healthy young adult males (n = 6) and females (n = 10), the mean Cmax and AUC for ceftaroline were similar between males and females, although there was a trend for higher Cmax (17 %) and AUC (6–15 %) in female subjects. Population pharmacokinetic analysis did not identify any significant differences in ceftaroline AUC based on gender in Phase 2/3 patients with ABSSSI or CABP. No dose adjustment is recommended based on gender.
TOVIAZ (Fesoterodine Fumarate)	10/31/08	8/1/12	Clinical pharmacology	Following a single 8 mg oral dose of fesoterodine, the mean (±SD) AUC and Cmax for the active metabolite

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
				5-hydroxymethyl tolterodine in 12 elderly men (mean age 67 years) were 51.8 ± 26.1 h*ng/mL and 3.8 ± 1.7 ng/mL, respectively. In the same study, the mean (±SD) AUC and Cmax in 12 elderly women (mean age 68 years) were 56.0 ± 28.8 h*ng/mL and 4.6 ± 2.3 ng/mL, respectively. The pharmacokinetics of fesoterodine were not significantly influenced by gender.
VICTOZA (Liraglutide)	1/25/10	6/13/13	Clinical pharmacology	Based on the results of population pharmacokinetic analyses, females have 34 % lower weight-adjusted clearance of Victoza compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.
VFEND (Voriconazole)	5/24/02	4/7/14	Clinical pharmacology	In a multiple oral dose study, the mean Cmax and AUCτ for healthy young females were 83 % and 113 % higher, respectively, than in healthy young males (18–45 years), after tablet dosing. In the same study, no significant differences in the mean Cmax and AUCτ were observed between healthy elderly males and healthy elderly females (>65 years). In a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45 % higher than in healthy young males whereas the mean Cmax was comparable between genders. The steady state trough voriconazole concentrations (Cmin) seen in females were 100 % and 91 % higher than

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Table 2.1 (continued)

Brand name (drug name)	Date of drug approval	Date of the cited approved label	Labeling section	Labeling statement
				in males receiving the tablet and the oral suspension, respectively. In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary.
VYVANSE (Lisdexamfetamine dimesylate)	2/23/07	12/6/13	Clinical pharmacology	Systemic exposure to dextroamphetamine is similar for men and women given the same mg/kg dose. In adults ages 55–64, d-amphetamine Cmax and AUC were 15 % and 13 % higher, respectively, in females compared to males.

'one size fits all' dose, leading to higher exposures in women due to their generally lower body weight.

Sex differences have been reported for all four phases of drug disposition: absorption, distribution, metabolism and excretion, (collectively abbreviated as 'ADME') in humans and are discussed in more detail below. Other factors such as anatomic, physiologic, biochemical and endocrine sex differences can also influence drug disposition and response in humans (Mattison 2013) and are further discussed below.

Sources of Pharmacokinetic Data for Drug Labeling

In the major markets of the developed world PK information is now routinely included in approved drug labelings (Table 2.1) (Huang et al. 2007; Copeland and Parekh 2011). Most often the PK sex difference data are derived from small clinical pharmacology studies with typically 12–24 healthy subjects. Studies with small patient numbers may be adequate to detect large sex-based differences in clearance; however, if the sex-based PK difference is small, the relatively small size of most clinical pharmacology studies makes it difficult to interpret small differences observed, or to confirm if there is no difference in PK (Huang et al. 2007).

Some approved drug labelings have also reported PK sex differences from population PK analysis with sparse PK sample data from Phase 2 and Phase 3 clinical trials (Table 2.1). The population PK model generated is used to explore the effect of various covariates (factors) such as sex, age, ethnic group, and smoking status on drug PK and can therefore be used to describe sex differences in exposure (FDA Guidance for Industry 1999; Sun et al. 1999). Compared to dedicated PK evaluation, the population PK approach encompasses some or all of the following features (FDA Guidance for Industry 1999; Sun et al. 1999):

- the collection of relevant PK information in patients who are representative of the target population to be treated with the drug.
- the identification and measurement of variability during drug development and evaluation.
- the explanation of variability by identifying factors of demographic, pathophysiological, environmental, or concomitant drug-related origin that may influence the PK behavior of a drug.
- the quantitative estimation of the magnitude of the unexplained variability in the patient population.

Population PK analyses are now routinely performed during drug development and the results for PK sex differences are included in several approved US drug labelings including those for ofatumumab, gemifloxacin, perampanel, golimunab, ceftaroline fosamil and liraglutide (Table 2.1).

Mechanisms and Observed Sex-Specific Differences in Pharmacokinetics

Below, we will address two major questions about the potential importance of sex-specific PK for applied pharmacotherapy:

1. What are the potential mechanisms for sex differences in PK?
2. What are the observed PK differences between women and men and are there examples where such PK differences result in different pharmacological responses and in subsequent different dosing recommendations?

In addition, we will present some examples of PK sex differences resulting in different labeling for men and women.

What Are the Potential Mechanisms for Sex Differences in Pharmacokinetics?

As mentioned earlier, sex differences have been reported for all four phases of drug disposition: absorption, distribution, metabolism and excretion (ADME). Each of these phases will be discussed in more detail below.

Absorption

Sex differences in the gastrointestinal system have been demonstrated. For example, gastric pH is higher in women than men and gastric and bowel transit times are usually longer in women (Freire et al. 2011; Mojaverian et al. 1987). However, it is not clear if the sex differences in gastric pH or gastric emptying have any clinical relevance. It has been shown in one study that the rate of absorption of aspirin is higher in women but there was no difference in the extent of absorption (Aarons et al. 1989). The bioavailability of ethanol is greater in women compared to men partly due to differences in volume of distribution (Vd) and gastric alcohol dehydrogenase activity (Frezza et al. 1990) which may explain why there was no sex difference in alcohol blood concentrations after intravenous administration (Baraona et al. 2001). There may be differences in absorption depending on the drug route of administration (e.g., oral, inhalation, dermal, subcutaneous, rectal, vaginal, intramuscular, intrathecal, intraperitoneal) because factors that influence absorption are both drug- and route-specific, but may also be sex-specific. Most drugs are administered through the oral route following which absorption may be affected by sex differences in intestinal metabolism cytochrome P-450 (CYP) enzymes and active transporter p-glycoprotein (P-gp) (Gandhi et al. 2004; Waxman and Holloway 2009) (see below). Some studies have shown that concentrations of inhaled aerosol drugs such as cyclosporine and ribavirin are less in women compared to men but the clinical significance is unknown (Rhatagi et al. 2000; Knight et al. 1988) and the bioavailability of intramuscular cephradine is lower in women (Vukovich et al. 1975). Additionally, women have greater minute ventilation and a lower tidal volume, both of which may have the potential to affect drug absorption via the respiratory tract. Inactive ingredients may affect the bioavailability of drug formulations and this could occur in a sex-specific way, at least in some cases. For example, the excipient polyethylene glycol enhances the bioavailability of ranitidine in men (up to 63 %), whereas it is decreased in women (up to 24 %) (Ashiru et al. 2008).

Sex differences have been reported in bioavailability of medicines, which is then used to establish bioequivalence (BE) of generic drugs. Analysis of sex differences in intrasubject variability and PK from 26 BE studies showed that although there was no sex difference in intrasubject variability, there was a $\geq$20 % difference in PK parameters in one third of the data set (Chen et al. 2000). The PK sex differences were primarily the result of greater exposure in women who were given the same dose as men. When the parameters were corrected for weight, only 15 % showed

statistically significant differences. Sex differences in the PK parameters should not affect BE studies since they use the crossover design in which each subject serves as his or her own control (FDA Guidance for Industry 2013 (Draft)).

Distribution

Since body composition varies by sex, there are also sex differences in drug distribution. Women have a higher percentage of body fat compared to men (approximately 25 % vs. 16 % in men), although this difference decreases as age increases (Vahl et al. 1998). Due to this larger amount of lipophilic tissue, women have a greater Vd for lipophilic drugs such as diazepam, nitrazepam, chlordiazepoxide and cyclosporine (Soldin and Mattison 2009; Ochs et al. 1981; Greenblatt et al. 1980; Greenblatt et al. 1985; Roberts et al. 1979; Kahan et al. 1986). Increased Vd may translate into prolonged elimination half-life, tissue accumulation over time, and exposure-related adverse reactions. Conversely, women have a smaller volume of distribution for hydrophilic drugs, such as propanol (Ernstgård et al. 2003). Women are also reported to have a lower plasma volume when compared to men, as well as a lower organ blood-flow rate and lower concentrations of α-1 acid glycoprotein (Piafsky and Borga 1977; Verbeeck et al. 1984), a binding protein for neutral and basic drugs which may impact the distribution process leading to different exposures. As opposed to albumin, α-1 acid glycoprotein has its expression controlled by circulating sex hormones (Beierle et al. 1999). Hormonal contraceptives and pregnancy both further decrease plasma α-1 acid glycoprotein. As a result, the unbound fraction of various drugs that bind to α-1 acid glycoprotein is significantly higher in females than in males, as described for diazepam, chlordiazepoxide, and imipramine (Ochs et al. 1981; Greenblatt et al. 1980; Roberts et al. 1979; Kristensen 1983). However, no sex differences have been found in the unbound fractions of verapamil and disopyramide or other highly bound drugs in patients receiving oral contraceptives (Keefe et al. 1981; Kishino et al. 1995; Gleichmann et al. 1973).

According to the "free drug hypothesis," (which states that the pharmacological activity is correlated with unbound drug concentrations in plasma) this should translate into more drug being able to penetrate tissues, but the clinical impact of protein binding of drugs has not been elucidated (Rolan 1994).

Metabolism

The liver plays an important role in the metabolism of many drugs. Hepatic drug metabolism is mainly by two phases- Phase I, which includes oxidation, reduction, and hydrolysis with the majority of Phase I metabolism catalyzed by CYP enzymes, and Phase II, which includes conjugation, e.g., glucorondination, sulfation, acetylation, methylation, and glutathione conjugation.

Table 2.2 Sex differences among major CYP enzymes

CYP enzyme	Sex differences in activity	Examples of substrate drugs
CYP1A2	Women < men	Clozapine (Lane et al. 1999), Olanzapine (Zofran® US FDA product labeling)
CYP2D6	Women < men	Dextromethorphan, Metoprolol (Anderson 2005; Labbé et al. 2000)
	Women = men	Debrisoquin (Bebia et al. 2004)
CYP3A	Women > men	Midazolam, Nifedipine, Triazolam (Greenblatt and von Moltke 2008; Hu and Zhao 2010)
CYP2C9	Women = men	Fluvastatin (Schwartz 2003)
CYP2C19	Women = men	Mephenytoin (Bebia et al. 2004)

The CYP 'superfamily' has a diverse range of enzymes responsible for drug metabolism, and various enzymes have sex-related differences in activity. Caffeine is metabolized by CYP1A2. This isoenzyme also metabolizes drugs such as theophylline and clozapine. Studies have shown a higher activity of CYP1A2 in men than in women (Anderson 2005). In one study, women had a 35 % higher concentration of clozapine compared with men after normalization for dose, age, and body weight (Lane et al. 1999). The sex differences among major CYP enzymes are summarized in Table 2.2.

CYP2D6 is the second most common enzyme involved in therapeutic drug biotransformation (Franconi et al. 2007). It metabolizes several drugs including antidepressants, antiarrhythmics, analgesics, and beta blockers. Although there have been reports showing faster clearance of CYP2D6 substrates (such as dextromethorphan and metoprolol) in men than in women, there have been other reports showing either no sex-based differences or higher CYP2D6 activity in women (Labbé et al. 2000; Bebia et al. 2004).

CYP3A enzymes are the most common CYPs for metabolism, metabolizing greater than 50 % of commonly prescribed drugs. Many drugs that are substrates for CYP3A exhibit higher clearance in women leading to lower exposure (Franconi et al. 2007; Mattison 2013; Greenblatt and von Moltke 2008; Chetty et al. 2012). For example, Midazolam is a well-known substrate for CYP3A. A meta-analysis (Hu and Zhao 2010) on sex-dependent differences in midazolam disposition for both intravenous and oral exposures showed that women had higher clearance rates than men, and the sex differences were more pronounced for intravenous midazolam. There was no difference in oral bioavailability between the sexes. The authors concluded that women exhibited significantly greater hepatic CYP3A activity than men. Similarly, an earlier study that analyzed 38 datasets for 14 CYP3A substrate drugs tested in healthy young males and females showed a difference in the overall mean ratios of female to male weight-normalized clearance of the drugs (parenteral drugs: 1.26 ± 0.07; oral drugs: 1.17 ± 0.07), i.e., women cleared the drugs faster than men and sex differences were more pronounced for intravenous route (Greenblatt and von Moltke 2008). They also looked at absolute bioavailability of the oral drugs and identified no difference in this parameter

between males and females. The authors concluded that gender had a small and statistically significant influence on CYP3A metabolism, although they felt that it was probably not clinically important (Greenblatt and von Moltke 2008).

CYP2C9 and CYP2C19 do not appear to have significant sex differences in activity (Schwartz 2003; Anderson 2005).

In addition to sex differences observed in Phase I metabolism, Phase II metabolism also has shown sex differences. However, these Phase II enzymes have not been as extensively studied as the CYP enzymes. Phase II enzymes such as glucoronyltransferases and methyltransferases are generally faster in men (Franconi et al. 2007). However, there have been data that suggest that there are sex differences in the glucorondination of some drugs and not others (Franconi et al. 2007). Another consideration is that many drugs go through multiple metabolic pathways, which can contribute to widely varying sex differences. Because women take more prescription medicines (see Chap. 14) and more OTC/herbal products (see Chap. 13) than men (Franconi et al. 2007) women have a greater possibility of exposure differences simply due to a higher frequency of possible drug interactions (Gurwitz 2005).

Excretion

The kidney is the major organ of drug excretion of both parent drug compounds and drug metabolites. There are known sex differences in all three renal processes for renal clearance – glomerular filtration, tubular secretion, and tubular reabsorption (Fig. 2.1). Renal clearance is generally higher in men than in women (Gaudry et al. 1993; Berg 2006). This is accounted for by body weight differences, since glomerular filtration is directly proportional to lean body weight. Men have significantly higher creatinine clearance compared to women, but this difference diminishes once results are adjusted for weight. There are sex-specific algorithms available for routine estimation of glomerular filtration or creatinine clearance to guide dosing of renally cleared medications to reduce adverse effects due to exposure differences in men and women (Cockcroft and Gault 1976; Manjunath et al. 2001). There is also some evidence that drugs that are actively secreted or reabsorbed by the kidney may also show sex difference in rates of excretion (due to possible sex-based differences in transporter activities). For example, one study in humans has shown that renal clearance of amantadine, an organic cation transported by organic cation transporters in the kidney, is increased in men compared to women (Gaudry et al. 1993).

Transporters

Transporters are membrane-bound proteins that translocate endogenous compounds or drugs across the membrane (Giacomini and Sugiyama 2006; Giacomini and Huang 2013). They are expressed in all tissues including intestine, liver, kidney

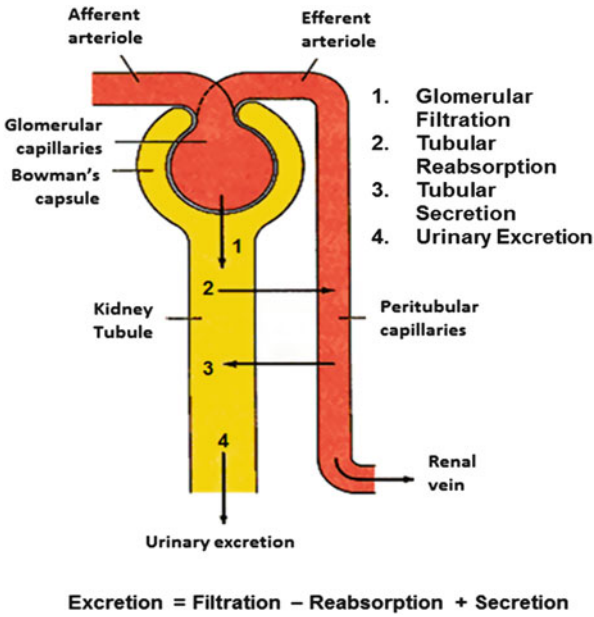

Fig. 2.1 Drug excretion processes in the kidney

and brain. They work in concert with metabolizing enzymes in the absorption, distribution, metabolism and excretion of drugs, thus affecting exposure to the medicine. Similar to enzymes, sex discrepancies in transporter expression probably contribute to disparities in drug disposition and toxicity between men and women. Sex differences in the expression of transporters in rodents have been reported. For example, a number of liver transporters demonstrate female predominant (Oatp1a4, −1a6, −2b1, Ntcp, Mrp4, Mate1) or male-predominant (Oatp1a1, Bcrp, Abca1) mRNA expression patterns in mice (Klaassen and Aleksunes 2010). However, data regarding sex differences in human transporters are quite limited.

P-gp encoded by MDR1 gene is an efflux transporter that expresses in multiple tissues including intestine, liver, and kidneys. Sex differences in the expression of P-gp in the gut have been studied showing a lower level in female enterocytes or no difference among sex (Gandhi et al. 2004; Waxman and Holloway 2009; Potter et al. 2004; Paine et al. 2005), and a higher expression of P-gp has been reported in male liver biopsy samples (Schuetz et al. 1995). In addition, in the literature there are reports that expression of another efflux transporter, Breast Cancer Resistant Protein (BCRP), is higher in male liver than in female liver (Merino et al. 2005). More Na^+-dependent Taurocholate Co-transporting Polypeptide (NTCP, a liver uptake transporter) mRNA in female human livers was reported, although it was not statistically significant because of large interindividual variation (Cheng et al. 2007). Whereas the majority of sex difference studies have focused upon mRNA expression, additional work is needed at the protein and functional levels to better understand the in vivo significance. A recent study using LC-MS

quantification methodology showed that sex was not associated with transporter protein expression of OATP1B1, OATP1B3, OATP2B1, and P-gp in frozen human livers (Prasad et al. 2014). There is a need for characterization of sex differences in human transporter proteins to more clearly understand any possible clinical effects.

Hormonal Differences

The assessment of sex-related differences is important as women experience a changing internal hormonal environment during the menstrual cycle (follicular, ovulatory, and luteal phases), during pregnancy, as well as during and following menopause. Furthermore, hormonal contraceptives can lead to increased or decreased drug clearance, most likely due to induction and/or inhibition of CYP isoforms in the liver and gut.

There are numerous examples supporting the contention that female sex hormones impact drug-metabolizing pathways (Schwartz 2003; Gandhi et al. 2004; Kashuba and Nafziger 1998; Bigos et al. 2009). Increased levels of estrogen and progesterone alter hepatic enzyme activity, which can increase accumulation or decrease elimination of some drugs. Estrogen is a substrate for CYP3A4 and CYP1A2 and it has been shown that antidepressant metabolism may be significantly impacted during the late luteal phase of the menstrual cycle or with estrogen replacement therapy (Bigos et al. 2009). Physiological changes during pregnancy in the cardiovascular, respiratory, renal, gastrointestinal, endocrine and hematologic/coagulation systems may also induce profound alterations to the PK of many drugs and thus the response to these drugs (Costantine 2014; Mattison et al. 1991). Additionally, changes in Vd and elimination rates may modify the PK of drugs in pregnant women during gestation. The clinical relevance of these changes is less certain (Loebstein et al. 1997).

Although sex hormones are thought to play a dominant role in modulating sex-based differences in PK, studies examining this theory have yielded conflicting results. For example, midazolam clearance (reflecting CYP3A4 metabolic activity) failed to show fluctuations during the menstrual cycle (Kharasch et al. 1999) and studies of eletriptan (another CYP3A substrate) demonstrated no sex-related or menstrual cycle-related differences (Shah et al. 2001).

What Are the Observed PK Differences Between Women and Men and Are There Examples Where Such PK Differences Result in Differing Pharmacological Responses and in Subsequent Different Dosing Recommendations?

PK Differences Observed

Although PK differences between men and women are possible based on sex-based differences in the mechanisms described above, not all drugs exhibit sex-based PK differences. In addition, the magnitude of many PK differences is often small (i.e. <20 %) and may not be clinically relevant. For example, a survey of clinical pharmacology data contained in 300 new drug applications (NDAs) submitted to the U.S. Food and Drug Administration (FDA) between 1994 and 2000 found that 163 (54 %) NDAs had sex-based PK information (Huang et al. 2007). Of the 163 drugs, 51 (31 %) showed a possible sex effect, i.e. a PK sex difference of greater than 20 %; (20 % was arbitrarily chosen as describing a difference that was potentially clinically significant). The survey results showed that (Huang et al. 2007):

- The majority (90 %) of PK sex differences were less than 40 %
- Except for one drug, where PK sex difference was greater than 40 %, women consistently showed higher plasma exposure
- Regardless of the disposition pathways involved, more than 50 % of the drugs studied showed PK differences of less than 20 %.

A more recent survey of the U.S. FDA labelings of 69 new molecular entity (NME) drugs and biologics approved by the FDA between September 2007 and August 2010 showed that out of 52 NMEs with sex-based PK information (in either the approved labeling or the clinical pharmacology review) the majority (38/52, 73 %) had no sex difference in PK. Four NMEs reported PK difference less than 20 %, 10 reported PK difference greater than 20 % but only 1 NME reported a >40 % PK difference (Copeland and Parekh 2011). No sex-based difference in dosage recommendation was made based on the observed PK sex difference because the differences were not clinically relevant. Examples of recent PK differences included in approved drug labelings are shown in Table 2.1.

Examples of Sex Differences in Pharmacokinetics and Safety Considerations

A few examples where sex-based PK differences resulted in modified pharmacological response and/or subsequent different recommendations are highlighted here.

Ondansetron

Ondansetron, approved for the prevention of nausea and vomiting resulting from chemotherapy or in the postoperative setting, has been shown to display a significant PK sex difference (Jann et al. 1998). The FDA-approved labeling for ondansetron states that women have 1.5–2 times the peak drug plasma concentrations and a lower oral clearance, but no sex-based dosage adjustment is recommended (Zofran® US FDA product labeling). Similar lower oral clearances are reported in elderly patients and patients with mild-to-moderate hepatic impairment and no dosage adjustment is recommended in these patients either, possibly based on similar exposure-response analysis for these patient populations. The recommended adult dose of ondansetron is 24 mg administered before emetogenic chemotherapy or 16 mg before anesthesia, and is not dosed on an mg/kg basis.

Olanzapine

Olanzapine is an atypical antipsychotic approved for the treatment of schizophrenia and bipolar disorder for which the label recommends a lower dose for patients in whom higher exposures are anticipated. For schizophrenia, the starting dose is 5–10 mg daily with a target dose of 10 mg/day within several days (Zyprexa® US FDA product labeling). However, given that some treatment related adverse events are dose and exposure dependent, a lower dose is recommended in specific populations who may have higher plasma concentrations. For instance, olanzapine clearance is lower in women. Clearance is also lower in the elderly ($\geq$65 years), causing higher plasma concentrations. Olanzapine is extensively metabolized and CYP1A2 has been identified as one of the enzymatic pathways of metabolism. As noted earlier, CYP1A2 shows a lower activity in women, possibly leading to a lower clearance of olanzapine in women. CYP1A2 can be induced by cigarette smoking and as a result, olanzapine clearance is about 40 % higher in smokers than in nonsmokers.

Although each of these factors may not independently justify dosing adjustment, the combined effects of age, smoking, and a patient's sex could lead to substantial PK differences and increase the likelihood of adverse effects from higher exposures. The plasma concentrations in elderly nonsmoking females, for example, may be higher than those in young smoking males. The labeling for olanzapine recommends a lower starting dose of 5 mg daily for patients who exhibit a combination of factors (e.g., nonsmoking female patients $\geq$65 years of age), as higher plasma concentrations are expected in these patients (Zyprexa® US FDA product labeling).

Table 2.3 Sex differences in the safety of amlodipine (Norvasc® US FDA product labeling)

Adverse event	Male (%) (N = 1,218)	Female (%) (N = 512)	Male (%) (N = 914)	Female (%) (N = 336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

Amlodipine

Amlodipine is a long-acting calcium channel blocker indicated for the treatment of hypertension and coronary artery disease. The recommended adult starting dose is 5 mg once daily with a maximum dose of 10 mg once daily, however, a lower starting dose of 2.5 mg once daily is recommended for small, fragile, or elderly patients or patients with hepatic impairment. The labeling contains information on the adverse effects of the higher dose in women, which is most likely related to higher blood levels. For several adverse experiences that appear to be drug- and dose-related, there was a greater incidence in women than in men associated with amlodipine treatment as shown in Table 2.3 (Norvasc® US FDA product labeling). It has been shown that the bioavailability of amlodipine is slightly higher in women, but these differences were attributed to the lower body weight of women, as when data were adjusted for weight, the bioavailability did not differ (Abad-Santos et al. 2005).

Zolpidem

Zolpidem, a sedative-hypnotic medicine used in adults for the treatment of insomnia, displays PK sex differences. The rate (measured by the peak plasma concentration or Cmax) and extent (measured by the area under the plasma concentration-time curve or AUC) of absorption of zolpidem following oral absorption were both approximately 45 % higher in women compared to men for immediate-release zolpidem and approximately 50 % and 75 % higher, respectively, for controlled-release zolpidem (Intermezzo® US FDA product labeling; Ambien® US FDA product labeling; Ambien® CR US FDA product labeling). When the immediate-release oral formulation (Ambien® US FDA product labeling) was originally approved by the FDA in 1992, there was concern regarding morning impairment, even after a 7-to-8- h period of sleep, and also recognition that people's risk of impairment could vary (Farkas et al. 2013). This led to the individualization of labeling recommendation for Ambien® US FDA product labeling with a lower dose of 5 mg for the elderly (who had higher blood levels of the drug the next morning)

and for patients with hepatic impairment who metabolized the drug more slowly (Farkas et al. 2013).

When the sublingual formulation (Intermezzo® US FDA product labeling) was approved in 2011, a sex-based dosage recommendation (i.e., 1.7 mg for women and 3.5 mg for men) was made based on new data that revealed a relationship between blood zolpidem level and driving impairment. The data showed that a blood level of zolpidem of >50 ng/ml could impair driving. With this threshold blood level, FDA retrospectively assessed the safety of other dosage forms of zolpidem based on the blood level of zolpidem 8 h post-doing. Sex-based dose recommendations were subsequently made to all formulations of zolpidem products based on reanalysis of PK data. Following administration of 10 mg Ambien® tablet (an immediate-release zolpidem product), about 15 % of women and 3 % of men had zolpidem concentrations that exceeded 50 ng/mL approximately 8 h post-dosing (Farkas et al. 2013).

A higher percentage of both men and women experience potentially impairing morning zolpidem levels after use of extended-release zolpidem products (Ambien® controlled-released products at 12.5 mg), which is expected given that approximately 33 % of women and 25 % of men had zolpidem blood concentrations exceeding 50 ng/mL 8 h post-dosing. In studies of zolpidem extended-release 6.25 mg, at 8 h after dosing, about 15 % of adult women and 5 % of adult men had a zolpidem level of ≥50 ng/mL, whereas for both elderly men and women, about 10 % had such a zolpidem level (Ambien® CR). These findings are consistent with the sex differences observed with various formulations of zolpidem. In January 2013, the FDA lowered the recommended dose for zolpidem, in particular for women (FDA drug safety communication: FDA approves. . .; FDA drug safety communication: risk of. . .) and included these recommendations in the labeling for all the zolpidem formulations (Intermezzo® US FDA product labeling; Ambien® US FDA product labeling; Ambien® CR US FDA product labeling).

Although the labeling of zolpidem products also suggests that the lower doses should be considered for men, the stronger recommendation for reduced dosage in women underscores the clear sex-associated differences in zolpidem PK observed in studies. A study of patients in the Taiwan National Health Insurance reimbursement database has shown that even the use of zolpidem for one day prior might be associated with an increased risk of motor vehicle accidents (Yang et al. 2011). These sex-specific labeling recommendations reflect an evidence-based approach to risk management and dose individualization. These examples suggest that both the exposure differences as well as the corresponding response changes are considered when dosing adjustments are recommended in labeling.

Moving to the Future

The following questions need to be routinely considered for sex-based dosing recommendations for therapies:

- Are there differences in PK between men and women other than those resulting from body weight differences?
- What are the effects of oral contraceptives and hormonal replacement therapy on metabolism of drugs? What drugs affect the efficacy of oral contraceptives? (see Chap. 5 for more detail)
- In general, are there more adverse event reports resulting from exposure differences in women as compared with men? Is this due to a higher percentage of use, higher reporting, or increased sensitivity of certain adverse events in women? The issues around whether women experience more adverse drug reactions than men is complex, but the evidence (discussed more in Chap. 14 on primary care prescribing) suggests they do have higher rates which are not just due to higher rates of use and reporting.
- When should drugs be labeled differently for women and men based on PK sex differences?

Sex is one of many factors that can affect a drug's PK. Tools need to be developed that can evaluate the effect of multiple intrinsic and extrinsic factors on PK of an individual patient. A computational tool such as physiologically-based PK (PBPK) modeling can integrate multiple factors in the system model to simulate the effect from multiple intrinsic (including sex) and extrinsic (including concomitant medications) factors on the PK of a drug. Recently, PBPK models have been used in drug development to assist in clinical trial design and answer "what if" questions (Rowland et al. 2011; Huang and Rowland 2012). Such models can be used to predict and understand why sex differences observed for certain drugs but not others by considering multiple factors.

Conclusions

Women and men differ in numerous physical parameters. Among others, women have a lower total body weight, a higher proportion of body fat, a lower body surface area, a lower muscle mass, smaller organ size, lower glomerular filtration rate, and lower gastric acid excretion – factors that may influence drug disposition. Physiological differences, such as hormonal fluctuations during the menstrual cycle, may also influence drug PK. Menstrual cycle variations do occur in renal, cardiovascular, and hematological systems, with the potential to impact protein binding and volume of distribution. Similarly, hormonal changes during menopause, pregnancy, and hormonal contraceptive therapy are likely to have the same effects. Finally, there are molecular factors that account for sex differences in PK (e.g., difference in drug-metabolizing enzymes and transporters). These physical, physiological, and molecular factors may influence the processes that determine drug disposition (i.e., ADME) (Nicolas et al. 2009).

Understanding the mechanisms of sex differences in drug therapy is critical for optimal dosing in both sexes. Evaluation of sex differences in PK of drugs will further enhance understanding of sex-based differences in the safety and efficacy of

drugs and minimize therapeutic adverse events. PK differences are the most common sex differences and early detection of these differences during drug development can lead to clinical trial design that will use sex-based dosing and better individualization of therapy. Because men and women may differ in specific drug PK it is essential to understand those sex differences in drug disposition and response, as in turn they may affect drug safety and effectiveness.

In conclusion, several mechanisms relevant to drug absorption and disposition have been shown to exert sex-specific activity differences, and for some drugs these have the potential to result in clinically relevant differences in pharmacological response. Thus, the importance of the evaluation of sex-specific PK during drug development is to optimize therapy for both men and women which is highlighted by the regulatory requirements and guidance recommendations.

Take Home Messages

- There are sex differences in the PK of several drugs due to molecular and physiological factors.
- The molecular factors involved in drug disposition include drug-metabolizing enzymes and drug transporters while physiological factors include lower body weight, higher percentage of body fat, lower glomerular filtration rate, and slower gastric motility in women.
- Correction for height, weight, surface area, and body composition eliminates some but not all of the sex-dependent PK differences. Only few drugs have shown sex-related differences in PK that have resulted in different pharmacological response (either safety or efficacy) and subsequent sex-based dosing recommendation. Exposure-response data is needed to determine the clinical implications of sex differences in PK of drugs.
- Understanding the science of sex differences in the PK of drugs will lead to optimal dosing for both men and women and reduce the undesirable side effects of pharmacotherapy.
- Multiple factors in addition to sex need to be considered to understand the clinical consequence of sex differences.

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Chapter 3
Prescribing Medicines to Adolescent Women

Sue Bagshaw

Introduction

This chapter will cover some information about young people's development, how that affects the ability to consent to treatment, how that can be judged, and how it affects the ethics of prescribing. Following this, the practical applications of prescribing to adolescent women will be discussed using two key examples: contraceptive products and treatments for mental health disorders, specifically depression.

What's So Different About Adolescent Women?

It is important to define who we are talking about when considering the topic of prescribing for adolescent women. There are many ways to consider human development. There are cultural definitions such that in some cultures a child undergoes some sort of ceremony and then they are an adult: adolescence lasts all of a few minutes. In Western culture it may even last up to 20 years if the concept of young adulthood is included in the definition of adolescence, as outlined by Arnett in 2006 (Arnett 2006).

There are various social markers such as leaving school, gaining employment, leaving university, or leaving home, all of which are very variable and dictated by family social standing and cultural norms, more than any other factor.

In terms of marking a difference between adults and children, physiological definitions may be more helpful, in deciding how we treat people who are not children but not adults. If we think about children we think about people who are

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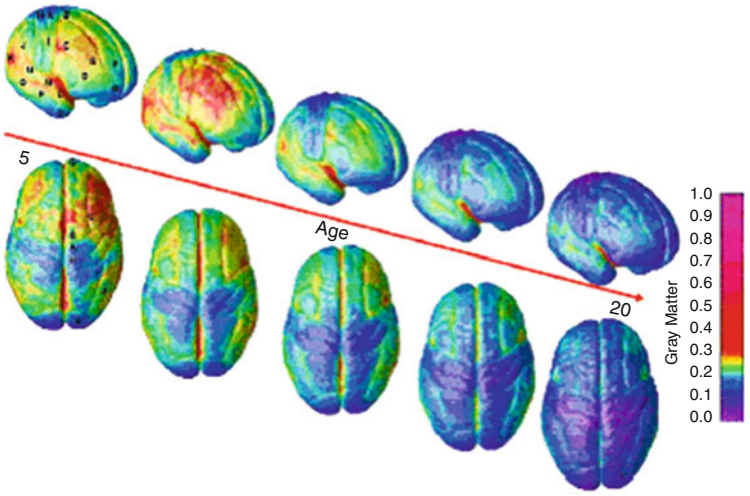


Fig. 3.1 MRI scans of the changing brain

dependent and need nurturing as they develop. In the past it was thought that the end of puberty marked the end of a child's development. When MRI scans became available it was realized that much of the ongoing brain development that occurs takes place for a long time after the end of puberty (Pujol et al. 1993). Shakespeare recognized this when he wrote in the Winter's Tale:

> I would there were no age between sixteen and three and twenty or that youth would sleep out the rest; for there is nothing in the between but getting wenches with child, wronging the ancientry, stealing, fighting. . .. (The Shepherd, Act III, Scene III, The Winter's Tale)

More recently, MRI scans have revealed that around the time of puberty there is an extra burst of developmental activity. This consists of a large number of connections occurring connecting the cortex with the hind and mid brains, shown in Fig. 3.1 as the blue areas covering the brain. The myelin sheaths of the neural connections show up as blue.

It is now known that not only is there a burst of connections, but also a pruning of neural pathways that aren't being used. There is a rearrangement of dopamine receptors, changes in hormonal levels, including a rise in oxytocin in addition to the sex hormones androgen, oestrogen and progesterone. Changes occur in the levels of leptin, insulin, growth hormone and then finally the frontal lobes, where the ability to make fine judgments, and understand consequences are linked in to the rest of the brain (Paus 2005; Sowell et al. 2001)

During adolescence there is a lot going on in the brain, with the prefrontal lobes gradually taking control of the rest of the brain functions (Yurgelun-Todd 2007) and of course that is reflected in big changes in the body. There is often a 25–50 % change in height and weight to reach adult size, secondary sexual characteristics develop, hair distribution changes and for women ovulation and menstruation begins and also changes in fat distribution occur. In young men there are changes in voice, muscle size and the ability to have erections and ejaculation.

No wonder adolescents are so tired. Not only do they have to cope with all this, but they also have to cope with a big change in the way adults treat them. More expectations are placed on behaviour, but at the same time parental support is being withdrawn, and there are big pressures to be independent, even though they are often disciplined like children.

It is well recognized that society generally defines adolescence by chronological age. The World Health Organisation (WHO) defines the ages of 10–19 years as adolescents, 15–24 as youth and 10–24 as young people. The Ministry of Youth Development in New Zealand (NZ) defines 'Young people' as from 12 to 24 years and states that in the 2006 census there were 757,000 people in this age group.

The ages at which physiological changes take place are not uniform. Pubertal changes may start as young as 8 years and as old as 16 years. It is well accepted that boys start this development later than girls, but what initiates the changes is not as well defined. As puberty can take as long as 3 years, the age of completing puberty can again range from 11 to 19 years, depending on what age it started at. The age at which the end of brain development occurs is also ill defined and has the same wide range of age at which it may be taking place, as puberty. It may take as long as four years to take place and range from 18 to 28 years before it is complete (Stiles and Jernigan 2010). In this chapter people between the ages of 12–24 will be referred to as 'young people', whereas many people think of adolescence as the teenage time, and of course issues of consent and capacity concern teenagers more than the wider group.

Thus how do we decide to treat people who have still got developing brains and bodies? There are a variety of legal definitions and countries vary around the world as to when the age of majority or adulthood is reached. In New Zealand, the age at which a person is no longer under legal guardianship is 18 years but they can leave home without the consent of their parents at 16 years and they are made to leave the guardianship of the State on their 17th birthday. The legal ages for various activities of children and young people in New Zealand are found in Fig. 3.2.

The latest age to dictate behaviour is 24 years, after 24 the young person is no longer assessed on their parent's income for a student loan.

The ages in Fig. 3.2 do not necessarily correspond to the ages at which the body and brain are developing in different individuals, but the law finds it necessary to use chronological age of young people for practical reasons.

The table in Fig. 3.2 refers to the age of 16 as when consent can be given to medical and dental treatment, but in fact in New Zealand it is widely accepted that consent to treatment is based on competency not age. These issues will now be discussed in more detail.

Consent

No health or disability service can be provided to a consumer without his or her informed consent in most countries in the western world. The right to make an informed choice and give informed consent is fundamental to individual autonomy,

Ages	Activities
5	starting school (earliest age)
6	starting school (latest age)
7	starting school (latest age if the child must walk more than 3 km to school)
14	babysitting — a babysitter's minimum age
14	leaving a child alone in your house
16	getting a learner's driving licence
16	leaving school (earliest age)
16	living with a partner
16	to leave home without parental consent
16	age of consent for sex
16	deciding on which parent to live with (if separated)
16	parental consent is required for medical/dental treatment
16	starting full time work
16	getting a tattoo
16	getting married or having a civil union (with parents' consent)
17	getting a full driving licence
17	joining the Navy, Army, Airforce without parental consent
18	getting married or having a civil union (without parents' consent)
17	buy a Daily Keno (lottery "scratch and win") ticket
18	buy a Lotto ticket

Fig. 3.2 (continued)

18	can be legally independent of their parents' guardianship
18	enter into contracts
18	buying alcohol
18	buying cigarettes
18	buying firecrackers
18	borrowing money
18	joining the Police Force and the Army
18	electoral voting
18	making a Will
19	the right to free education ends
20	if adopted applying to Births Death and Marriages for a copy of the birth certificate (to find out birth parents)
20	adopting a child if they are related.
25	adopting a child – if the child is at least 20 years younger.
20	enter a casino

Fig. 3.2 Legal ages for activities of children and young people in NZ (Source: Youth Law: http://www.kiwifamilies.co.nz/articles/legal-age-guidelines/)

and is one of the central elements in the Code of Health and Disability Services Consumers' Rights in NZ (http://www.hdc.org.nz/the-act--code/the-code-of-rights/the-code-(full)). The law tends to refer to people under 18 years as 'children' in keeping with the United Nations Convention on the Rights of the Child (UNCROC). The Health and Disability Commissioner's Code of Health and Disability Services Consumers' Rights Regulation 1996 is helpful in defining the right to informed choice and informed consent. It underlines the principle that informed consent is related to capacity not to age. Capacity to consent is presumed unless shown to be otherwise.

The rights as described in Fig. 3.3 sound simple enough until consideration is given to how to decide competence.

In NZ the law is unclear on how to decide competence. Section 36(1) of the Care of Children's Act (which replaced the Guardianship Act of 1968) states that children over 16 are able to give and refuse consent in the same way as an adult patient, but the child must be competent. If the child is not competent then s36 (3) states that consent can be given by the parent or guardian, or someone standing in place of a parent or guardian, or a District Court Judge or the chief executive if neither of the former are available (http://legislation.govt.nz/act/public/2004/0090/latest/DLM317233.html). The law does not say whether or not a competent child under 16 can give and refuse consent to treatment (Grimwood 2010).

The New Zealand Bill of Rights Act 1990, s11 (BORA), dictates "everyone has the right to refuse to undergo any medical treatment". This right is further embodied in the Health and Disability Code. (Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996, Sch 2, Right

Right 7

Right to Make an Informed Choice and Give Informed Consent

1) Services may be provided to a consumer only if that consumer makes an informed choice and gives informed consent, except where any enactment, or the common law, or any other provision of this Code provides otherwise.

2) Every consumer must be presumed competent to make an informed choice and give informed consent, unless there are reasonable grounds for believing that the consumer is not competent.

3) Where a consumer has diminished competence, that consumer retains the right to make informed choices and give informed consent, to the extent appropriate to his or her level of competence.

4) Where a consumer is not competent to make an informed choice and give informed consent, and no person entitled to consent on behalf of the consumer is available, the provider may provide services where -

a) It is in the best interests of the consumer; and

b) Reasonable steps have been taken to ascertain the views of the consumer; and

c) Either, -

i. If the consumer's views have been ascertained, and having regard to those views, the provider believes, on reasonable grounds, that the provision of the services is consistent with the informed choice the consumer would make if he or she were competent; or

ii. If the consumer's views have not been ascertained, the provider takes into account the views of other suitable persons who are interested in the welfare of the consumer and available to advise the provider.

Fig. 3.3 Code of health and disability services consumers' rights in NZ: right 7 on informed consent

7(7)) "Every consumer has the right to refuse services and to withdraw consent to services".

Other pieces of legislation that are relevant in NZ (Hedly 2014) are:

- ***Consent to abortion by a girl of any age*****:** consent, or refusal to consent, to termination of pregnancy has the same effect as if the female was of full age (s 38 C of C Act)
- ***Blood transfusions in urgent situations*****:** there is some immunity from liability for health practitioners who provide blood transfusions to children in certain urgent situations (s 37 Care of Children Act 2004)
- ***Operation for sterilisation***: no person can consent to an operation of sterilisation on another person if that person lacks capacity to consent on her own behalf by reason of age only (s 7 Contraception Sterilisation and Abortion Act)
- ***Treatment for mental disorder:*** The consent of a parent or guardian to assessment and treatment for a mental disorder shall not be sufficient if person has attained 16 years of age (s 87 MH(CAT) Act)
- ***Crimes Act***: Duties to provide necessaries of life. Medical examination of children in public schools (s125 Health Act)
- Medical examination if suspicion of ill treatment or abuse by **court order** (s 49 CYPF Act)
- **Presumption of competence** in the Code of Rights applies to all patients (right 7 (2)) Even patients with diminished competence retain a right to be involved with decision making as appropriate (right 7(3))

The above details relate to NZ law and the details of legislation relating to age and consent will vary from country to country. It is important to be familiar with the law operating in the country or State in which you practice. The Guttmacher Institute published an excellent summary of the ages for consent in the different States in March 2014 (Guttmacher Institute 2014).

Competence: Gillick, Scarman and Fraser

New Zealand has no legislation specifically describing the threshold of children's consent to medical treatment. Grimwood points out in a paper submitted to the Victoria University Law Review in 2010 (Grimwood 2010) that practitioners may assume that because people under 16 years can give their own consent in terms of abortion, then they can extrapolate this to other situations, which of course is not necessarily true.

In place of statute law New Zealand follows the common law principles of the United Kingdom in this circumstance, namely the case of *Gillick v West Norfolk and Wisbech Area Health Authority and the Department of Health and Social Security*.

In this case Mrs Gillick pursued the interests of her right to have to give permission for her under 16 year old daughter to receive contraception as her

legal guardian. The outcome was some guidelines for giving permission to give contraception to minors (Gillick v West Norfolk Area Health Authority 1986). These did not really include any other treatment. Even so, the case is now often quoted and a phrase has emerged called "Gillick competence" which will be discussed later in this chapter.

The UK House of Lord's decision on the Gillick case delivered a number of statements and guidelines or tests of competency. For example, Lord Scarman's test describes how the rights of the parents over the child decline as the child increases in understanding and maturity:

> . . . the parental right to determine whether or not their minor child below the age of 16 will have medical treatment terminates if and when the child achieves a *sufficient understanding and intelligence to enable him or her to understand fully what is proposed.* (Guttmacher Institute 2014)

The problem with this test is the phrase "fully understand". For decisions about complicated treatments even some adults would find it hard to fulfill the requirement. However, Lord Scarman did establish that parental guardianship is not necessarily a right but more a responsibility and duty to assist the child's development.

Fraser's Guidelines on Providing Contraceptive Advice or Treatment to Young Patients Without Parental Consent

Lord Fraser's guidelines describe the steps a health professional should go through to determine whether to give contraceptive advice or treatment to a minor without parental consent (Gillick v West Norfolk Area Health Authority 1986):

The health professional should be satisfied "on the following matters:

1. that the girl (although under 16 years of age) will understand his advice
2. that he cannot persuade her to inform her parents or to allow him to inform the parents that she is seeking contraceptive advice
3. that she is very likely to begin, or to continue having, sexual intercourse with or without contraceptive treatment
4. that unless she receives contraceptive advice or treatment her physical or mental health or both are likely to suffer
5. that her best interests require him to give her contraceptive advice, treatment or both without the parental consent."

Lord Fraser remarked that a minor is competent "provided the patient, whether a boy or a girl, is capable of understanding what is proposed, and of expressing his or her own wishes".

This still does not distinguish between judging the young person's capacity to understand versus understanding the proposed treatment. The latter principle is implied by the importance of the right to informed consent no matter what the

capacity. In NZ, the Health and Disability Commissioner states "Before making a choice or giving consent, every consumer has the right to the information that a reasonable consumer, in that consumer's circumstances, needs to make an informed choice or give informed consent." (Code of Health and Disability Services Consumers' Rights 1996)

The decision to provide advice and/or prescribe a contraceptive then comes down to testing the capacity of the young person to understand and whether that can be over ridden by an adult (parent, guardian, doctor or judge) in the best interest of the young person, even though they have capacity. The problem here is not what is in the best interests of the young person, but who decides what is in the best interest of the young person.

Thresholds for Deciding 'Best Interests' of Young People

One of the major principles of the NZ Children, Young Persons and Their Families Act 1989 is that the safety and best interests of the child are paramount (Care of Children Act 2004, s 4). Section 12 of the United Nations Convention on the Rights of the Child (UNCROC), in relation to the right to freely express their views, states:

> the views of the child being given due weight in accordance with the age and maturity of the child.

The best interests of the child should take into account the best interests as the child sees them, as well as the adults around him or her.

The question arises as to what is the threshold to decide when an adult can decide best interests and when the child/young person can decide. South Australian legislation decrees that children (those under 16) can give consent to treatment if the medical practitioner who is to administer treatment is of the opinion that the child is capable of understanding the nature, consequences and risks of the treatment and that the treatment is in the best interest of the child's health and well-being (The Consent to Medical Treatment and Palliative Care Act 1995).

British Columbia uses similar guidelines for health practitioners who need to ensure that the minor "understands the nature and consequences and the reasonably foreseeable benefits and risks of the health care" (Infants 1996)

When deciding whether or not the young person has capacity to decide, the guide lines used in Canada for mental capacity may be helpful:

> ..... a patient is capable with respect to treatment if the patient is, in the health practitioner's opinion, able
>
> (1) (a) to understand the information that is relevant to making a decision concerning the treatment;
> (b) to understand that the information applies to his or her particular situation;
> (c) to understand that the patient has the right to make a decision;
> (d) to appreciate the reasonably foreseeable consequences of a decision or lack of a decision.

(2) In determining a patient's capacity, a health practitioner shall, where he or she considers it necessary, inform the patient of the right to assistance and take into account such assistance as may be provided by an associate (Health Care Directives Act 1988).

Grimwood suggests that this guideline for determining the threshold of capacity is the most appropriate because it requires a minor to have understood the proposed treatment and it requires an understanding of the relevant information about the treatment being offered and the reasonably foreseeable consequences of that treatment. The threshold, therefore, prevents an investigation into moral and familial questions, which have little relevance to the minor's capacity. Instead, it focuses more on a realistic cognitive ability to comprehend the information given by the health professional under their duty to facilitate an informed choice.

The reasonable foreseeability component also accords with the sliding scale approach of *Gillick*, that with the increasing gravity of the procedure the greater the appreciation the minor must have of the consequences of a decision. The sliding scale idea has already been adopted by New Zealand statute, as the duties of guardians include "determining for or with the child, or helping the child to determine, questions about important matters affecting the child", which recognizes the developing maturity and understanding of minors, which was central to the majority judgment in *Gillick* (Care of Children Act 2004, s 16).

Privacy

In NZ, the Privacy Act 1993 is applicable to any person no matter what their age, but can be superseded by other legislation if there is a conflict. It governs the collection, use and storage of personal information under 12 principles. The most relevant section for the purposes of deciding whether or not information about the health of young people should be given to their parents, in terms of the giving of consent for treatment, is principle 11 (see Fig. 3.4). This governs the limits on disclosure of information. The issue at stake is that if the young person has the capacity to consent to their own treatment then their information should be kept private to them. They can be assured confidentiality from any adult they talk to.

This is the legislation that requires health practitioners to explain to young patients **that everything is confidential unless there is the potential for serious harm to themselves, or other people.** It is often helpful to increase understanding of the importance of this exception, to add that to tell someone else is important as it will get them more assistance.

In Principle 11 agencies are allowed to disclose personal information if any of the following conditions are fulfilled:

1. that is part of the declared purpose for collecting it;
2. if it is publicly available elsewhere;
3. if it is to the individual person who the information is about or they have authorized it;
4. if it is necessary to maintain the law, to protect the public revenue, or to obtain a fine;
5. that the disclosure of the information is necessary to prevent or lessen a serious threat to public health or public safety; or the life or health of the individual concerned or another individual;
6. that the disclosure of the information is necessary to facilitate the sale or other disposition of a business as a going concern;
7. that the information— is to be used in a form in which the individual concerned is not identified, or for statistical or research purposes and will not be published in a form that could reasonably be expected to identify the individual concerned.

In this list it is item 5 that is of relevance to whether or not to disclose a young person's information[19].

Fig. 3.4 Principle 11 of the Privacy Act 1993

Cognitive Development: Communication

The various legal guidelines discussed above should assist health practitioners to be able to judge whether or not a young person can consent to treatment, without the consent of their parent or guardian. However it is still difficult to make that judgment, unless there is an understanding of cognitive development.

Future Thinking

Alongside all the anatomical changes in the brain of the child and young person, the way the brain functions is also changing. At 2 years old a child does not have the capacity to understand what tomorrow means. If a much loved adult promises to see them tomorrow, they still cry at departure time as for them there is no such concept as tomorrow and effectively, in their understanding, the person is leaving forever. The capacity to understand what tomorrow means extends to "yesterday, a week, or a month" but at early puberty it may not have extended beyond more than a month.

This is important to judge because if the conversation extends beyond their capacity, the "glazed look" appears and it is hard to get their attention again. A young person's ability to understand those reasonably unforeseeable circumstances so important for capacity to consent, is also affected.

Abstract Thinking

Another important change in cognitive ability that occurs at this age is the ability to think about abstract concepts i.e. to think about thinking. Children think in concrete terms, the symbolism of fairy tales is often lost on them unless it is explained. Risks and consequences of receiving or refusing treatment are difficult to comprehend unless they are presented in very concrete terms. Thus judging where a young person is on the concrete abstract continuum, is vital to sufficiently explaining choices, without getting the "glazed look", accompanied by smiling, and nodding agreement just to get out of the room as fast as possible.

Complex Thinking

In addition, the growing number of linkages between all the parts of the brain (see MRI in Fig. 3.1) leads to the ability to think about more complex subjects and to take into account different ideas and thoughts at the same time. If the linkages are just starting to develop then this ability to handle many choices at the same time is limited. This is of course very important to judge when trying to decide if a young person understands the choices before them. It is also important to limit explanation to a very few choices until an understanding is gained of which stage of development the young person's brain has reached.

Unfortunately until we are able to have hand-held MRI scanners or other brain function detection equipment in our clinic rooms, all this remains a matter of clinical judgment. The importance of listening to *how* questions are answered as much as to the content of what is said cannot be overstated.

The difficulty in making these judgments is compounded by the fact that all these different parts that are developing are doing so at different rates and times in different individuals. Even in the same individual progress may be made in one area, but then because of stress or strain produced by life circumstances, that progress may regress and go back to an earlier stage. It is important to recognize how life circumstances, genetics and epi-genetics can affect the way the brain develops to a great extent. This can even be in terms of structural changes but may also affect the speed of development.

Gender Differences in Brain Structures

In a newsletter put out by the Columbia Consultancy in the USA, Ginny O'Brien notes that there are several differences in brain structure brought about by hormones. For example, the amygdala which is often seen as the emotion centre and which influences the production of adrenaline in the "flight, fight or freeze" reaction to danger is bigger in men. Anxiety and anger both make the body ready to fight or run. Some postulate that men are more likely to respond with anger. It may be an evolutionary construct to assist men in the protective role.

The prefrontal cortex is the decision-making executive center of the brain. It oversees emotional information and puts a check on the amygdala. The prefrontal cortex is larger in women and matures faster in women than in men. The anterior cingulate cortex, which is another part of the rational decision making centre of the brain that weighs options, is also larger in women, and has been labeled as the "worrywart" centre of a woman's brain. Again in evolutionary terms this makes sense for women to be worrying about their children. It is probably too early in our knowledge to draw conclusions about how that affects behaviour in current social norms (O'Brien 2007).

Gap Between Biological and Social Adulthood

In the Western World there is without doubt a big gap between the age of biological adulthood when young people can physically reproduce and the age of social adulthood, when it is deemed responsible (by society) to have children,. The range of biological adulthood or the end of puberty could be 11–14 years for girls but this varies between individuals as a result of many different influences, Including level of nutrition and genetics (Ellis 2004; Zacharias et al. 1970).

The median age of first birth is now 28 years according to the 2012 census in NZ. In Afghanistan it is 20, Bangladesh and the Niger 18, 24.5 in Russia, 31.2 in Greece and 25.4 in the USA (http://www.nationmaster.com/country-info/stats/Health/Births-and-maternity/Average-age-of-mother-at-childbirth). This is taken as a mark of the efficacy of Family Planning programmes by the WHO.

In past centuries the age of biological adulthood has often coincided with the age at which society recognizes the young person as an adult. According to Gluckman in 'hunter gatherer' times and even in agricultural settlements, every member of the family or community unit had a proscribed role fitting to their stage of development, and reproductive biology coincided with social aspirations (Gluckman and Hanson 2006). When children are seen as the property of their parents and assets of the family, it could be seen as a benefit to them because as assets they are nurtured. Figure 3.5 illustrates Gluckman's concept of 'mismatch', where in the last 20,000 years the age of menarche in young women has risen and then fallen, whilst

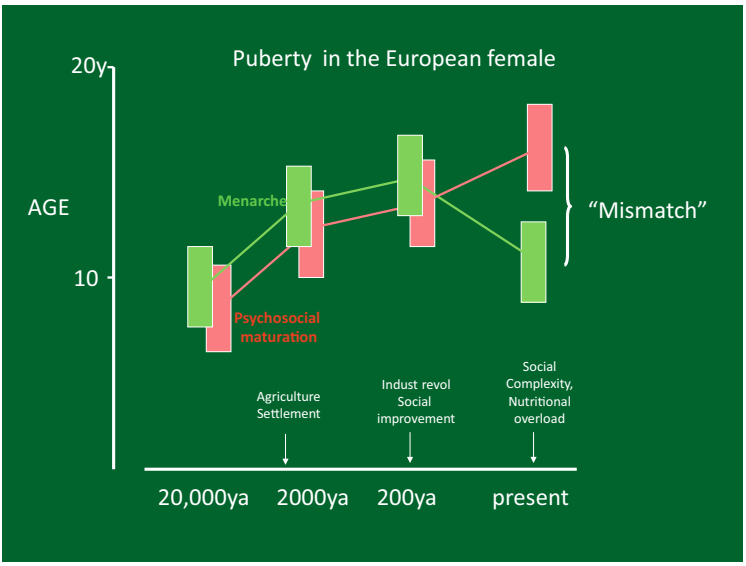


Fig. 3.5 From Gluckman "Mismatch: Why our world no longer fits" (Gluckman and Hanson 2006)

psychosocial maturation has steadily increased, resulting in a mismatch between these two markers of development in the present day.

In the so called "technical revolution" of the last 50 years the gap between biological and social adulthood has widened considerably. Is this because society considers that more nurturing is required, or is it because parents in Western culture are more afraid to let go? Or is it that brain development is taking longer and young people should not be allowed more adult roles in their own interests?

The role of culture in consent is important. Western culture is now accepting of individualism and more understanding and accepting about the rights of children after UNCROC. However, in many cultures children are still seen as being in need of control, and developmental needs are subsumed in the need of the parent to be seen as "in charge". This is easier to accept when there is a marker of the change from having someone else in charge to being in charge yourself. It is not easy to accept when there is no marker.

Ethics of Prescribing or Not Prescribing

The principles of consent and capacity, and the effect of development, as outlined in this chapter have clearly outlined the major differences between prescribing for a child and prescribing for an adolescent and an adult. In children the major concern is the suitability of any medication to a child's metabolism and especially the

correct dose for weight and height. In adolescents although the body is changing a lot, the major issue is the changing brain function and capacity and social standing in society, in addition to the suitability of the treatment. In adults although the ability to consent to treatment is still relevant, it is not nearly as common or difficult.

A dilemma about whether to treat is created for almost every adolescent patient if the ethics of consent are considered. There may be harm done, for instance, if the young woman is prescribed contraception when full capacity to understand and therefore consent on their own behalf has not been demonstrated. However, if she persists in sexual activity without contraception, there is even more potential for harm. Occasionally parents insist on the young woman being given contraception when it may be against her consent. If she has the capacity to consent or refuse consent whose wishes are uppermost? Who decides what is in the best interests of the "child". This presents another ethical dilemma.

It must be remembered that the capacity to consent is also affected by substance use. This always needs to be taken into account for adults, but adolescents and in particular youth (aged 15–24 years) also partake of a wide variety of substances as they learn by experience and explore adult behaviour. Alcohol is particularly important, not just because it is widely available and its use is culturally acceptable, but because it affects the adolescent developing brain in a different way to the adult brain. It is also important as the earlier the brain is exposed to alcohol the more likely it is that problems with the use of alcohol will arise in adulthood (Witt 2010).

Research in mice shows that there may be a gradual tolerance of the cerebellum to the affects of alcohol before it plateaus off at adulthood, which means that their co-ordination is less affected than adults (Karaçay et al. 2008). In contrast the memory of an adolescent is easily disrupted, but for adults to have "blackouts" they usually need to have consumed quite large quantities (Silveri 2012).

Churchwell et al. found that cannabis affects impulsivity and decreases future thinking, and this seemed to be correlated with age of first initiation (Churchwell et al. 2010).

The question of whether legal advice or court action is necessary for prescribing (or not prescribing) will always be a matter of individual judgment. However, the following factors may be 'red flags' that indicate situations of risk where legal advice or even court action may be appropriate (Hedly 2014):

- Where the course of action proposed has permanent, long term or serious consequences, or is experimental or high risk
- Where there is a conflict between clinicians and a child's guardians about the treatment that should (or shouldn't) be provided
- Where there is a conflict between the child and the guardians (particularly where a child is under 16 but appears to be competent to make their own decisions)
- Where there is a conflict between a child's guardians
- Where there is clinical uncertainty or disagreement about what treatment is necessary or appropriate

- Where there is doubt about the child's or the guardian's competence to give (or refuse) consent
- In situations of urgency

Court action is rare for contraception but may be more relevant for operations or treatment of mental illness and behavioural disorders.

Practical Application

So how does all this affect how you prescribe to teenage women? The following section will look at applying some of these principles to two common areas for prescription: contraception and mental health. In particular the oral contraceptive pill and antidepressants will be considered in some detail.

Many teenage women will have capacity to consent below 16 years, but obviously it would be important to establish that capacity and to establish how far along the continuums of concrete to abstract thought, future thinking and complexity of thought, they have progressed. If in doubt, it is often best to start from using communication that is about now, is concrete and one or two thoughts at a time.

Contraception

Fraser's guidelines – as mentioned earlier in this chapter – are useful here. If the young woman has already started having sexual intercourse and has come for contraception, the important concept to establish is that she can understand how contraception works. The use of diagrams is helpful and an example is shown in Fig. 3.6.

Use of simple but effective diagrams may assist in limiting the number of choices to avoid information overload. The diagram in Fig. 3.6 also helps discussion and understanding of why one method might be better than another, and why condoms may be useful to use whatever else they choose.

Intra-uterine devices (IUDs) can be used in young women as is discussed in some detail in Chap. 8 (contraceptive devices) and may be a valuable option in adolescents for whom compliance with oral contraceptive methods may be difficult. Recent research now shows that having an IUD does not increase the risk of infertility, but having a Chlamydia infection does, whether an IUD is in situ or not (Hubacher et al. 2001; Rivera and Best 2002).

One disadvantage however, is that it may be more difficult to insert because of the tighter cervical os in nulliparous women.

A major risk for failure of any contraception is of course the ability of the user to comply with using it correctly. Thus methods which do not involve much input from the user may be ideal for many young women: IUDs, progestogen implants

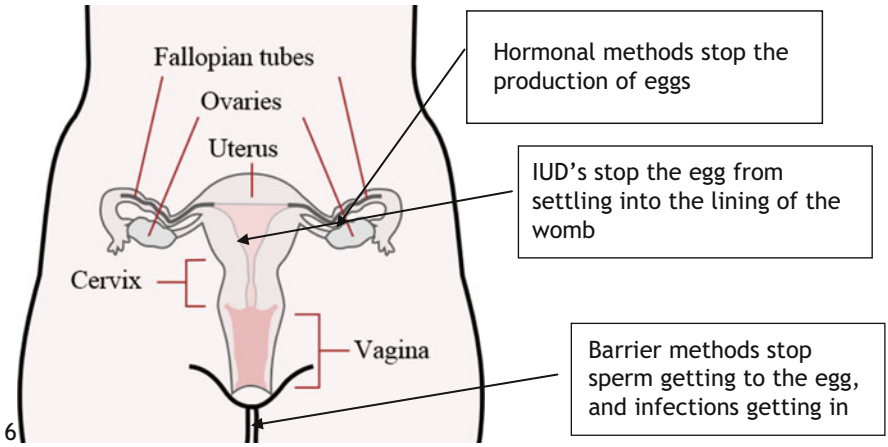


Fig. 3.6 Diagram of how contraception methods work

such as Jadelle or Implanon (see Chap. 8), or injectable methods such as Depo Provera. However young women often do not like needles or the "thought of something inside them", which may well be linked to their level of development, in which emotional thinking is much stronger than logical thought until the frontal lobes are well connected.

Communicating Benefits and Risks of Contraceptives to Adolescent Women

It is probably a mistake to describe hormonal contraception by telling the young woman that it makes it seem like they are pregnant. For concrete thinkers the simile is taken literally. It is important to stress that if the level of hormone in the body goes down because they haven't taken any pills, then eggs will be produced again and they could get pregnant. Never tell any young woman that her chances of becoming pregnant are low because she has polycystic ovarian syndrome (PCOS) endometriosis or pelvic inflammatory disease (PID). They will assume that they can't get pregnant and not use contraception, only to become pregnant in a few months.

When trying to explain risks it is even more important to estimate cognitive development. Some young women are innate worriers and emotional thinking enhances the anxiety even more. A discussion on the risks of thrombosis, increased blood pressure and breast cancer is important (see Chaps. 5 and 6) but take care to find out what the young person has understood, as it may mean that she takes the prescription but does not take the pills because of her anxieties. It is sometimes helpful to compare the extent of risk to something that is more tangible like the risk of being run over by a bus, which may not be accurate but is at least understandable.

Research has shown that teenage women think more with their amygdalas (i.e. their emotions) than with their frontal lobes as the connection of the frontal lobes is not fully developed (Yurgelun-Todd 2007). This means that emotions are heightened and worry is more intense.

One small study on communicating the risks and benefits of contraceptives showed that explanation by another young person was more effective than a doctor or nurse. A review of strategies showed that further research is needed, but this finding may be more to do with the nature of the explanation than the development of the young person (Halpern et al. 2013).

Recent research has shown that many of the more minor side effects that were attributed to the use of contraceptive hormones are also attributable to many other causes and whilst it may be helpful to outline the standard list of headaches, acne, emotional changes and weight gain, none of these effects has been definitely causally associated with COCs (see Chap. 5) and this may also lead to problems including non-compliance (Grimes and Schulz 2011).

When this kind of symptom occurs the pill will be blamed and then use may cease. Irregular bleeding may also lead to non-compliance so this is very important to explain and reassure, that if bleeding occurs it will most likely settle. It is advisable to use a 30 ug pill at first to avoid the risk of irregular bleeding (Akerlund et al. 1993)

When prescribing the OCP explain how it works, the importance of taking it every day, explain risks but also emphasize the advantages: – the decrease in risk of ovarian and uterine cancer, regular and lighter periods, and missing periods if desired (see Chap. 5). The '7 day rule' is not as important as it once was thought to be and is often quite confusing. If the young woman is likely to find it difficult to remember to take the pills then encourage her to take it continuously as this is much more effective. This advice should also be accompanied by the warning that irregular bleeding may occur and if it does, to come back to see you, and have a 3 day break instead of 7 days (Cho et al. 2014).

There is a lot of information to take in when first starting to use contraception. It is advisable to perhaps provide a short prescription at first and encourage her to return to see you so that explanations can be repeated and understanding reinforced. It is also helpful to provide written explanation in the form of pamphlets to take away, but there is no guarantee that this will be read. Make sure that they have been tested with a teenage audience (most FPA pamphlets have been).

If the young woman is living at home it is important to encourage her to inform her parents about her medication so that if complications or side effects do arise the parent will be able to assist. There are many reasons why young people don't want to tell their parents amongst them may be:

- fear of getting into trouble,
- they do not want to share private information that they consider is no business of their parents,
- they are concerned about not adding to the worries their parents already have,

- they may have had experience of their parent/carer then telling everyone else their private information, which of course they do not want.

If you are going to be successful in persuading a young woman to tell her parents, then addressing the concerns for her is the first step. Sometimes role playing how she might tell her parents can be useful, so that the dread of telling is removed.

Mental Health

This section will not cover prescribing of all medications for mental illness, but it is important to note that much mental illness begins in the under 25 year old age group. Many of the illnesses are not diagnosed or treated but they can often be traced back to starting at this age. One of the factors that may lead to lack of diagnosis may be due to the fact that many symptoms are attributed to "adolescent moodiness". This section will first discuss clinical assessment of adolescents presenting with possible mental health disorders and then discuss medicines used for these conditions.

Clinical Assessment of Adolescents with Mental Health Issues

Whilst it is true that mood control is being learnt by teenagers just as behaviour control is being learnt by the under fives, that does not mean that they are ill. When deciding how to treat low mood in teenagers the first thing to determine is their developmental stage but also to take a psychosocial history to find out the factors that might be affecting mood and anxiety. The HEADSS assessment tool (Home, Education, Employment, Exercise, Activities, Drugs, Sexuality, Suicide/mental health, Spirituality/Culture, Safety, Strengths) is an excellent tool to use (Klein et al. 2014). This is summarised in the Box 3.1 below as published by The Collaborative Trust in conjunction with Skylight resources (2011),

It is important to screen for the signs of depression as a defined illness. The Diagnostic and Statistical Manual of Mental Disorders Fifth edition DSM-V May 2013 says: *"The common feature of all of these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. What differs among them are issues of duration, timing, or presumed etiology."*

The HEADSS assessment will help discover aetiological issues such as family history, episodes of loss, sources of stress etc. as it is important to determine the difference between depression and other issues such as grief. In teenagers the grief response can be intense as a response to a loss, which adults feel is unwarranted.

Medication is not a useful treatment for grief unless accompanied by depression (see below). Validation of the emotion and an empathetic response is much more effective, especially if parents can be encouraged to respond in this way too.

Another important distinction is between post-traumatic stress disorder (PTSD) in its chronic form and depression. Trauma in the past, especially when it occurred when the child was not verbal, can be an important stressor leading to low mood which may be thought to be depression unless careful enquiry is undertaken. Treatment in this situation is therapy for the trauma over and above medication.

However two Cochrane reviews on the use of psychological therapies in depression, grief and PTSD have shown that there are not enough studies to come to any conclusion as the relative merits of any particular therapy (Cox et al. 2012; Gillies et al. 2012).

Box 3.1: Summary of HEADSS Assessment Tool

Headss is a tool for engagement, a screening tool that helps gather information to form a picture of the context for the person and their presenting complaint. It is also a tool for planning what the next step should be, together with the young person.

Headss is not a recipe to follow. It is a framework upon which to weave a conversation which eventually forms a bigger picture. Thus the questions don't stem from the letters in the order of the mnemonic, but from the answer given to the last question.

The aim is to gather information on parenting style, strengths such as sports, academic skills, artistic ability, people to talk to, groups to belong to and behaviours that may lead to harm such as unsafe sex, alcohol and other drug use, and mental health and abuse issues.

HOT TIPS – Avoid "Dunno" answers by asking for a description rather than an opinion

Use "I wonder", and "how come" rather than why

Ask yourself two questions – how far along the journey towards adulthood is the young person, mentally, socially, economically and spiritually, and what stage of cognitive development are they at? Consider capacity to think abstractly, extent of future thinking, and ability to handle more than one idea/choice at a time

Home – Who lives with you at home? Who makes the rules and what happens when you break them? Do you have you own room? Do your parents get on? Do they shout at each other or at you or your siblings? Do they hit each other or you or your siblings? Is there anyone you can talk to if you are worried about anything?

Education – Do you go to school every day? Which school/what year? What subjects do you do? What do you do at lunch time? Have you been

(continued)

Box 3.1 (continued)
bullied/have you bullied? Are you involved in after school things? Do you do a sport? Is there anyone you can talk to if you are worried about anything?

Employment – do you have a job? If so what, how many hours? What do you do with the money you get? Is there anyone you can talk to if you are worried about anything? Do you volunteer?

Exercise – how do you get to school? Do you exercise for fun? What sort of exercise do you like

Eating – what's your favourite take away? Who cooks at home and what? Does your family eat together? Do you worry about your weight? Do you control your eating?

Activities – do you do stuff with your family? What do you do with your friends? What music do you like? Do you belong to any groups? Do you go to parties?

Drugs – are you on any medication? Do you have any allergies? Do your parents smoke nicotine/ cannabis/drink alcohol? Do your friends? Do you? – If yes, how much/how often? Do you ever use party pills? (E, P, BZP, etc.) Have you ever used needles? Do you gamble?

Sexuality – What did you think of sex education at school? Are your friends having sex? Are you? OR If it is ok with you I'd like to ask you about sexuality in case I can take this opportunity to help with contraception or check for sexually transmitted infections? We know that some people are only attracted to the same sex, some people only attracted to the opposite sex and some can be attracted to both, but only have sex with the opposite sex. If you want to talk further about this sort of thing let me know. Have you ever been forced to have sex when you didn't want to?

Suicide – should be Mental Health. Do you have good days and down days? Do you have more down days than good? How's your sleep? Do you sleep more or less than you would like to? Do you lie awake worrying? Do you worry a lot about other things? Does worry stop you doing what you would like to do? How are your energy levels? Do you feel hungry? Do you eat more than you would like to or less? Do you ever have negative thoughts? Do you ever harm yourself? Have you ever thought of killing yourself? (if so do you have a plan? Have you tried? Do you know anyone who has?) Do you ever hear voices?

Spirituality – Does your family go to church/synagogue/temple/mosque? Do you? What do you think about it? For the older ones – Do you believe in something bigger than yourself? What culture do you identify with? (If Maori – Do you spend time on the Marae? Do you speak Te Reo? Do you know your whakapapa?)

Safety – summing up question if you haven't asked already- Do you get bullied at school? Has anyone tried to have sex with you when you didn't

(continued)

Box 3.1 (continued)
want to? Have you ever driven a car drunk? Do you always use a seatbelt / cycle helmet?

Strengths – summing up question Recap on who the young person can talk to. What groups do they belong to, what they are best at, what skills do they have, do they help other people? Helpful question – If I were to talk to your best friend how would they describe you. What would they say is the reason they are friends with you? OR what would your primary school teacher say about you?

Treatment Options

If depression is established then a decision needs to be made about treatment. The treatment for adolescents with depression study (TADS) team in 2004 undertook a study to investigate whether medication alone or cognitive behavioural therapy (CBT) alone, or a combination, was the most efficacious treatment for depression in adolescents (March et al. 2004). 439 patients between 12 and 17 years of age were randomized to four groups consisting of fluoxetine alone, CBT alone, CBT with fluoxetine and placebo, over 12 weeks of treatment. Overall, the combination of fluoxetine with CBT was the most effective using comparisons of the Children's Depression Rating Scale and the Clinical Global Impression score at the end of the 12 weeks. The authors were careful to point out that during the study there were seven attempted and no completed suicides.

Another study in 2007 showed that CBT and SSRIs combined were no more effective than SSRIs alone in terms of depression and the CBT did not provide protection against an increase in suicidal thinking (Goodyer et al. 2007).

The use of e-therapy is now growing with the numbers of websites such as the Lowdown, Urge and Beyond Blue, all giving good advice. 'Sparx' is an avatar game that has just been launched from its own website. This was developed by Professor Sally Merry from the University of Auckland, is based on CBT principles and been shown to be effective in mild to moderate depression in both young men and women (Merry et al. 2012).

Substance use will also have an effect on mood so this needs to be enquired about, and behaviour problems arising in the context of poor mood control or a dysfunctional family also need to be differentiated, from depression the illness.

A similar study to the TADS was conducted in 2007 by Riggs et al. in which 126 adolescents aged 13–19 years recruited from the community and meeting Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) diagnostic criteria for current major depressive disorder, lifetime Conduct Disorder (CD), and at least 1 nontobacco Substance Use Disorder (SUD) were randomized to 16 weeks of fluoxetine hydrochloride, 20 mg/day with CBT, or placebo with CBT (Riggs et al. 2007). Fluoxetine combined with CBT had greater efficacy than did placebo

and CBT according to changes on the Childhood Depression Rating Scale-Revised (effect size, 0.78) The study showed that there may have been a difference for those with substance use disorder in the CBT group. The proportion of substance-free weekly urine screen results was higher in the placebo-CBT group than in the fluoxetine-CBT group (mean difference, 2.10; 95 % confidence interval, 0.37–4.15).

For clinical purposes, in light of the fact that there are so many conflicting studies on the efficacy of CBT and SSRIs, and on the incidence of adverse reactions, that the best determination is to look for more studies. It may be that the new brain research on the development of the brain will reveal more.

SSRIs and Suicidality in Young People

The studies that have been done of selective serotonin reuptake inhibitors (SSRIs) and depression in young people have been confusing with regard to the possible increased risk of suicidality. The Cochrane review referred to above (Cox et al. 2012) found that young people on SSRIs had significantly more suicidal ideation than young people using psychological therapy. There were no completed suicides and the review pointed out that the studies all had size and methodological limitations.

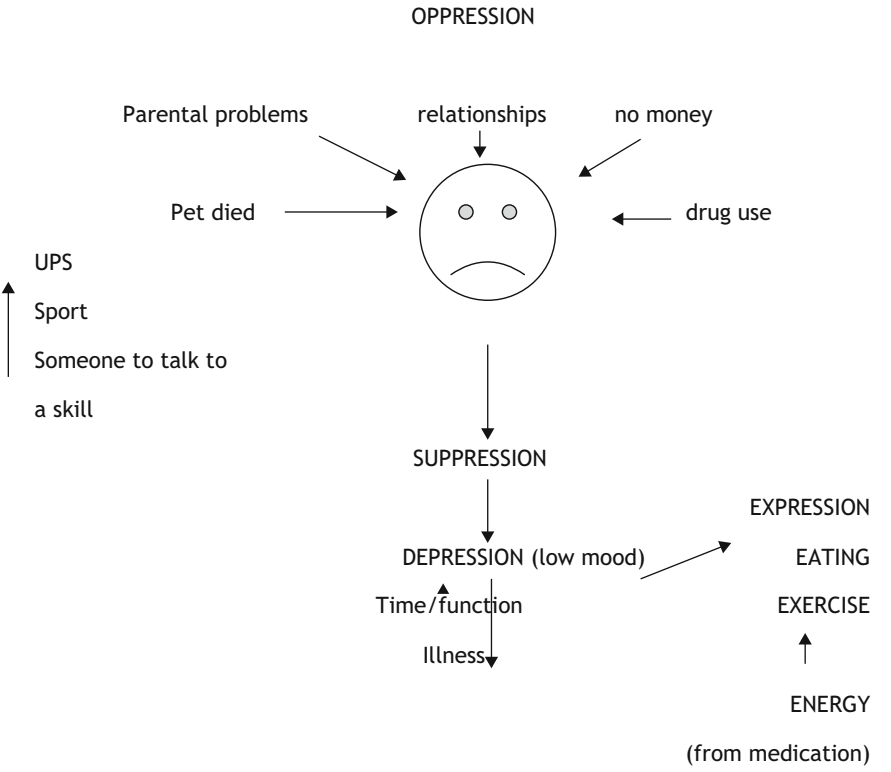
As Steven Cuffe points out in his article in 2007, when the FDA issued a black box warning for the use of antidepressants in young people in 2004 it was based on data which showed a small increase in suicidal thinking from 2 % in the placebo group to 4 % in the medication group, when data from all trials were combined. There were no completed suicides in any of the studies and the warning was given despite data which showed that suicide rates were decreasing in response to medication (Steven 2014). Since then other studies have shown that the rate of suicide with antidepressants has not been shown to rise appreciatively (Gunnell and Ashby 2004). Most of the advice now seems to revolve around being cautious in the use of antidepressants in teenagers, to monitor carefully in the first few weeks and to combine with CBT if it is accessible.

Tricyclic antidepressants should be avoided because of their danger in overdose (Urban et al. 2013). Although they may be efficacious in some individuals, they should not be used as first line treatment in young people and not in those with suicidal ideation because of their cardiac toxicity in overdose.

None of the studies on antidepressant medication in young people appear to have examined gender differences. This may be an important area for further study in light of the gender differences in prevalence in young people.

Application

One way of explaining all this is found in a model of depression that frames depression as a result of oppression or a feeling of being pushed under by a lot of different factors.



How to Use This in Consultations with Young People

Draw the sad face and then show the main things that are pushing down, find out other things from the patient that might be strengths and giving a "push up". Then show how the way they would want to react, they may often suppress and then how suppression and oppression lead to depression.

Talk about the difference between low mood and depression the illness. Then discuss how expression (talking about the problems that are pushing them under), eating brain food (fruit, vegetables, fish) and exercising to produce endorphins can all treat depression.

Medication can be explained on the lines that it helps to supply mental energy to do the other "E's" when they have the illness. In other words it is a "whole package" approach that works. This seems to be a much more acceptable way to refer to a counselor, as the young person knows why they are going and what they are trying to achieve. Parents find it helpful as they know what the role of medication is and the whole family can be encouraged to improve their lifestyle.

It is important to explain about the increased risk of thoughts about suicide and the need for some supervision. If the young person can't tell their parents, they need to tell another adult who can "keep an eye" on them daily. Prescribing 2 weeks of medication only at first and seeing again even sooner if it seems necessary, is advisable, especially if they are at an earlier cognitive developmental stage, and may be more likely to act on impulse.

The above model of care may be called for more often in adolescent women, as depression is more common in young women (Fortune et al. 2010). However, with this method there are no particular differences between managing young women and young men, other than tailoring treatment to each individual patient's circumstances as required.

Conclusions

The prescribing of medication to young women is probably very similar to older women in terms of which and how medication is given. The main difference is in the nature of communication needed. To diagnose and to give instruction it is vital to form an assessment of stage of cognitive development and where the young person is on their journey to adulthood, in terms of being able to live independently and gain an income to support themselves. This then helps in forming a diagnosis, determining capacity to consent and in giving instructions on taking the medication.

Some medications are more relevant to young women (e.g. contraception). With others such as antidepressants, there does not seem to be an effect by gender on the medication, but symptoms of depression are more common in women and especially younger women.

Take Home Messages

- For young people consent for medical advice and/or treatment is based on competence not age
- Competence is based on the stage of cognitive development, determined by biological brain development which is affected by puberty, genetics, epigenetics and societal and family influences, not chronological age.
- If an adolescent has the capacity to consent then they have the right to confidentiality.
- Judge competency on the stage of cognitive development and where they are on the continuum of concrete to abstract thinking, how far ahead they can think, and the level of the complexity of their thought.
- 'Gillick competence' implies that the level of complexity of the decision also needs to be taken into account.
- When explaining a decision about medication to young people the use of diagrams, explaining the reasons for taking medication, how it works, what it does and risks or side-effects are all important.
- Be aware that girls start their cognitive development earlier than boys and may therefore be more advanced than boys in terms of their chronological age.

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Chapter 4
Medication Use in Pregnancy; Treating the Mother: Protecting the Unborn

Yifat Gadot and Gideon Koren

Introduction

Each year, numerous new medications enter the market. The formal labeling for most of these drugs does not contain safety data related to exposure during gestation. However, millions of pregnant women have conditions that need to be treated such as diabetes, urinary tract infections and nausea and vomiting. The paucity of knowledge in regard to fetal safety of medications introduces significant challenges for practitioners, and situates the mother at risk of insufficient therapy for her disease, and her unborn baby at a potential risk of toxicity (McBride 1978; Koren 2013).

Since thalidomide was demonstrated to be a major human teratogen, many practitioners practice as if any medication is hazardous to the fetus, leading physicians and pregnant women to refrain from the use of medications, even for the management of serious conditions. Presently, we must change the climate whereby pregnant women and their unborn babies become therapeutic orphans. Ultimately, this knowledge gap may prevent the mother from obtaining needed therapeutics, or make her decide not to treat serious conditions, or even to terminate otherwise wanted pregnancies.

For the vast majority of drugs which have been evaluated in pregnancy, including first trimester exposure to ACE inhibitors, oral contraceptives and benzodiazepines, large amounts of data have failed to show fetal risks in humans (Koren et al. 1998). Before considering potential fetal risks of drugs, it is imperative to note that all pregnancies have a birth defect baseline risk of 1–3 %, by chance alone (Heinonen et al. 1977). Hence, any attempt to prove fetal safety/risk must compare exposure to a given drug to this baseline risk.

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Overall 80–90 % of pregnant women take at least one medication during pregnancy, commonly before they realized they have conceived. During the last 30 years, there has been a 60 % increase in first trimester use of prescription drugs, while use of four or more drugs tripled (Mitchell et al. 2011). Moreover, 12 million prescriptions for potentially teratogenic medications are prescribed annually in the U.S. for women in their reproductive years (Schwarz et al. 2005). Contraceptive counseling is given in less than 50 % of women prescribed potentially teratogenic medications (Schwarz et al. 2005) and approximately 6 % of US pregnancies are exposed to potentially teratogenic medications (Andrade et al. 2004; Lee et al. 2006).

Timing of Fetal Exposure to Medicines

All-or-None Period

The "all-or-none" period is the period of time between fertilization and implantation. At this time the embryo is not yet in contact with the maternal circulation, and any injuries sustained by the conceptus are likely to result in either recovery, repair or death (Fabro and Scialli 1986). It is improbable that exposure to teratogens in the "all-or-none" period will result in malformations.

The timing of implantation is approximately 14 days post-ovulation, although recent information suggests that it may occur several days prior (Wilcox et al. 1999). Implantation in the uterus lining induces the production of human chorionic gonadotropin (hCG) which enters the maternal circulation, creating a connection between the mother and the conceptus (Wilcox et al. 1999).

Period of Organogenesis/First Trimester

The period of organogenesis (menstrual weeks 5–10) is the period of time when the differentiation of fetal tissues takes place and thus in this period the fetus is susceptible to the impact of teratogens. The organ systems that are most influenced by the effects of teratogens are those developing at the time of teratogenic exposure. For example, limb development has a relatively short duration of susceptibility to teratogenicity, while the fetus is susceptible to central nervous system defects over a period of months (Brent 1986).

Further Fetal Development in Second and Third Trimesters

The second and third trimesters of pregnancy are characterized by cell growth and differentiation. Exposure to teratogenic agents at this period may cause cell growth

retardation, decrease the cell population by cell death, or inhibit differentiation. For example, chronic exposure to antenatal corticosteroids may decrease birth weight (French et al. 1999).

Estimating the Risk of Drugs in Maternal Milk

There are serious concerns among mothers and health professionals regarding neonatal exposure to drugs through breast milk. In order to confirm the safety of use of drugs during breastfeeding one needs to estimate the extent of infant's exposure to the drug through breast milk, by calculating the infant's weight-adjusted dose (referred to as" relative infant dose"). The calculation of infant's weight- adjusted dose is based on maternal weight and dose, concentration of the drug in breast milk, and an estimation of infant's daily milk consumption of 150 ml/kg. If an infant's weight adjusted dose is less than 10 % of the maternal weight adjusted dose, it is unlikely that it would elevate the risk for adverse neonatal effects above baseline risk (Bennett 1996).

Medicines with Safety Concerns During Pregnancy and Lactation

In this chapter we will discuss selected medications for which there are potential or proven concerns for fetal safety.

The reader is referred to Table 4.1, where we summarize drugs which are apparently safe to the developing fetus when used in therapeutic doses. Table 4.2 summarises data related to neonatal safety of drug exposure through breastfeeding.

Table 4.1 Summary of safety of medicines in pregnancy

Drug	Overall assessment	Existing evidence
ACE inhibitors	In 1st trimester-no relation to congenital malformations	Meta-analysis, prospective and retrospective cohort studies, case reports
	In 2nd and 3rd trimesters- fetal hypotension and renal failure	
Acetaminophen	Safe for use in pregnancy	Large retrospective cohort studies, prospective cohort studies
Acetazolamide	Limited data on first trimester is reassuring	Cohort studies, case reports, case series
Acetylcysteine	Limited data on first trimester is reassuring	Case reports, case series

(continued)

Table 4.1 (continued)

Drug	Overall assessment	Existing evidence
Biological therapies	Safe for use in pregnancy- avoid live vaccine in baby up to 6 months	Cohort studies, case reports, case series
CA channel blockers	Limited data on first trimester is reassuring	Cohort studies
Cephalosporins	Safe for use in pregnancy	Cohort studies
Chloroquine	Safe for use in pregnancy	Prospective and retrospective cohort studies, reviews, case reports
	Long half life	
Clavulonic acid	Safe for use in pregnancy	Cohort studies
Clindamycin	Limited data on first trimester is reassuring	Randomized case-control, Cohort studies
Codeine	Safe for use in pregnancy	Case-control studies, cohort studies
	Withdrawal may occur in neonates	
Dextromethorphan	Safe for use in pregnancy	Case-control study, cohort studies
Digoxin	Safe for use in pregnancy	Cohort studies, case series, case reports
	Monitor maternal drug levels	
Flecainide	Limited data of no malformations, should only be used if potential benefit justifies potential fetal risk	Case series, case reports
Furosemide	Limited data of no malformations	Meta-analysis, cohort study, review
Gabapentin	Limited data on first trimester is reassuring	Cohort studies
Heparin	Safe for use in pregnancy	Review, cohort studies, case reports
	Maternal osteopenia in prolonged use	
Hydralazine	Limited data on first trimester is reassuring	Cohort study, case series
Isoniazid	Limited data on first trimester is reassuring. Vitamin K recommended (to prevent haemorrhage), Vit B6 supplementation	Case-control study, prospective and retrospective cohort studies, case reports
Lamotrigine	Safe for use in pregnancy	Prospective and retrospective cohort studies
Levetiracetam	Safe for use in pregnancy	Cohort studies, case series
Low molecular weight heparin	Safe for use in pregnancy	Cohort studies
	Does not cross the placenta	
	Might be related to increase in maternal osteoporosis	
Macrolides	Safe for use in pregnancy	Cohort studies
Mesalamine	Safe for use in pregnancy	Meta-analysis, cohort studies
Methyldopa	Safe for use in pregnancy	Meta-analysis, cohort studies
Metronidazole	Safe for use in pregnancy	

(continued)

Table 4.1 (continued)

Drug	Overall assessment	Existing evidence
		Meta-analyses, cohort studies, review
Montelukast	Safe for use in pregnancy	Cohort studies
Nitrofurantoin	Safe for use in pregnancy	Meta-analysis, cohort studies
	Hemolytic anemia of fetus/newborn-discontinue >37 weeks	
NSAIDS	Safe for use in 1st and 2nd trimesters, not recommended in 3rd trimester-premature closure of ductus arteriosus	Case-control study, cohort studies, case reports
Oral contraceptives	Safe for use in pregnancy	Meta-analysis, case-control studies, cohort studies
Oseltamivir	Relatively safe for use in pregnancy	Cohort studies
Penicillins	Safe for use in pregnancy	Case-control study, prospective and retrospective cohort studies
Propafenone	Very limited data	Case report
Quinolones	Safe for use in pregnancy	Meta-analysis, prospective and retrospective cohort studies
Rifampin	Limited data on first trimester is reassuring. Vitamin K recommended (to prevent hemorrhage)	Cohort study, case reports
Salbutamol	Safe for use in pregnancy	Cohort studies
Salmeterol	Safe for use in pregnancy	Cohort studies
Spironolactone	Limited data on first trimester is reassuring	Cohort study, case reports
Sulfasalazine	Safe for use in pregnancy	Cohort studies, case reports
	Folic acid supplementation advised to reduce toxicity	
Tetracyclin	Bone growth suppression, teeth discoloration>mainly after 4 months of gestation	Cohort studies
Theophylline	Limited data on first trimester is reassuring	Prospective and retrospective cohort studies
Thiazide	Limited data on first trimester is reassuring	Meta-analysis, case reports, review
Trimethoprim-sulfonamide	1st trimester-increased risk of neural tube defects	Case-control studies, cohort studies
	Not recommended >32 weeks due to risk for kernicterus	
Triptans	Safe for use in pregnancy	Systematic review, prospective and retrospective cohort studies
Vancomycin	Limited data on first trimester is reassuring	Small cohort studies

Table 4.2 Summary of safety of medicines during breast feeding

Drug	Compatibility	Pharmacokinetics	Evidence
ACE Inhibitors	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
Acetaminophen	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case reports, case series, review, prospective cohort study
Acetazolamide	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case reports
Acetylcysteine	No information		No studies or reports
Acyclovir	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
Aminoglycoside	Compatible with breastfeeding	Excreted in breast milk in very low concentrations	Case series, case reports
	Observe for diarrhea, candidiasis		
Amiodarone	Careful breastfeeding because of large proportion of iodine in the drug	Excreted in breast milk in low concentrations, stays in breast milk days-weeks after stopping to breastfeed	Case reports
	Monitor cardiac and thyroid function		
Angiotensin II-AT1 Receptor Blockers	No information		No studies or reports
Aspirin-high dose	Not recommended	Excreted in breast milk in high concentrations	Case series, case reports
	Metabolic acidosis, Reye synd with viral infections		
Aspirin-low dose	May be considered	Excreted in breast milk in high concentrations	Case series, case reports
Atenolol	Contraindicated	Accumulates in potentially high levels in breast milk	Case series, case reports
	Adverse effects such as bradycardia		
Biological therapies	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case reports
	Live vaccines are contraindicated		
β blockers (labetolol, metoprolol, nadolol)	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
CA channel blockers	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
Cephalosporins	Limited information	Excreted in breast milk in low concentrations	Case series, case reports
	Compatible with breastfeeding		

(continued)

Table 4.2 (continued)

Drug	Compatibility	Pharmacokinetics	Evidence
	Observe for diarrhea		
Chloroquine	When given once a week-might be safe, no information in breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
	Other drug may be preferred		
	Long half life-over a month		
Clavulonic acid	Compatible with breastfeeding	Excreted in breast milk in very low concentrations	Two small, controlled, prospective studies, case series, case report
	Observe for diarrhea, rash, restlessness		
Clindamycin	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
Codeine	Other agents are preferred. Max 4 days treatment is recommended	Variability in excretion to breast milk (due to maternal polymorphism of CYP2D6)	Guidelines, retrospective cohort studies, case series, case reports
	Can cause drowsiness, central nervous system depression and even death		
	Newborn infants particularly sensitive		
	Monitor mother and infant		
Dextromethorphan	No reported adverse events		No reports
	Probably compatible with breastfeeding		
Digoxin	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
Flecainide	Limited data, no adverse effects	Monitor breastfed infants, including serum levels	Case series, case report
Furosemide	No information	Increased diuresis might decrease lactation	Case report
Gabapentin	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
	Surveillance infant		
Heparin	Compatible with breastfeeding	Estimated Excretion in breast milk in low concentrations	No reports
			Data related on low molecular weight heparins data (case series)
Hydralazine	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports

(continued)

Table 4.2 (continued)

Drug	Compatibility	Pharmacokinetics	Evidence
Isoniazid	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
Lamotrigine	Surveillance infant carefully	Excreted in breast milk in high concentrations-30 % of maternal plasma level	Small cohort studies, case series, case reports
Levetiracetam	Limited data	Excreted in breast milk in low concentrations	Case series, case reports
	Compatible with breastfeeding		
	Surveillance infant		
Low molecular weight heparin	compatible with breastfeeding	Excreted in breast milk in negligible -very low concentrations	Case series
Macrolides	Compatible with breastfeeding monitor infant GI symptoms, related to pyloric stenosis?	Excreted in breast milk in low concentrations	Cohort study, case series, case reports
Mesalamine	Monitor for diarrhea	Excreted in breast milk in low concentrations	Case series, case reports
Methyldopa	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case reports
Metronidazole	Compatible with breastfeeding, with caution	Excreted in breast milk in very low concentrations	Case-control study, case series
Montelukast	No information		No reports
Nitrofurantoin	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
	Under 1 month or infants with G6PD-not recommended, risk of hemolysis		
NSAIDS	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case reports
	COX 2-exposure small, risk expected to be minimal		
Oral contraceptives	Affect growth negatively in first month of life, may suppress breastfeeding		Cohort studies, case series, case reports
	Not recommended in the first 4 weeks postpartum		
	Generally, progesterone only pills are preferred		
Oseltamivir	Limited data compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series, case report

(continued)

Table 4.2 (continued)

Drug	Compatibility	Pharmacokinetics	Evidence
Penicillins	Compatible with breastfeeding	Excreted in breast milk in very low concentrations	Case series, case reports
	Monitor infant GI symptoms		
Phenobarbital	Compatible with breastfeeding with caution	Variability in excretion in breast milk, in some cases very high- dosage is 72 % of the maternal adjusted dose	Case series, case reports
	Can cause drowsiness		
	Monitor the infant		
	If suspected toxicity-check levels in infant		
Propafenone	Compatible with breastfeeding, especially after 2 months of age	Doses up to 900 mg produce very low levels in milk	Case reports
Quinolones	Short-term use is acceptable	Excreted in breast milk in low concentrations	Case series, case reports
	Avoid breastfeeding 4–6 h after the dose		
Radionuclides	Guidelines vary with the specific agent and the test performed	Variability in excretion in breast milk between the different kinds, the dosage is between 0.01 % and 70 % of the maternal adjusted dose	Reviews, guidelines
	Elective diagnostic nuclear medicine procedures should be delayed until the patient has interrupted breastfeeding (hours-weeks-depending on substance)		
	In some cases there is a need to refrain from close contact with the infants		
Rifampin	Limited data	Excreted in breast milk in very low concentrations	Case series, case reports
	Compatible with breastfeeding		
Salbutamol	Compatible with breastfeeding	Excreted in breast milk in very low concentrations	No reports
			Data related on terbutaline data (case series, case reports)
Salmeterol	Compatible with breastfeeding	Excreted in breast milk in very low concentrations	No reports
			Data related on terbutaline data (case series, case reports)
Spironolactone	Usually compatible with breastfeeding	Excreted in breast milk in low concentrations	Case report

(continued)

Table 4.2 (continued)

Drug	Compatibility	Pharmacokinetics	Evidence
Sulfasalazine	Other drug without sulfonamide may be preferred	Excreted in breast milk in low concentrations	Case series, case reports
	Monitor for diarrhea		
Tetracyclins	Short-term use is accepted, refrain from long or repeat treatments	Excreted in breast milk in low concentrations	Cohort study, case series
Theophylline	Toxic effects of infant	Excreted in breast milk in high concentrations	Case series, case reports
	Avoid breastfeeding a few hours after drug given		
Thiazide	Scarce data	Low doses are acceptable Increased diuresis might decrease lactation	Case reports
Trimethoprim-sulfonamide	Acceptable for healthy, term babies		Systematic review, prospective controlled study, cohort study, case series
	Avoided in G6PD, preterm, ill, jaundiced (risk for kernicterus)		
Triptans	Compatible with breastfeeding	Excreted in breast milk in low concentrations	Case series
Vancomycin	Limited data compatible with breastfeeding	Excreted in breast milk in low concentrations	Case report

The medications selected below are either known teratogens, or have been the center of much debate on their potential adverse effects on the child, and although they ultimately have been not shown to cause fetal damage, their use have been curtailed by misperception and anxiety by women and prescribers alike.

Antibiotics

Antibacterial drugs are among the most common medications used by pregnant women. Most antibiotics are safe for use in pregnancy (e.g. cephalosporins, clavulonic acid, macrolides, metronidazole, nitrofurantoin, penicillins and quinolones). Regarding nitrofurantoin, increased risk for hemolytic anemia of the newborn has been suggested, with the recommendation for discontinuation at >37 weeks gestation recommended.

Few antibiotics are considered not safe in pregnancy, such as tetracyclins and trimethoprim-sulfonamides. Tetracyclins are associated with bone growth suppression, teeth discoloration after 4 months of gestation. Trimethoprim-sulfonamides

have been associated with first trimester-increased risk of neural tube defects and are not recommended after 32 weeks gestation due to risk of billirubin displacement and kernicterus. Some of the antibacterial medications have limited data, although the data are reassuring. (e.g. clindamycin, isoniazid, rifampin, vancomycin) (Nahum et al. 2006).

Trimethoprim-Sulphonamide (T-S) combinations (e.g., Septra®, Bactrim™) are commonly used for urinary tract infections in pregnant women. Some evidence suggests that when prescribed in pregnancy, these folic acid antagonists may elevate the risk for neural tube defects and possibly other congenital malformations (Briggs et al. 2011).

Biological Therapies

An increasing number of biological therapies are IgG monoclonal antibodies. There is limited information currently available on the use of biological therapies during pregnancy, but they do not appear to elevate the risk of congenital malformations above the baseline risk in the general population (Mahadevan et al. 2005; American Gastroenterological Association Institute 2007; Johnson et al. 2011; Association of Rheumatology Health Professionals 2008; Ojeda-Uribe et al. 2006; Food and Drug Administration Dermatologic and Ophthalmic Drugs Advisory Committee 2012; Mahadevan et al. 2013). The high molecular weight of biologicals does not allow them to cross the placenta in early pregnancy; however they do cross later on (as do other IgGs when the placenta develops higher levels of the Fc transporter, and many of them have neonatal levels exceeding maternal concentrations. Biologicals which are not IgG, (e.g. CIMZIA)- minimally cross the placenta even in late pregnancy (Mahadevan et al. 2011). A case of a neonate who succumbed to vaccinia after maternal use of infliximab highlighted a potential risk of immunological deficiency in exposed babies (Mahadevan et al. 2011).

Therefore it is now widely agreed that live vaccines should be contraindicated in patients treated by biological therapies. Because biological medicines were found in exposed infants up to 6 months after birth, The World Congress of Gastroenterology (WCOG) states that: "Vaccination of infants exposed to biological therapy in utero should be given at standard schedules, except for live-vaccines, which are best not given if circulating biological agents are detectable in the infant" (Mahadevan et al. 2011).

Breastfeeding

Only very small amounts of biological therapies are excreted into breast milk, which would be predicted due to their high molecular weight. Considering biological therapies are proteins, they are most likely not to be absorbed systemically.

The infants' systemic circulation exposure to biological therapies in human milk appears to be minimal (Murashima et al. 2009). These data imply that biological therapies may be safe during breastfeeding, but long-term follow-up information is not available.

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

Angiotensin-converting enzyme (ACE) inhibitors are effective antihypertensive agents, with few adverse effects. They are often used in women of reproductive age. The use of ACE inhibitors in the first trimester only, does not appear to be related to an elevated risk of major congenital malformation above the average risk in hypertensive pregnant women (untreated or treated with other drugs) (Diav-Citrin et al. 2011; Moretti et al. 2012; Walfisch et al. 2011; Li et al. 2011; Kreft-Jais et al. 1988; From the Centers for Disease Control and Prevention 1997; Lip et al. 1997; Steffensen et al. 1998; Yip et al. 1998).

In contrast, exposure to ACE inhibitors in the second and third trimesters appears to be fetotoxic, inducing fetal hypotention and renal failure. Oligohydramnios (reflecting renal failure), reduced urine formation, neonatal anuria and fetal hypotension shown in published cases, are a direct consequence of these medications on the fetal renin-angiotensin system (Boutroy et al. 1984; Guignard et al. 1981; Rosa et al. 1989). The degree of fetal and neonatal morbidity correlated with ACE inhibitors exposure in the second and third trimesters is estimated to be significant (between 10 % and 20 %) (Al-Maawali et al. 2012).

The anuria related to oligohydramnios may result in pulmonary hypoplasia, fetal limb contractures and craniofacial deformities. Severe neonatal hypotension, intrauterine growth retardation, persistence of patent ductus arteriosus, prematurity, hypocalvaria, neonatal anuria, and neonatal or fetal death have also been shown with exposure to these drugs in the second and third trimesters of pregnancy (Barr 1994).

Therefore, cessation of ACE inhibitor medication before the second trimester of pregnancy is recommended and physicians should then offer the patient an alternative medication. In cases where exposure in the second or third trimester take place, patients should be surveyed by ultrasound for toxic signs including growth restriction, oligohydramnios and fetal distress (Barr 1994).

ACE-I and Breastfeeding

ACE-I are secreted into human breast milk in low amounts. The peak milk level is about 1 % of the peak plasma concentration, while average milk levels over 12 h following a dose is about 3 % of the average serum levels. Based on this information, the maximum daily dosage in milk is less than 0.014 % of the maternal

weight-adjusted daily dose (Devlin and Fleiss 1981; Redman et al. 1990). There have been no observed adverse effects in breastfed infants (Devlin and Fleiss 1981; Huttunen et al. 1989; Rush et al. 1989).

Angiotensin II-AT1 Receptor Blockers

Another group of medication for hypertension are the angiotensin II-AT1 receptor blockers (ARBs), including losartan, valsartan, telmisartan, eprosartan and irbesartan. Based on limited data from first trimester exposure (Walfisch et al. 2011; Schaefer 2003; Gersak et al. 2009; Serreau et al. 2005; Chung et al. 2001; Biswas et al. 2002; Mann et al. 1999), there does not appear to be an elevated risk of major congenital malformations above the risk in pregnant hypertensive women, untreated or treated with other medications.

Similar to the ACE inhibitors, ARBs are fetotoxic when used in the second and third trimesters. They have been also reported to produce oligohydramnios, fetal anuria, limb contractures, pulmonary hypoplasia, fetal growth retardation and hypoplastic skull bones (Serreau et al. 2005; Kato et al. 2008; Simonetti et al. 2006; Vendemmia et al. 2005; Bald et al. 2005; Alwan et al. 2005; Lambot et al. 2001; Briggs and Nageotte 2001; Cox et al. 2003).

Antidepressants

The second leading cause of burden of disease for women in the United States is major depressive disorders (Michaud et al. 2006). Up to 20 % of women of reproductive age are afflicted by depression (Bennett et al. 2004) and between 1 % and 8 % of pregnant women are treated by antidepressants (Engeland et al. 2008). The selective serotonin reuptake inhibitors (SSRIs) have been in clinical use for the last two decades and are generally regarded as safe in pregnancy, in terms of dysmorphology and in neurodevelopmental measures (Koren and Nordeng 2012). The selective serotonin and norepinephrine reuptake inhibitors (SNRI) – for example: venlafaxine, duloxetine, desvenlafaxine – and Tricyclic antidepressants (TCA) are also considered safe (Einarson et al. 2012; Moses-Kolko et al. 2005; Santos and Pergolizzi 2004).

Importance of Treatment Proper control of maternal psychiatric illness during pregnancy is necessary to provide optimal outcome for the infant and mother. Untreated depression in pregnancy has been related to increased risk of miscarriage, pre-eclampsia (pregnancy-induced hypertension), perinatal complications, bleeding during pregnancy and postpartum bleeding (Reis and Källén 2010), increased admissions to Neonatal Intensive care Unit (NICU) and increased risk of postpartum depression (PPD) (Bonari et al. 2004).

Abrupt Discontinuation Abrupt discontinuation of these medications can have both physiological and psychological withdrawal symptoms (general somatic, gastrointestinal and affective symptoms, and sleep disturbances), including suicidal thoughts and relapse of the psychiatric illness (Einarson et al. 2009).

Spontaneous Abortions Studies have reported an elevated risk for spontaneous abortions of 5.5–13.0 % with antidepressants use (compared to non use) with a relative risk/odds ratio of 1.63–2.09 (Einarson et al. 2009; Nakhai-Pour et al. 2010). However, it is not known whether this effect is induced by the antidepressant or the depression itself.

Poor Neonatal Adaptation Symptoms (PNAS) Exposure to an SSRI or an SNRI during pregnancy has been associated with feeding and breathing difficulty, jitteriness, low blood sugar, and neurological symptoms (increased motor activity and sleep disturbances) (Costei et al. 2002; Levinson-Castiel et al. 2006). In most cases, symptoms subside within a week, but may continue up to 3 weeks (Moses-Kolko et al. 2005; Chambers et al. 2006). Most studies document that 10–30 % of infants exposed to SSRI's prenatally exhibit PNAS with more than half having mild symptoms (Costei et al. 2002; Levinson-Castiel et al. 2006).

Infants exposed to SSRI's or SNRI's (mainly in the 3rd trimester) should be closely monitored for several days after birth. Symptoms tend to be self-limited with supportive care.

Persistent Pulmonary Hypertension of the Newborn (PPHN) Several studies have associated late pregnancy SSRIs exposure with PPHN (Chambers et al. 2006; Källén and Olausson 2008; Kieler et al. 2012). However other studies have failed to show it (Kieler et al. 2012; Wichman et al. 2009; Andrade et al. 2009; Wilson et al. 2011). Kielers reported that women who did not use antidepressants in pregnancy but who were hospitalized for psychiatric reasons had an increased likelihood to deliver infants with pulmonary hypertension in the newborn with an OR 1.3 (CI 1.1–1.7) (compared to non psychiatric pregnant population) (Koren and Nordeng 2011). PPHN may occur in less than 1 % of babies exposed prenatally to SSRI (Koren and Nordeng 2011; Jong et al. 2012). Moreover, no mortality has been documented in any infants exposed to SSRIs prenatally that developed PPHN, compared to mortality rate of 10–15 % among other causes of PPHN (Occhiogrosso et al. 2012).

Preterm Birth Numerous prospective observational studies with thousands of pregnant women reported a small increase in premature births among babies exposed to antidepressants in late pregnancy. However, it is unknown whether this is the result of the antidepressants or depression itself (Wisner et al. 2009; Einarson et al. 2010; Lewis et al. 2010).

Teratogenicity Published information from 2004 and onward proposed, based on registries, that some SSRIs may be associated with increased risk of cardiovascular malformations, mainly ventricular septal defects (VSD). However, for each study postulating such risk there were two studies refuting such an association (Koren and Nordeng 2012). It should be taken into account that there is a substantial ascertainment bias because depressed women who use antidepressants undergo significantly more

ultrasound and echocardiography. Therefore, their babies are much more likely to be diagnosed with congenital malformations (Bar-Oz et al. 2007). Outcomes of more than 20,000 women exposed to all classes of antidepressants documented no overall increased risk for congenital malformations (Koren and Nordeng 2013; Riggin et al. 2013).

The Risk Benefit ratio of antidepressant use in pregnancy is strongly tilted toward use of the medication in symptomatic women, due to the high and serious risks of not treating depressed pregnant women, including hospitalization, suicide attempts, and increased risk of postpartum depression (Koren and Nordeng 2012).

Antidepressants and Breastfeeding Typically SSRI's, SNRIs and TCAs generate low levels in breast milk (Berle et al. 2004; Lanza di Scalea and Wisner 2009; Rampono et al. 2006; Newport et al. 2009). The average concentration of drug in breast milk is higher with fluoxetine (and its active metabolite) in comparison to most SSRIs. There have been reports of adverse effects such as colic, fussiness, and drowsiness in some breastfed infants. If fluoxetine is required by the mother, it is not a reason to discontinue breastfeeding. Otherwise, antidepressants with lower excretion into breast milk may be preferred, especially while breastfeeding a preterm infant (Kristensen et al. 1999; Moretti et al. 1999).

The breastfed SSRI/SNRI/TCA infant should be monitored for adverse events such as colic, fussiness or sedation and for inadequate weight gain (Newport et al. 2009; Kristensen et al. 1999; Moretti et al. 1999).

Lithium

Lithium is used in the management of bipolar disorder and has been on the market for more than 30 years. The malformation associated with lithium is the Ebstein anomaly which is characterized by apical displacement of the septal and posterior tricuspid valve leaflets. It may lead in severe cases to right heart failure and death and increased birth weight (Giles and Bannigan 2006; Schou 1976; Källén and Tandberg 1983; Pinelli et al. 2002; Abstracts of the Teratology Society 2012).

Higher lithium levels at delivery have been associated with an increased risk of perinatal complications, including cyanosis, disturbances of cardiac rhythm, hypotonia, nephrogenic diabetes insipidus, and hypothyroidism (Newport et al. 2005; Karlsson et al. 1975; Mizrahi et al. 1979; Krause et al. 1990).

A level II ultrasound and fetal echocardiogram are recommended. Toxic effects can be monitored by serum lithium levels and adjusting to minimally effective plasma levels, particularly in late pregnancy. Short withdrawal of lithium treatment may be considered peri-partum, if it does not compromise the mother. Importantly, neonatal symptoms are self-limited and can be treated effectively.

Lithium and Breast Feeding

Although there have been documentations of high levels of lithium in breast milk, more recent research has failed to document excessive exposure (Moretti 2003; Viguera 2007; Bogen et al. 2012). Based on available information, maternal lithium treatment should not be a contraindication for breastfeeding, and the decision needs to be made on an individual case basis. Monitoring drug levels in serum and breast milk can be performed as necessary.

Corticosteroids

Corticosteroids are used for various conditions during pregnancy, including arthritis, asthma, nephrotic syndrome and inflammatory bowel disease. The most common corticosteroid in use is prednisone but others include dexamethasone, cortisone and prednisolone. Betamethasone and dexamethasone can accelerate fetal lung maturity and are given to women at risk of preterm delivery, to decrease risk for prematurity complications (ACOG 2011).

Corticosteroids do not present a major teratogenic risk in humans, although there is an apparent elevated risk for oral cleft (Rodríguez-Pinilla and Martínez-Frías 1998; Czeizel and Rockenbauer 1997; Carmichael and Shaw 1999; Gur et al. 2004; Park-Wyllie et al. 2000) which is consistent with animal data (Walker 1971; Pinsky and Digeorge 1965). Both human and animal studies have documented an increased risk of low birth weight and stillbirth, but this may be related to the maternal underlying diseases (Gur et al. 2004; Reinisch et al. 1978; Scott 1977; Mercer et al. 2001; Thorp et al. 2002; Bloom et al. 2001).

Corticosteroids should be used based on specific indications without safe alternatives or to life threatening maternal illnesses. Since the formation of the lip and palate is completed by 12 weeks of gestation, therapy may be continued after that time. If exposure has occurred during the critical period in pregnancy, a level II ultrasound may detect some cases of oral cleft.

Corticosteroids (Inhaled)

Inhaled corticosteroids are used for the treatment of asthma or other respiratory conditions. Several studies including a meta-analysis on inhaled corticosteroids have not found an increased risk for congenital malformations (Greenberger and Patterson 1983; Rahimi et al. 2006; Källén and Otterblad 2007; Choi et al. 2007; Lim et al. 2011). No adverse fetal outcomes such as pregnancy-induced hypertension, preterm delivery or low birth weight were documented (Rahimi et al. 2006; Lim et al. 2011). Treatment during pregnancy with inhaled corticosteroids

decreases the risk of an acute asthma attacks in the mother and therefore leads to more favorable fetal outcomes.

Thiopurines

The thiopurines azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective medications for inflammatory bowel disease (IBD), generating a steroid-free, endoscopic and clinical remission (Mowat et al. 2011; Timmer et al. 2007). These drugs are being used more extensively in pregnancy (Goldstein et al. 2007; Kwan and Mahadevan 2010) and they have not been shown to cause increased malformation rates in observational studies and meta analyses (Mowat et al. 2011).

Based on recent studies, azathioprine exposure is not associated with increased risk of congenital malformations (Goldstein et al. 2007; Schramm et al. 2006; Moskovitz et al. 2004; Armenti et al. 2002; Cleary and Källén 2009), spontaneous abortions, stillbirth (Schramm et al. 2006) or neurocognitive impairment (Teratology Society 2011). Risks of other adverse pregnancy outcomes such as intrauterine growth retardation, prematurity (Goldstein et al. 2007; Armenti et al. 2002; Pirson et al. 1985), and immunosuppression (Alter 1985; Davison et al. 1985; DeWitte et al. 1984; Sahasranaman et al. 2008) have been reported, although these may be the results of the disease itself.

Thiopurines and Breastfeeding

Azathioprine exerts low risk to the breastfed infant and breastfeeding can continue during treatment. Studies reported low or unmeasurable concentrations of the active metabolites in breast milk and in infant serum (Christensen et al. 2008; Mahadevan et al. 2012). Mothers with reduced activity of the enzyme thiopurine methyltransferase (TPMT), involved in azathioprine metabolism, may excrete higher levels of drug. Cases of asymptomatic mild neutropenia have been documented (Coulam et al. 1982), thus it might be advisable to monitor breastfed infants. Refraining from breastfeeding for 4–6 h after a dose may reduce the dose received by the infant through breast milk (Sau 2007).

Leflunomide

Leflunomide (Arava®) is an inhibitor of pyrimidine biosynthesis with an antiproliferative activity. The drug is marketed for rheumatoid arthritis. The product label for Arava® contains a warning against treatment by this drug during pregnancy based on animal studies, which reported an elevation in congenital

malformations. Leflunomide is transformed into an active metabolite which has a long elimination half-life of approximately 2 weeks. Due to concerns of leflunomide exposure in pregnancy, the label advises to treat with cholestyramine for 11 days (to increase drug elimination) with two plasma levels taken 14 days apart showing no detectable drug (Hajdyla-Banaś et al. 2009).

The organization of Teratology Information Specialists assessed the safety of leflunomide when used in early pregnancy. Of 64 leflunomide-exposed pregnancies there was no increased rate of major and or minor malformations. After adjustment for confounders, no increase in prematurity or small for gestational age babies were reported either (Chambers et al. 2010). Another study of 16 pregnant exposed women also did not find an elevated risk for malformations or other adverse events in pregnancy (Cassina et al. 2012). This is an example of an agent where, at equal serum concentrations, animal species are much more sensitive to teratogenicity than humans, due to higher affinity of the drug to the enzyme.

Methotrexate

Methotrexate (MTX) is in use for the treatment of rheumatoid arthritis, psoriasis and cancer. MTX and its congener aminopterin (AMPT) are structural analogues of folic acid, competitively impeding dihydrofolate reductase and hindering folinic acid formation.

Daily supplementation of folic acid with MTX decreases the toxicity but not the efficacy of MTX and will decrease the occurrence of neural tube defects (Morgan et al. 1990). The fetal aminopterin syndrome was illustrated in aborted fetuses (Thiersch 1952) and infants born after unsuccessful abortion (Shaw and Steinback 1968). Malformations include limb defects, intrauterine growth retardation, CNS defects and mental retardation. In older studies on rheumatoid patients treated by low-dose MTX, no malformations or apparent neurobehavioral defects were reported (Kozlowski et al. 1990; Lewden et al. 2004).

However, a recent large study showed increased risk of malformations when the mothers used the low weekly dose of MTX (Martín et al. 2014), and there is one prospective case of aminopterin embryopathy with this dose range (Martín et al. 2014).

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a purine synthesis inhibitor in use as an immunosuppressant in rheumatoid arthritis and organ transplantation. There is a pattern of malformations associated with mycophenolate mofetil exposure during pregnancy (Hoeltzenbein et al. 2012; Coscia et al. 2010). The most common malformations include abnormal ear development, facial clefts, ocular, skeletal and heart defects

(Merlob et al. 2009; Perez-Aytes et al. 2010). Increased risk for spontaneous abortions and preterm delivery have also been documented however those may be related to the maternal disorder rather than the exposure to the medication.

Anticonvulsants

Treatment of epilepsy cannot usually be discontinued during pregnancy since seizures may lead to falls, injury, and physical stress that can put the health of the woman and fetus at risk (Matlow and Koren 2012). Whereas earlier studies suggested an increased rate of malformations with untreated epilepsy, more recent studies refuted such association (Holmes et al. 2001; Pediatric Academic Societies' annual meeting 2002; Holmes et al. 2000). The teratogenic risk increases as the number of antiepileptic drugs (AEDs) is increased (5 % with 2 drugs, 10 % with 3 and more than 20 % when 4 drugs are used) (Lindhout et al. 1984). Therefore, AEDs should be given at the lowest effective dose and as mono-therapy whenever possible. Essentially all first line AEDs are teratogenic in humans. Valproic acid and carbamazepine cause Neural Tube Defects (NTDs) which can be detected prenatally, with a recommendation of combination of a level II U/S and either maternal blood or amniotic fluid α-fetoprotein at 16–18 weeks of gestation.

Carbamazepine

Carbamazepine (CBZ) is used for various seizure disorders, as well as for bipolar manic-depressive disorder and for pain control of various etiologies. Carbamazepine has been regarded by many as the antiepileptic drug (AED) of choice in pregnancy. CBZ monotherapy is considered to have one of the lowest risks of teratogenicity among antiepileptic drugs (Matlow and Koren 2012). First trimester exposure carries a 0.2–1 % risk of NTDs (baseline risk is 0.1 %) (Rosa 1991; Matalon et al. 2002; Kaaja et al. 2003; Morrow et al. 2006). No adverse association between CBZ and neurobehavioral measures in humans has been reported (Meador et al. 2009; McVearry et al. 2009).

Carbamazepine and Breast Feeding

Carbamazepine is excreted in relatively high levels into breast milk and breastfed infants have measurable serum levels, but they are usually within the anticonvulsant therapeutic range (Kaneko et al. 1979). Most infants have no adverse effects (Meador et al. 2010; Froescher et al. 1984; Veiby et al. 2013), but poor sucking, sedation, withdrawal symptoms and a few cases of hepatic dysfunction have been documented (Kuhnz et al. 1983; Kaneko et al. 1982). If carbamazepine is essential

for the mother, it is not necessary to discontinue breastfeeding. It is advised to monitor the breastfed infant for jaundice, adequate weight gain, lethargy and developmental milestones, especially in younger, exclusively breastfed infants and when the mother is treated by polytherapy of anticonvulsant or psychotropic drugs (Stowe 2007).

Phenytoin

Phenytoin is used for treatment of many types of epilepsy except for petit mal epilepsy. A pattern of malformations has been associated with prenatal phenytoin exposure, referred to as Fetal Hydantoin Syndrome which includes craniofacial abnormalities such as microcephaly, broad nasal bridge, metopic ridging, cleft lip/palate and ptosis, as well as hypoplasia and ossification of the distal phalanges (Briggs et al. 2008; Mountain et al. 1970; Artama et al. 2005; Harden et al. 2009). Congenital heart defects and impaired physical and mental growth frequently accompany the syndrome (Meador et al. 2009; Harden et al. 2009; Thomas et al. 2008; Scolnik et al. 1994). Furthermore, phenytoin may create hemorrhagic disease of the newborn (Briggs et al. 2008; Mountain et al. 1970).

Phenytoin and Breast Feeding

Due to low levels of phenytoin in breast milk (Bar-Oz et al. 2000), the concentrations infants will be exposed to are modest and are not anticipated to cause adverse events (Meador et al. 2010; Mirkin 1971; Livingston 1956). Combination therapy with sedating anticonvulsants may produce sedation or withdrawal symptoms in the infant (Kok et al. 1982; Finch and Lorber 1954). Since idiosyncratic reactions cannot be excluded for any drug, all infants should be monitored for adverse events.

Valproic Acid

Valproic acid was originally introduced for seizure control, however, over the last two decades it has gained large popularity in the treatment of psychiatric conditions such as bipolar disorder. In recent decades, extensive evidence has documented that prenatal exposure to valproic acid increase the risk for major congenital malformations, including NTD (in 1–2 %) (Gram and Bentsen 1985; Lammer et al. 1987; Lindhout and Omtzigt 1992; Wyszynski et al. 2005), limb and cardiac anomalies (Koren et al. 2006; Jentink et al. 2010), and cognitive deficiencies (Adab et al. 2004; Vinten et al. 2005; Eriksson et al. 2005; Gaily et al. 2004; Adab et al. 2001; Banach et al. 2010).

Codeine

Codeine is the pro-drug of morphine. Although the opioids have not been implicated as human teratogens, new concerns have arisen about their use during breastfeeding (see Table 4.2).

Codeine in Breastfeeding Maternal treatment by oral opioids during breastfeeding can cause central nervous system depression and even death in the neonate, with mothers who are ultra rapid metabolizers of CYP 2D6 at higher risk (Willmann et al. 2009; Nauta et al. 2009). Newborn infants appear to be especially sensitive to the effects of even modest doses of narcotic analgesics. Once the mother's milk starts to flow, it is best to provide non narcotic analgesic pain control and limit maternal codeine intake to 4 days at a low dose with close infant surveillance (Willmann et al. 2009; Madadi et al. 2009). If the neonate shows signs of increased drowsiness, breastfeeding difficulties, breathing difficulties, or limpness, a physician should be involved immediately (US Food and Drug Administration 2007). Maternal excessive sedation often is associated with excess sedation in the breastfed infant (Kelly et al. 2013; Sachs and The American Academy of Pediatrics committee on Drugs 2013).

Misoprostol

Misoprostol is a synthetic prostaglandin E1 (PGE1) analogue in use for the treatment of gastric and duodenal ulcers. It has the ability to induce uterine contractions and vaginal bleeding and is licensed for induction of labour, treatment of missed miscarriage and also therapeutic abortion in some countries. The use of misoprostol vaginally or orally during the first trimester of pregnancy is associated with an increased risk of pregnancy loss and of Möebius sequence (Gonzalez et al. 1993; Pastuszak et al. 1998; Vauzelle et al. 2013; da Silva Dal Pizzol et al. 2006). Limb defects were also proposed by some of the reports (Gonzalez et al. 1993).

In a case-control study (Pastuszak et al. 1998) 48.9 % (47/96) of infants with Möebius sequence had been exposed to misoprostol in the first trimester. A systemic review and meta-analysis on the data of 4,899 cases of congenital anomalies and 5,742 controls (da Silva Dal Pizzol et al. 2006) found a relationship between prenatal exposure to misoprostol and elevated risk of Möbius sequence (OR = 25.31; 95 % CI: 11.11–57.66) and terminal transverse limb defects (OR = 11.86; 95 % CI: 4.86–28.90).

While this odds ratio (OR) is extremely high, the incidence of Möebius sequence is very low in the general population (1:1,000–1:200,000) and hence the risk for developing the syndrome, after exposure to misoprostol during the first trimester is probably less than 1–2 %.

Warfarin (Coumadin)

Warfarin is an oral anticoagulant that impedes vitamin K dependent clotting factors. It is in use mainly for the prophylaxis or treatment of deep vein thrombosis, and thrombosis and embolism in patients with mechanical heart valves, atrial fibrillation and myocardial infarction.

Many case reports and case series linking warfarin with embryopathy have been published. The use of warfarin in the first trimester can result in the Fetal Warfarin Syndrome (FWS) (Hall et al. 1980; Harrod and Sherrod 1981; Wong et al. 1993). These malformations include skeletal defects, such as nasal hypoplasia and stippled epiphyses, intrauterine growth retardation, developmental delay, eye malformations and hearing loss. The critical period for malformations is between 6 and 12 weeks of gestation (Hall et al. 1980; Chan et al. 2000; Iturbe-Alessio et al. 1986). Exposure in the second and third trimesters may be associated with an increased risk of CNS damage and stillbirth due to fetal hemorrhage (Hall et al. 1980; Iturbe-Alessio et al. 1986; Ville et al. 1993; van Driel et al. 2002). There is also a reported increase in spontaneous abortions in women taking warfarin although this could be related to the underlying disease (Born et al. 1992).

Warfarin therapy after the first trimester induces a minor risk, if any, to a child's skeletal development and neurobehavioral achievements (Van Driel et al. 2000, 2001). The effects of warfarin are probably dose dependent. The rates of minor neurological dysfunction are elevated with increasing dose (Wesseling et al. 2001). The risks of pregnancy and fetal complications are increased when warfarin doses exceed 5 mg/day (Cotrufo et al. 2002; Vitale et al. 1999).

The present guidelines state that warfarin should be avoided in pregnant women, except in those women considered especially high risk (e.g., maternal mechanical heart valve) [Guyatt et al. 2012]. High risk women should be advised to continue oral anticoagulation until they are pregnant because the risk of embryopathy is low in the first 6 weeks of pregnancy. As soon as pregnancy is achieved they should substitute to a treatment with low molecular weight heparin. If warfarin is used during pregnancy (after the first trimester), it should be discontinued after 34–36 weeks of gestation to prevent fetal intra-partum and postpartum bleeding, and substituted by an alternative anticoagulant. A dosage $\leq$5 mg should be maintained, if appropriate, to prevent fetal bleeding related complications (Guyatt et al. 2012).

Isotretinoin

Isotretinoin is a synthetic vitamin A derivative which is an effective treatment for severe acne. Isotretinoin (13-cis-retinoic acid; Accutane®) is a potent human teratogen at therapeutic doses. The highest risk for malformation is when exposure to the drug continues beyond day 15 after the last menstrual period. Exogenous

isotretinoin is undetectable 1 week after a given dose. However, the main metabolite requires 10 days to be eliminated.

There is an estimated risk of 20–35 % for congenital malformations in infants exposed to isotretinoin prenatally (Lammer et al. 1985; Adams and Lammer 1993). The typical anomalies include cardiac (transposition of the great arteries, Tetralogy of Fallot), craniofacial (microtia/anotia, micrognathia), central nervous system (hydrocephalus) and thymic malformations (Lammer et al. 1985). Up to 30–60 % of prenatally isotretinoin- exposed children have been reported to exhibit neurocognitive impairment (Lammer et al. 1985; Adams and Lammer 1993).

The US and Canadian guidelines for preventing fetal exposure to isotretinoin include the following: awareness of the risks, ruling out pregnancy at the beginning of treatment; parallel use of two forms of contraception during treatment, monitoring for pregnancy throughout treatment and avoiding pregnancy 1–3 months after the drug has been cleared from the body (Choi et al. 2013; Pastuszak et al. 1994).

Health Canada requires that women treated by isotretinoin sign a written informed consent, receive information about the drug teratogenicity and use two contraceptive methods while on the medication. Similar measures in US were not effective in protecting fetuses (Koren et al. 2004; Andresen 2006). The SMART (System to Manage Accutane Related Teratogenicity) and iPLEDGE (an integrated isotretinoin risk management system for all isotretinoin compounds) systems, introduced by FDA were both disappointing (Koren et al. 2004; Andresen 2006).

Rubella Vaccine

While the Rubella virus is highly teratogenic, there are no reports in the literature to date, of any child that has been born with Congenital Rubella Syndrome (CRS) from the live attenuated vaccine. The Centre for Disease Control (CDC) assessed the fetal theoretical risk of CRS following rubella vaccination to be at 0.5–1.3 % and hence it is currently advised that the rubella vaccine and the combination MMR vaccine should not be administered during gestation and that women should be recommended to avoid becoming pregnant for 28 days after vaccination (Marin et al. 2010).

Alcohol

Alcohol (ethanol) consumption during gestation explains the etiology of fetal alcohol spectrum disorder (FASD), a principle cause of congenital handicap worldwide. Thereupon, any effort to avoid or manage FASD must begin from extensive understanding of women's alcohol consumption in general, and specifically by women of reproductive years (Zelner and Koren 2013).

While women usually stop or reduce ethanol consumption once a pregnancy is confirmed, many fetuses are exposed to alcohol before pregnancy is detected, while other women simply continue drinking (Ethen et al. 2009). The Centers for Disease Control and Prevention estimated that 51.5 % of non-pregnant women in the reproductive age and 7.6 % of pregnant women used alcohol in 2006–2010 (Centers for Disease Control and Prevention 2012).

Fetal Alcohol Spectrum Disorder (FASD), is characterized by pre and post–natal growth retardation, microcephaly, developmental delay and neurobehavioral deficits, and dysmorphic facial features, including short palpebral fissures, poorly developed philtrum, and thin upper lip (Jones et al. 1973). Retarded growth in weight, length and head circumference both intrauterine and after birth is the most prevalent sign of FASD (Rossett and Weiner 1984). Full expression of the Syndrome generally arises only with chronic ingestion of at least 2 g/kg/day of alcohol. With full blown FAS, the rate of malformation is increased by 2–3 folds compared to moderate or rare drinkers (Rosett et al. 1978). Presently it is not apparent whether the rate of malformation of moderate drinkers is similar to that of non-drinkers.

Alcohol and Breast Feeding

Maternal alcohol consumption passes readily into the breast milk reaching comparable concentrations in the breast milk (Lawton 1985). Although the amount a breastfed infant is exposed to is only a portion of what the mother consumes (Mennella and Beauchamp 1991; Haastrup et al. 2014), an infant's detoxifing alcohol rate in the first weeks of life is half of the adult's rate (Abel 1984).

A study reported that at moderate amounts of alcohol in breast milk appears to influence the infant's gross motor development in a dose-dependent manner (Little et al. 1989). Another study reported disrupted sleep-wake patterns amidst infants who exhaust milk containing alcohol at rates corresponding to maternal ingestion of 1.5 drinks (Mennella and Gerrish 1998). Such sleep pattern disruption may generate potential long-term effects because the brain is still developing in infancy. Another study showed elevated infant arousal after maternal and infant alcohol consumption (Schuetze et al. 2002).

As there are no recognized advantages of maternal alcohol consumption for the breastfed infant, mothers should be discouraged to expose their nursing babies to alcohol. A normogram published by the Motherisk Program illustrates the clearance time for a given alcohol consumption level to be extracted from the milk (Fig. 4.1).

Maternal weight		Drinks											
kg	lb	1	2	3	4	5	6	7	8	9	10	11	12
40.8	90	2:50	5:40	8:30	11:20	14:10	17:00	19:51	22:41				
43.1	95	2:46	5:32	8:19	11:05	13:52	16:38	19:25	22:11				
45.4	100	2:42	5:25	8:08	10:51	13:34	16:17	19:00	21:43				
47.6	105	2:39	5:19	7:58	10:38	13:18	15:57	18:37	21:16	23:56			
49.9	110	2:36	5:12	7:49	10:25	13:01	15:38	18:14	20:50	23:27			
52.2	115	2:33	5:06	7:39	10:12	12:46	15:19	17:52	20:25	22:59			
54.4	120	2:30	5:00	7:30	10:00	12:31	15:01	17:31	20:01	22:32			
56.7	125	2:27	4:54	7:22	9:49	12:16	14:44	17:11	19:38	22:06			
59.0	130	2:24	4:49	7:13	9:38	12:03	14:27	16:52	19:16	21:41			
61.2	135	2:21	4:43	7:05	9:27	11:49	14:11	16:33	18:55	21:17	23:39		
63.5	140	2:19	4:38	6:58	9:17	11:37	13:56	16:15	18:35	20:54	23:14		
65.8	145	2:16	4:33	6:50	9:07	11:24	13:41	15:58	18:15	20:32	22:49		
68.0	150	2:14	4:29	6:43	8:58	11:12	13:27	15:41	17:56	20:10	22:25		
70.3	155	2:12	4:24	6:36	8:48	11:01	13:13	15:25	17:37	19:49	22:02		
72.6	160	2:10	4:20	6:30	8:40	10:50	13:00	15:10	17:20	19:30	21:40	23:50	
74.8	165	2:07	4:15	6:23	8:31	10:39	12:47	14:54	17:02	19:10	21:18	23:26	
77.1	170	2:05	4:11	6:17	8:23	10:28	12:34	14:40	16:46	18:51	20:57	23:03	
79.3	175	2:03	4:07	6:11	8:14	10:18	12:22	14:26	16:29	18:33	20:37	22:40	
81.6	180	2:01	4:03	6:05	8:07	10:08	12:10	14:12	16:14	18:15	20:17	22:19	
83.9	185	1:59	3:59	5:59	7:59	9:59	11:59	13:59	15:59	17:58	19:58	21:58	23:58
86.2	190	1:58	3:56	5:54	7:52	9:50	11:48	13:46	15:44	17:42	19:40	21:38	23:36
88.5	195	1:56	3:52	5:48	7:44	9:41	11:37	13:33	15:29	17:26	19:22	21:18	23:14
90.7	200	1:54	3:49	5:43	7:38	9:32	11:27	13:21	15:16	17:10	19:05	20:59	22:54
93.0	205	1:52	3:45	5:38	7:31	9:24	11:17	13:09	15:02	16:55	18:48	20:41	22:34
95.3	210	1:51	3:42	5:33	7:24	9:16	11:07	12:58	14:49	16:41	18:32	20:23	22:14

Time is calculated from the beginning of drinking. Assumptions made: alcohol metabolism is constant at 15 mg/dl; height of the women is 162.56 cm (5 feet, 4 inches). 1 drink = 340 g (12 oz) of 5% beer or 141.75 g (5 oz) of 11% wine or 42.53 g (1.5 oz) of 40% liquor.

Example 1: for a 40.8-kg (90-lb) woman who consumed 3 drinks in 1 h, it would take 8 h 30 min for there to be no alcohol in her breast milk, but for a 95.3-kg (210-lb) woman drinking the same amount, it would take 5 h 33 min.

Example 2: for a 63.5-kg (140-lb) woman drinking 4 beers starting at 8.00 p.m., there would be a zero level of alcohol in her breast milk 9 h 17 min later (i.e. at 5.17 a.m.).

Fig. 4.1 Alcohol and breastfeeding: time (h:min) until the zero level in milk is reached for women at different body weights (Ho et al. 2001)

Regulatory Guidance on Prescribing Medicines in Pregnancy

FDA Pregnancy Categories

The FDA-assigned pregnancy categories as used in the Drug Formulary are as follows:

Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits (http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf).

However, this system has been heavily criticized as three quarters of the drugs are in Category C, and there are major ambiguity in translation these recommendation for clinical use. Over the last few years the FDA has approved moving into a new system that will be based on individual evidence-based narratives for each drug rather than on the ABC system.

The Australian Pregnancy Categorisation System

The Australian categorisation system and database for prescribing medicines in pregnancy have been developed by medical and scientific experts based on available evidence of risks associated with taking particular medicines while pregnant.

Definitions of the Australian Categories for Prescribing Medicines in Pregnancy

Category A

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Category B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Category B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Category B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Category X

Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy (http://www.tga.gov.au/hp/medicines-pregnancy-categorisation.htm).

Guidelines on Medicines During Lactation

The American Academy of Pediatrics committee on drugs has updated their guidelines on the transfer of medications into the breast milk. They state that the benefits of breastfeeding exceed the risk of exposure through breast milk for most medications. Most therapeutic agents do not pose a risk to the mother or breastfeeding infant however, certain medications should be handled with care, principally those that are concentrated in human milk or result in exposures in the infant that correlate to the relative infant dose. Caution is also recommended for medications with unproven benefits, drugs that may lead to drug accumulation through long half-lives or with known toxicity. Furthermore, specific infants may

be more susceptible to adverse effects (e.g., preterm infants, neonates or infants with underlying medical conditions) (Sachs and Committee On Drugs 2013).

Pregnancy Registries and Other Monitoring Schemes

There are increasing numbers of registries linking prescription information with pregnancy outcome in an attempt to assess drug safety/risk in pregnancy in jurisdictions where prescription is covered by either governments or insurance companies. The main strength of such systems is their large sample sizes, however, prescription of a drug to a woman does not necessarily mean that she has chosen to take the medication in pregnancy.

The Motherisk Program

There are also a few registries collecting information directly from pregnant women, and we will describe here the Canadian Motherisk Program as an example. The Motherisk program is a counseling service offering a teratogen information phone line. Established in 1985, it provides information on the safety or risk of exposures to prescription and over-the-counter (OTC) drugs, radiation, chemicals, herbal products, chronic diseases and infections during gestation and while breastfeeding. Trained counselors answer calls from pregnant women or their partners as well as from health care professionals including physicians, nurses, midwives, pharmacists, genetic counselors, dietitians and nutritionists. Follow up of these calls after the expected date of confinement allow studying of safety/risk of medications, typically long before drug prescription registries can yield their safety signals. Detailed information about the program has been published (Moretti and Koren 2001).

Conclusions

While most women are exposed to medications in pregnancy, and quite few have been shown to be teratogenic in humans, high levels of anxiety, coupled with misinformation and misperception, lead women and their prescribers to commonly avoid drug therapy even in life threatening conditions.

It is critical for clinicians to always consider the risks of the untreated conditions in pregnancy and as needed, to empower women to use medications during gestation.

Take Home Message

- To ensure that women are counseled based on evidence based medicine and not emotionally based medicine

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Part II
Specific Medicinal Products for Women: Benefits and Risks

Chapter 5
Oral Contraceptives: Benefits and Risks

Julie Craik and Louise Melvin

Introduction

There are two main types of oral contraceptives, combined oral contraceptives (COCs) that contain both synthetic estrogen and progestogen, and progestogen-only pills (POPs), also known as 'mini-pills'. Despite the availability of longer acting reversible methods of contraception, which are more effective with typical use than oral contraceptives, oral contraceptives remain one of the most commonly used hormonal contraceptives worldwide (United Nations. Department of Economic and Social Affairs. Population Division 2013).

In the early 1960s, the COC or 'the pill', as it is often referred to, was first approved for use in countries such as the US, UK and Australia with the POP becoming available later that decade. However, in Japan, it wasn't until 1999 that the COC became available as a contraceptive medicine for women.

In the 1960s and 1970s COC formulations contained doses of estrogen and progestogen that were far higher than those administered in COCs today. The first COC marketed in the USA contained 150 mg of mestranol (Enovid®), which is roughly equivalent to 100 μg of ethinylestradiol. In Australia, the first marketed pill contained 50 μg of ethinylestradiol (Anovlar®). Ethinylestradiol and mestranol have been the principal synthetic estrogens used in COCs since the pill's inception. It is only in recent years that COCs have been introduced onto the market which utilise estradiol either as estradiol valerate or as estradiol hemihydrate (e.g. Qlaira® and Zoely®).

Whereas the type of synthetic estrogen has remained fairly constant until recently, in contrast, a variety of progestogens have been used within COCs during the past

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Table 5.1 Examples of progestogens contained in COCs and POPs by generation

Generation of progestogen	Progestogen	Examples of COCs[a]	Examples of POPs[b]
First generation	Norithisterone (norethindrone), norethisterone acetate, norethynodrel acetate, ethynodiol diacetate, lynestrenol	Brevinor®	Micronor®
		Loestrin®	
Second generation	Levonorgestrel, norgestrel	Microgynon®	Norgeston®
Third generation	Desogestrel, gestodene, norgestimate	Cilest®	Cerazette®
		Gedarel®	Cerelle®
		Mercilon®	
Fourth generation	Drospirenone, dienogest, nomegesterol acetate	Qlaira®	n/a
		Yasmin®	
		Zoely®	

Notes
[a]Combined oral contraceptives
[b]Progestogen only pills
Examples listed are UK products. Trade names may vary between countries and may not be available in all countries

50 or so years. Progestogens can be classified by their structure, or often they are categorised by their 'generation' which reflects the timing of their launch onto the market. These different progestogens have been used in an attempt to combat some of the side effects experienced by women when using COCs. Examples of oral contraceptives using the different progestogens are shown in Table 5.1.

Currently marketed COC formulations contain between 15 and 50 μg of ethinylestradiol or 50 μg of mestranol (equivalent to 35 μg of ethinylestradiol). In the UK, there are currently no monophasic ethinylestradiol pills containing more than 35 μg (Joint Formulary Committee. British National Formulary 2014).

Soon after their introduction, concerns were raised about an observed increased risk of venous thromboembolism (VTE) amongst 'pill' users compared to non-users (Anon 1967) which resulted in lower dose formulations. Current formulations have also been found to be associated with an increased risk of VTE (de Bastos et al. 2014; European Medicines 2014a) and there is continuing debate about the role of progestogens in mediating this risk (see Chap. 6).

Because of the COC's impact on cardiovascular health, it has periodically attracted negative press and the issues around 'pill scares' are discussed further in Chap. 19. However, there are many benefits in the use of oral contraceptives which tend to be understated. An overview of the risks and benefits of oral contraceptives will be explored throughout this chapter.

Mechanism of Action and Effectiveness

Mechanism of Action: COCs

Combined oral contraceptives have several mechanisms of action which contribute to their effectiveness (Faculty of Sexual and Reproductive Healthcare 2011a). Their main mechanism of action is to prevent fertilisation via inhibition of ovulation (Rivera et al. 1999; Faculty of Sexual and Reproductive Healthcare 2011a). Suppression of ovulation occurs via a negative feedback system whereby the action of the hormones on the hypothalamic pituitary axis reduces the availability of luteinising hormone and follicle stimulating hormone, particularly mid cycle (Killick et al. 1987).

Traditionally COC regimens have involved taking 21 days of 'active pills' followed by a 7-day hormone-free interval. The estrogen and progestogen within the 'active pills' is delivered either steadily throughout the cycle (monophasic pills) or at differing doses (phasic pills). The first seven pills are used to suppress ovulation, with the remaining pills maintaining this suppression (Faculty of Sexual and Reproductive Healthcare 2011a). The hormone free interval involves no pill taking or taking a number of inactive/placebo pills, which in turn usually induces endometrial shedding and a so-called 'withdrawal bleed', thus mimicking the natural menstrual cycle. The withdrawal bleed tends to be lighter than the woman's period and occasionally women may remain amenorrhoeic during the hormone-free interval, particularly if it is shorter than 7 days – increasingly COCs are being marketed with a shortened hormone free interval or fewer placebo pills, for example 24/4 or 26/2 regimems. (Bayer PLC 2013; Merck Sharp and Dohme Limited 2014a). While these shorter interval regimens are available, women can also be advised to use 21/7 monophasic pills with a shortened free interval or as part of an extended regimens such as tricycling (Faculty of Sexual and Reproductive Healthcare 2011a) – such use may be outside the product licence.

Mechanism of Action: POPs

The production of 'hostile' mucus that is impenetrable to sperm is one of several mechanisms by which POPs exert their effect (McCann and Potter 1994). It is the first line of defence, with the effect observed quickly after ingestion of a POP (McCann and Potter 1994). Some guidance advises that women starting a POP only need 2 days of pill taking to have contraceptive protection (Faculty of Sexual and Reproductive Healthcare 2015; World Health Organization 2004)- however, such advice may be outside the terms some product licences which advocate 7 days (Merck Sharp and Dohme Limited 2014b; Pfizer Limited 2010). POPs need to be taken daily, ideally at the same time each day, as the cervical mucus effect is quickly lost (McCann and Potter 1994).

In terms of their effect on ovulation, the ability to suppress ovulation is variable, with the desogestrel POP having been shown to do so more consistently than other pills such as the levonorgestrel pill (Rice et al. 1999).

Other documented mechanisms of action of POPs include reduction of cilia activity within the fallopian tube, suppression of mid-cycle peaks of the pituitary hormones, and, alterations to the endometrium which could hinder implantation (McCann and Potter 1994).

Efficacy and Effectiveness of Oral Contraceptives

The efficacy of oral contraception is a measure of its therapeutic effect i.e. how successfully it prevents pregnancy within a clinical trial setting. Effectiveness on the other hand is a measure of its effect in clinical practice or 'real life' use.

When used consistently and correctly i.e. perfect use, oral contraceptives are effective methods of contraception. For the COC, a gross 1 year cumulative failure rate based on clinical trial data has been calculated as being between 0.2 and 2.3 per 100 women (Mansour et al. 2010). However, to a greater extent than with some other methods, such as the progestogen-only implant or intrauterine methods (see Chap. 8), the effectiveness of oral contraceptives is largely dependent on the user. Human error is inevitable and missed pills are common amongst users of these methods (Aubeny et al. 2002; Potter et al. 1996). Trussell et al. reported that based on data from the National Survey of Family Growth within the USA, 9 % of women using oral contraceptives (COCs and POPs) will experience an unintended pregnancy in the first year (Trussell 2011).

In terms of what is the most effective oral contraceptive, data are often inadequate but no difference has been observed in contraceptive efficacy between 20 and 30 μg ethinylestradiol pills (Gallo et al. 2013) or different types and strengths of COCs. Similarly, there is insufficient evidence insufficient evidence to say if one POP is more effective than another or compare the efficacy of POPs to COCs (Grimes et al. 2013). In light of its greater potential for ovarian suppression, in theory it might be expected that the efficacy of the desogestrel pill would be higher than 'traditional' POPs. However, in the only comparative trial comparing a levonorgestrel pill to the desogestrel pill, no significant difference was noted in the rate ratio of pregnancy, even after excluding those who were breastfeeding (Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill 1998).

Factors Affecting the Effectiveness of OCs

Missed Pills

As indicated previously, missed pills are common with oral contraceptives. With COCs ovulation remains suppressed during the hormone free interval but there is

evidence of follicular activity during longer hormone-free intervals (Baerwald et al. 2004; Hedon et al. 1992; Killick 1989; Killick et al. 1990). Consequently, there is greater potential for ovulation and method failure when women forget to take pills before or after the 7 day break by effectively extending the hormone-free interval. The World Health Organization (WHO) advises that efficacy may be diminished if three or more 30–35 μg pills or two or more 20 μg pills are missed (World Health Organization 2004). In the UK and USA, the Faculty of Sexual and Reproductive Healthcare (FSRH) and the Centre for Disease Control (CDC) respectively, advise when two or more pills (of 20 or 30 μg) are missed (Centre for Disease Control and Prevention 2013; Faculty of Sexual and Reproductive Healthcare 2011a). The UK applies this advice only to monophasic pills and advises that for phasic pills the advice in the summary of product characteristics should be followed (Faculty of Sexual and Reproductive Healthcare 2011a). A missed pill is regarded by the WHO, FSRH and CDC as being one that is more than 24 h late (Centre for Disease Control and Prevention 2013; Faculty of Sexual and Reproductive Healthcare 2011a; World Health Organization 2004). Reducing the hormone free interval, either via COCs with a shorter hormone free interval, or via extended regimens, has the potential to reduce the risk of follicular activity, and subsequent risk of ovulation (Spona et al. 1996; Willis et al. 2006).

In contrast to COCs, when POPs are missed there is less of a potential safety margin. For most POPs which have not been shown to consistently suppress ovulation, women are advised that contraceptive efficacy may be reduced if the pill is more than 3 h late i.e. 27 h since the last pill was taken (Faculty of Sexual and Reproductive Healthcare 2015; World Health Organization 2004). However, with the desogestrel POP, suppression of ovulation is reported to be maintained even when there is a 12-h delay in tablet taking (Korver et al. 2005). Women can therefore take the desogestrel POP up to 12 h late (36 h after the last pill was taken) without an impact on contraceptive efficacy (Faculty of Sexual and Reproductive Health Care 2015). This longer window period presents the desogestrel pill with an advantage over other POPs.

Factors Affecting Metabolism and Absorption

Factors that affect the metabolism or absorption of oral contraceptives also have the potential to affect their efficacy by reducing the bioavailability of estrogen and/or progestogen. Examples of such factors are vomiting and diarrhoea (resulting in reduced absorption of OCs), or taking concomitant medicines that induce cytochrome P-450 enzymes (resulting in increased metabolism of estrogen/progesterone and therefore reduced bioavailability). Some examples of drugs known to be strong inducers of cytochrome P450 are listed in Table 5.2.

It is generally advised that if a woman has vomited within 2 h of taking an oral contraceptive, she should take another pill (Faculty of Sexual and Reproductive Healthcare 2011a; World Health Organization 2004). If a woman has severe diarrhoea or vomiting for more than 2 days, the advice for missed pills should be followed

Table 5.2 Examples of medicines which strongly induce cytochrome P450 (Faculty of Sexual and Reproductive Health Care 2011b)

Name of drug	Classification
Rifampicin	Antibiotic
Carbamazepine	Antiepileptic
Eslicarbazepine	
Oxcarbazepine	
Phenobarbital	
Phenytoin	
Primidone	
Ritonavir	Protease inhibitor

(Faculty of Sexual and Reproductive Healthcare 2011a; Faculty of Sexual and Reproductive Health Care 2015; World Health Organization 2004).

Women regularly taking medicines such as those listed in Table 5.2 would generally be advised to switch to a method which is unaffected by such drugs, for example an intrauterine method (see Chap. 8). For shorter term coverage, doubling the dose of COC or using condoms in addition to an oral method during treatment and for 28 days afterwards are suggested alternatives (Faculty of Sexual and Reproductive Health Care 2011b). The FSRH within the UK has published guidance entitled *Drug Interactions with Hormonal Contraceptives* designed to help practitioners give advice to women using such medications (Faculty of Sexual and Reproductive Health Care 2011b).

As oral contraceptives are absorbed via the small intestine and undergo extensive first pass metabolism before reaching the systemic circulation, factors that limit absorption may also impact on efficacy. With the increasing number of women being classified as obese, there has been interest in the effect surgical procedures designed to help with weight loss might have on absorption of oral contraceptives. There is unfortunately a lack of data on this issue, but it would not appear to impact significantly (Paulen et al. 2010). In the US, advice is that use of oral contraceptives is appropriate in those who have undergone surgery to reduce the storage capacity of their stomach, but for those who have undergone a procedure which limits a woman's ability to absorb nutrients and calories, the potential risks are thought to outweigh any potential benefit (Centre for Disease Control 2010).

A European evidence-based consensus on reproduction in inflammatory bowel disease (van der Woude et al. 2010) indicates that there are no studies investigating the efficacy of oral contraceptives in women with inflammatory bowel disease, although in theory efficacy may be reduced in those with small bowel disease and malabsorption e.g. Crohns disease. The theoretical risk should be highlighted to women with Crohn's disease (Faculty of Sexual and Reproductive Healthcare 2009c).

Effectiveness of OCs in Overweight and Obese Women

Women with a body mass index (BMI) that would classify them as obese ($\geq$30 kg/m^2) or of heavier weight (for example, women over 70 kg) have been included in

some trials of oral contraceptives, but there is a lack of prospective studies specifically examining the effectiveness of OCs in these women and which use clinically determined measures rather than self-reported indicators. A Cochrane review reported that based on low quality evidence there does not appear to be an association between BMI and the effectiveness of hormonal contraceptives generally, but that data for individual methods are limited (Lopez et al. 2013b).

The issue of weight and efficacy has been raised in relation to other methods such as the progestogen-only implant (see Chap. 8), the combined transdermal patch (Janssen-Cilag Ltd 2014) and recently there has been discussion internationally about the effect body mass or weight has on the effectiveness of oral emergency contraception (European Medicines Agency 2014).

It has been suggested from pharmacokinetic data, that on starting combined oral contraceptives, women who are classified as obese may take longer to reach the required steady state for ovulation suppression, than women who are not (Edelman et al. 2009). This pharmacokinetic difference may in turn create potential for follicular activity and consequently, pregnancy (Edelman et al. 2009). Another small pharmacokinetic study reported lower peak levels of hormone amongst women with a BMI of over 30 kg/m^2, although follicular activity was not increased (Westhoff et al. 2010).

In terms of what has been observed in 'real life' the findings are mixed. A population based case-control study reported a statistically significant increased risk of pregnancy amongst women with a BMI greater than 27.3 kg/m^2 using COCs than for those with a BMI less than that (Holt et al. 2005). A criticism of the paper was its dependence on recall in relation to pill taking behaviour (Creinin and Roberts 2005). Similarly, a retrospective cohort study reported an increased risk in women weighing over 70.5 kg compared with women of lower weight (RR 1.6 95 % CI 1.1–2.4) (Holt et al. 2002). However, other studies have not reported statistically significant increases by body weight or BMI (Brunner and Hogue 2005; Burkman et al. 2009; Dinger et al. 2009; Vessey and Painter 2001).

In the past it has been advised that women, who are classified as obese, take two POPs per day instead of one. While evidence to disprove reduced effectiveness of POPs is lacking in these women, so too is evidence to support doubling the dose of POP (Faculty of Sexual and Reproductive Health Care 2015).

In the UK, COCs tend to be more cautiously prescribed to women with a high body mass index, not because of concerns about efficacy but more in relation to vascular health. Obesity in itself is not a contraindication to use of COCs. However, some women who are classified as obese may be advised to use other methods, if they have other risk factors such as older age and or hypertension. WHO Medical Eligibility Criteria for Contraceptive Use (World Health Organization 2010), suggests that the benefits outweigh the risks in women with a BMI of over 30 kg/m^2, whereas, the UK document indicates that for those with a BMI of 35 kg/m^2 or more, the risks outweigh the benefits (Faculty of Sexual and Reproductive Healthcare 2009b).

Medical Eligibility Criteria for Contraceptive Use

The WHO first developed a Medical Eligibility Criteria (MEC) for Contraceptive Use in 1996; a fifth edition is due in 2015. It was designed to help policy makers and other specialists develop national guidelines on contraceptive service delivery rather than to be used as an actual guideline itself (World Health Organization 2010).

The FSRH within the UK and the CDC in the USA have both undertaken formal processes to adapt the WHO's document for the UK (Faculty of Sexual and Reproductive Health Care 2009b) and US (Centre for Disease Control 2010) respectively. The UK (Faculty of Sexual and Reproductive Health Care 2009b) and US (Centre for Disease Control 2010) Medical Eligibility Criteria for Contraceptive Use are designed to help guide individual practitioners when counselling individuals and couples about contraceptive use. All three documents (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010) are available online and are a useful reference for practitioners. These documents are designed to give a sense of where the balance of risk lies for each method in the presence of a particular medical condition, risk factor or specific characteristic.

Each condition listed is assigned a category which ranges from there being no restriction on the use of the contraceptive, to the use of the contraceptive method presenting an unacceptable health risk. The categories are a guide and there are no rules for taking into account co-morbidities. The decision to prescribe or not prescribe when the balance of risk seemingly outweighs the benefits will be a matter of clinical judgement in conjunction with patient preference and availability/suitability of alternative options. While it is acknowledged that hormonal contraceptives may confer some non-contraceptive benefits, the MECs have been designed for use in contraceptive prescribing rather than the prescription of contraceptives for other purposes, as the benefit to risk ratio may differ (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Table 5.3 highlights some examples of conditions where it is suggested that COCs or POPs should not be used. These are examples and the list is not

Table 5.3 Examples of conditions where concomitant use COCs or POPs presents an unacceptable level of risk (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010)

COC	POP
Current thrombosis	Current breast cancer
History of thrombosis	
Known thrombogenic mutations	
Current/History ischaemic heart disease	
Stroke	
Current breast cancer	
Malignant liver tumours	
Aged over 35 and smoking more than 15 cigarettes per day	

exhaustive. Practitioners should refer to the individual medical eligibility criteria for detailed information and updates as criteria may change and sometimes differ across the MECs.

Benefits and Risks of Oral Contraceptives

In this chapter we aim to provide an overview of the issues that are often of concern to women. It should be borne in mind that evidence often comes from observational studies and therefore may be limited by bias and confounding such as: being unable to control for women's use of several different contraceptive formulations; the limited number of different formulations included within studies; or long-term studies starting before modern formulations were available.

Overall Risk of Mortality and Cancer

Data largely support the view that use of oral contraceptives does not increase a woman's risk of death as compared with non-use (Colditz 1994; Hannaford et al. 2010; Vessey et al. 2010).

In the late 1960s a large prospective study was initiated in the UK (the RCGP oral contraceptive study) to investigate the health effects of oral contraceptives. By 2010, 39 years of follow-up and more than one million women-years of observation did not demonstrate any association between an increased risk of any cause mortality and oral contraceptive use compared with non-use, with a slightly protective effect reported (adjusted relative risk 0.88, 95 % confidence interval 0.82–0.93) (Hannaford et al. 2010).

Similarly, another large cohort study from the UK (Oxford Family Planning Association contraceptive study) with 602,700 woman-years of observation, found that compared to never users of oral contraceptives, the rate ratio for overall mortality was 0.87 (CI 0.79–0.96) (Vessey et al. 2010). While the ability to generalise from the findings may be limited by country specifications and changes in formulation over time (Hannaford et al. 2010), the findings are generally reassuring.

In terms of cancer risk, the International Agency for Research on Cancer (IARC), indicates that there is sufficient evidence from studies to demonstrate that COCs are carcinogenic in humans (group 1 classification), predominantly in relation to the breast, cervix and liver, although acknowledges that they may offer protection against certain other cancers (International Agency for Cancer 2012). These benefits and risks are discussed further in the sections below. Progestogen-only contraceptives are given an IARC group 2b classification, indicating the possibility of carcinogenicity (International Agency for Cancer 1999). Observational studies have reported no specific increased risk of mortality from all cancers

as a result of COC use and no overall increased risk of cancer (Cibula et al. 2010; Hannaford et al. 2007, 2010).

Benefits Associated with Oral Contraceptive Use

Reduced Risk of Ovarian, Endometrial and Colorectal Cancer

Observational studies have consistently demonstrated a reduced risk of ovarian cancer amongst those who use COC for contraception (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2008; Hannaford et al. 2007; Havrilesky et al. 2013; International Agency for Cancer 1999; Jick et al. 1993; Lurie et al. 2007, 2008; Ness et al. 2000; Poole et al. 2013; The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development 1987; Tsilidis et al. 2011; Tworoger et al. 2007; Vessey et al. 2003, 2010; Vessey and Painter 2006; Vessey and Yeates 2013; Weiderpass et al. 1999).

The duration of COC use has been shown to influence the level of protection against ovarian cancer such that women who have been using the COC for 10 years or more have half the risk of those who have never used a COC (Havrilesky et al. 2013). This non-contraceptive benefit has also been observed in women who are inherently at increased risk of ovarian cancer due to a BRCA gene mutation (Antoniou et al. 2009; Havrilesky et al. 2013; McGuire et al. 2004; McLaughlin et al. 2007; Narod et al. 2002; Whittemore et al. 2004).

The protective effect is provided not only whilst the woman is taking the pill but evidence shows that even after discontinuing a COC, women continue to experience a reduced risk of ovarian cancer for several decades; although the protective effect gradually lessens with time (Havrilesky et al. 2013; Lurie et al. 2008; Moorman et al. 2008).

In addition to offering a protective effect against ovarian cancer, data from observational studies suggest that COCs confer protection against endometrial cancer (Jick et al. 1993; Vessey and Painter 1995; Weiderpass et al. 1999; Cancer and Steroid Hormones (CASH) 1987) and possibly colorectal cancer (Bosetti et al. 2009; Campbell et al. 2007; Fernandez et al. 2001; Hannaford and Elliot 2005; Nichols et al. 2005; Troisi et al. 1997; Tsilidis et al. 2010). As with ovarian cancer, the protection against endometrial cancer afforded by COC use lasts for several years after stopping. However, less is known about the impact of duration of use on colorectal cancer risk with no apparent relationship evident from the available data.

While there is a well-documented benefit to use in terms of protection against ovarian cancer, available evidence does not yet allow recommendations to be drawn on the use of COCs for primary cancer prevention (Havrilesky et al. 2013).

Management of Acne

Acne is a common skin condition affecting women of reproductive age. A systematic review of randomised trials reported that there was evidence to demonstrate that COCs could result in a reduction in both inflammatory and non-inflammatory lesions and therefore should be considered for women with acne who also require contraception (Arowojolu et al. 2012). While some studies have shown benefits for particular pill types over others (see section on polycystic ovarian syndrome), the findings are often inconsistent and their clinical relevance undetermined. There is also a lack of data on which to draw conclusions about the effectiveness of COCs compared to other treatments (Arowojolu et al. 2012). An advantage over some medications such as isotretinoin is that COCs are not known to be teratogenic.

There is no evidence to advocate the use of progestogen-only pills for the management of acne and indeed acne can be a side effect of these pills (Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill 1998).

The use of co-cyprindiol tablets (Dianette®, Diane 35®, Clairette®) solely for contraceptive purposes is not advised (Faculty of Sexual and Reproductive Healthcare 2011a). These tablets, which contain ethinylestradiol and cyproterone acetate are licensed (in most countries) primarily for the treatment of acne and their use as a contraceptive should be reserved for women with acne that has not responded to antibiotics (European Medicines Agency Pharmacovigilance Risk Assessment Committee 2013).

Management of Heavy Menstrual Bleeding and Dysmenorrhoea

COCs are regarded as a viable non-surgical intervention for women experiencing heavy menstrual bleeding (National Institute for Health and Clinical Excellence 2007; The American College of Obstetricians and Gynecologists 2013). Their use has been shown to result in up to a 69 % reduction in bleeding amongst women with dysfunctional uterine bleeding (Matteson et al. 2013). The estradiolvalerate/dienogest COC (Qlaira®, Natazia®) is licensed in the UK for the management of heavy menstrual bleeding in those who wish to use oral contraceptives and for whom no pathology has been identified (Bayer PLC 2013). A pooled analysis of two randomised double-blind, placebo-controlled trials reported that following 6 months of treatment with the estradiolvalerate/dienogest COC the median menstrual blood loss in women with heavy and/or prolonged menstrual bleeding was reduced by 88 % from baseline, with most of the improvement being observed soon after starting and then maintained: for the placebo arm, the corresponding figure was 24 % (Fraser et al. 2011). Data comparing this product to other COCs is lacking and guidelines on the management of heavy menstrual bleeding do not, at present, advise the use of any one particular COC over another (National Institute for Health and Clinical Excellence 2007; The American College of Obstetricians and

Gynecologists 2013). Continuous regimens may offer some benefits over cyclical regimens (Edelman et al. 2014).

Wong and colleagues (2009), following a review of randomised controlled trials, concluded that COCs may be more effective than placebo at treating primary dysmenorrhoea, although they cautioned about the interpretation of their findings given the limitations of the included studies. In a small randomised controlled trial comparing continuous to cyclic oral contraceptive use for the treatment of primary dysmenorrhoea, the continuous regimen appeared to be superior in reducing pain in the first 3 months of use, but by 6 months there was no observed difference (Dmitrovic et al. 2012).

Similarly, Davis and colleagues (2007) in reviewing the evidence assessing the effects of oral contraceptives in comparison to other treatments for endometriosis-associated pain, found only one study which met their inclusion criteria. While this study showed the COC studied to be as effective as a Gonadotrophin-Releasing Hormone (GnRH) analogue, the authors of the Cochrane review could not fully evaluate the effects of COCs on endometriosis-associated pain due to the limited available evidence.

A subsequent systematic review and meta-analysis by Davis et al. (2007) reported that compared to surgery alone, the postoperative use of oral contraceptives had a statistically significant higher total remission (no renewed pelvic pain or identification of endometriosis by ultrasound, laparoscope or laparotomy) and recurrence rate of endometriosis (reappearance of pain or endometrial cysts). Oral contraceptives did not differ significantly from other postoperative hormonal treatments such as danazol and GnRH analogues, although had fewer side effects Wu et al. (2013b).

The European Society for Human Reproduction and Embryology advocate both cyclical and continuous COC use for the management of women with endometriosis and pain associated with endometriosis (Dunselman et al. 2014).

Whereas for most POPs their effect on ovulation is variable and thus their impact on ovulatory associated pain would be expected to be less, the desogestrel POP, which reliably suppresses ovulation has been found to confer some benefits (Ahrendt et al. 2007; Razzi et al. 2007). While it may offer some benefit in women who have these symptoms and are requiring contraception, it is not currently documented specifically as a recommended hormonal therapy for endometriosis associated pain within European Guidelines on the management of this condition (Dunselman et al. 2014).

Benign Breast Disease

Benign breast disease is common, with the peak incidence occurring in women in their 40s and 50s (Rungruang and Kelley 2011). Studies are largely supportive that oral contraceptives do not increase a woman's risk of developing benign breast diseases and in women with fibroadenomas, their use, particularly at higher doses,

may actually offer women some protection (Canny et al. 1988; Sitruk-Ware et al. 1989; Vessey and Yeates 2007).

Medical eligibility criteria do not suggest that the use of oral contraceptives need to be restricted in women with benign breast disease (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010). When women have an undiagnosed mass, oral contraceptives do not necessarily have to be stopped; although it may of course be a woman's preference to do so. Undiagnosed masses should be evaluated as soon as possible (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Use in Women with Polycystic Ovarian Syndrome

Women with polycystic ovarian syndrome commonly experience anovulatory cycles, oligomenorrhoea and hyperandrogenic symptoms such as hirsutism and acne. The lack of bleeding and increased estrogen levels may predispose women to an increased risk of endometrial hyperplasia and possibly endometrial cancer (Royal College of Obstetricians and Gynaecologists 2007a). To protect against this, in women with oligomenorrhoea or amenorrhoea, the UK Royal College of Obstetricians and Gynaecologists (RCOG) advises that oligomenorrhoeic women with PCOS use hormonal treatment such as oral contraceptives to protect the endometrium (Royal College of Obstetricians and Gynaecologists 2007a). Other guidelines similarly advocate the use of oral contraceptives (COC or POP) for endometrial protection in women with PCOS, although note that POPs may be associated with unpredictable bleeding patterns (Anon 2009).

There is currently insufficient evidence to say whether COCs are more effective than the insulin sensitizing drug metformin in the treatment of hirsutism and acne in women with PCOS (Costello et al. 2007). Guidelines (Anon 2009; Royal College of Obstetricians and Gynaecologists 2007a) currently do not recommend one COC formulation over another for the management of PCOS symptoms. However, in theory, COCs containing a progestogen with low androgenicity (e.g. some third generation progestogens) or anti-androgenic activity (e.g. drospirenone) may be more effective in treating symptoms than COCs that contain a mildly androgenic progestogen (e.g. levonorgestrel). The strength of a COC preparation may also make a difference as the higher the dose of ethinylestradiol the more hepatic production of SHBG is increased, which in turn reduces the activity of endogenous androgens (Layton 2010).

COCs containing cyproterone acetate are licensed for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism (Bayer PLC 2014), in women of reproductive age. There has been particular controversy about their use in recent years due to fears about the associated risk of venous thromboembolism (see Chap. 6), which resulted in the European Medicines Agency (EMA) undertaking an evidence review in 2013 (European Medicines Agency Pharmacovigilance Risk Assessment Committee

2013). As indicated earlier in this chapter such COCs are not advised solely for contraceptive purposes or for use in conjunction with other hormonal contraceptives (Bayer PLC 2014; European Medicines Agency Pharmacovigilance Risk Assessment Committee 2013).

Risks Associated With Oral Contraceptive Use

Breast and Cervical Cancer

Breast Cancer

Breast cancer is known to be influenced by endogenous hormone levels (Endogenous Hormones and Breast Cancer Collaborative Group et al. 2013) and it is important to consider potential effects of exogenous hormones on breast cancer risk. Over the years, many studies have attempted to quantify the risk associated with oral contraceptives: the findings of which are often conflicting.

A statistically significant increased risk of breast cancer amongst current users as compared with never users has been observed in several studies (Collaborative Group on Hormonal Factors in Breast Cancer 1996; Hunter et al. 2010; Kahlenborn et al. 2006; Rosenberg et al. 2009). Yet, other published studies have not reported this (Gill et al. 2006; Hannaford et al. 2007; Marchbanks et al. 2002; Nichols et al. 2007; Shapiro et al. 2000; Vessey et al. 2010; Vessey and Painter 2006; Vessey and Yeates 2013). In one of the largest studies demonstrating an increased risk amongst current users compared with non-users (RR 1.24 (1.15–1.33)), the authors also found that the excess risk declined with time after stopping, with no significant difference noted between user and never users 10 or more years after stopping (RR 1.01 (0.96–1.05)) (Collaborative Group on Hormonal Factors in Breast Cancer 1996).

For women who have an increased risk of breast cancer due to an inherited BRCA gene mutation, the findings have varied (Brohet et al. 2007; Lee et al. 2008; Milne et al. 2005); (Narod et al. 2002). Meta-analyses report that recent formulations of COC do not appear to be associated with a further increasing of breast cancer risk in BRCA 1/2 carriers (Cibula et al. 2011; Iodice et al. 2010). Similarly, the available evidence does not currently support the notion that, women with a family history of breast cancer, should be more cautious about use of COCs due to them further increasing their risk (Gaffield et al. 2009).

A similar level of risk was reported for the POP as for COCs in a large collaborative reanalysis of epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer 1996). However, there is far less evidence relating to the POP and breast cancer, making it difficult to draw conclusions about any association. For women with current breast cancer, neither COCs or POPs are advised (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Cervical Cancer

Data from observational studies have been consistent in showing an increased risk of developing cervical cancer in women who have used COCs long-term, even after adjustment for confounders. A large meta-analysis of data undertaken in 2007 demonstrated that compared with never users, women who had used the COC for 5 or more years had a relative risk of 1.9 (95 % CI 1.69–2.13) for the development of invasive cervical cancer (International Collaboration of Epidemiological Studies of Cervical Cancer 2007). The relative risk of cervical cancer was found to increase by a factor of 1 · 38 (95 % CI 1 · 30–1 · 46) per 5 years of use (International Collaboration of Epidemiological Studies of Cervical Cancer 2007).

Cross sectional data published in 2013, indicated that use of COCs for 10 or more years may have a role in the progression of HPV to pre-cancer (OR 1.97 95 % CI 1.12–3.46) (Luhn et al. 2013). However, studies have also been consistent in demonstrating that any risk declines with time after stopping; and that a user's risk of cervical cancer is not statistically different to that of a never user, 10 or more years after stopping (International Collaboration of Epidemiological Studies of Cervical Cancer 2007).

Cardiovascular Disease and Stroke

Myocardial Infarction

Myocardial infarction is a rare event in women of reproductive age. However, given their widespread use, there is much interest in whether use of oral contraceptives increases a woman's risk of such cardiovascular events. A pooled analysis of data from 11 observational studies, published in 2013, concluded there was a small statistically significant increased risk of MI associated with current use of COCs (pooled OR 1.7 95 % CI 1.2–2.3) (Plu-Bureau et al. 2013). An increased risk has also been noted in other reviews (Baillargeon 2005).

A meta-analysis and systematic review also published in 2013 (Peragallo et al. 2013), suggested that current use of oral contraceptives was not, as compared with non-current users (past or never users), associated with a statistically significant increased risk of MI (eight studies; OR 1.34, 95 % CI 0.87–2.08) (Peragallo et al. 2013). The authors however note that their meta-analysis was possibly underpowered because of the limited number of studies eligible for inclusion and that more evidence is required to provide clarity on the effect of oral contraceptives on risk of MI (Peragallo et al. 2013). The included studies differed between the two meta-analyses, which may explain the differing findings.

Observed differences in study findings related to the risk of MI with COCs may be a consequence of the inability to control for all lifestyle factors that may influence cardiovascular health, such as physical activity levels. As smoking and hypertension are significant risk factors for cardiovascular disease, it is unsurprising that the risk of MI has been found to be greater amongst current COC users who

smoke compared to those who do not (Croft and Hannaford 1989; Dunn et al. 1999; Khader et al. 2003; Vessey et al. 2003) and higher amongst users with hypertension compared to those with 'normal' blood pressure (Croft and Hannaford 1989; Curtis et al. 2006; Khader et al. 2003). Caution should be advised when considering prescribing COCs to women with multiple risk factors for cardiovascular disease as the risks may outweigh the benefits of use, or indeed be unacceptable depending on the factors involved (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

With so many different oral contraceptives available, women may wish to know if certain formulations are associated with more cardiovascular risk than others, particularly if they already have underlying health considerations which may put them at higher risk of cardiovascular complications. Therefore, as with VTE studies, researchers have sought to establish what (if any) influence the dose of estrogen and/or the dose of progestogen has on mediating risk of MI. Data are inconsistent (Lidegaard et al. 2012; Plu-Bureau et al. 2013; Wu et al. 2013a).

In light of ongoing concerns about the influence of progestogens within COCs on VTE, in 2013, the European Medicines Agency (EMA) completed a review of the risk of VTE associated with use of COCs. Their published findings indicate that there is an increased risk of MI associated with COCs and that while it was suggested that the progestogen type does influence the risk of VTE (see Chap. 6), the findings did not confirm a difference between progestogens in arterial thrombosis risk (European Medicines Agency 2014b).

There are limited data available on the risk of MI associated with use of POPs but an increased risk amongst users has not been demonstrated (Chakhtoura et al. 2011; Lidegaard et al. 2012). Therefore medical eligibility criteria indicate that the benefits of using the POP for contraception in women with multiple risk factors for cardiovascular disease generally outweigh any potential or theoretical risks (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Stroke and Migraine

There are global variations in the prevalence of stroke and mortality rates arising from stroke, but it remains one of the leading causes of death and adult disability (Feigin et al. 2014). Although in some countries there are trends towards an increased incidence of stroke amongst young adults (Feigin et al. 2014), as with MI, stroke is rare in women of reproductive age.

Migraine is an independent risk factor for stroke (Etminan et al. 2005). In one meta-analyses, the association with ischaemic stroke was only significant for those with migraine with aura (Schurks et al. 2009). In the meta-analyses investigating the link between migraine and haemorrhagic stroke, the association was not statistically significant in those with migraine with aura, but the authors noted the data were too few to be able to prove an association by type of migraine (Sacco et al. 2013).

The evidence as to the modifying effect of COCs is varied, with evidence generally suggesting that it may increase a woman's risk of ischaemic (Baillargeon et al. 2005; Peragallo et al. 2013; Plu-Bureau et al. 2013) but not haemorrhagic stroke (Peragallo et al. 2013; Plu-Bureau et al. 2013; WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1996; Yang et al. 2009).

COC use in women with migraine has been found to slightly increase a woman's risk of stroke compared to non-users with migraine (Chang et al. 1999; Lidegaard 1993; Schurks et al. 2009; Tzourio et al. 1995; WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception 1996). For women with migraine with aura, the use of a COC is therefore not advised as it is considered to present an unacceptable health risk (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010). For women with migraine but no aura, the advice varies – the WHO and CDC Medical Eligibility Criteria indicate that if a woman is aged over 35 when she starts the COC, the risks may outweigh the benefits, but for those under 35 years, the reverse is likely to apply (Centre for Disease Control 2010; World Health Organization 2010). Conversely in the UK, no age limit is applied to the advice for women who experience migraine without aura, and the benefits from starting a COC would generally be considered to outweigh any risks (Faculty of Sexual and Reproductive Health Care 2009b). Women who develop migraine while using the COC would generally be advised to consider an alternative method (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Similarly, COC use in women with hypertension, as compared to hypertensive non-users, has been found to adversely influence stroke risk (Curtis et al. 2006) and therefore should be restricted in women found to have hypertension. The use of combined hormonal contraceptives is generally not advised for women with hypertension, particularly in those with very high (systolic $\geq$160 mm Hg or diastolic $\geq$100 mm Hg) uncontrolled blood pressure or vascular disease (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

As with MI, there are limited data available, but it does not appear that the risk of ischaemic or haemorrhagic stroke is increased amongst users of POPs (Chakhtoura et al. 2009; Lidegaard et al. 2012). A meta-analysis (Chakhtoura et al. 2009) of six case control studies reported a combined odds ratio of 0.96 (95 % confidence interval: 0.70–1.31) for progestogen-only contraceptives and risk of stroke. The authors reported that the results were similar for progestogen methods regardless of their mode of administration. As POPs do not appear to increase the risk of stroke, medical eligibility criteria suggest that in women with hypertension who use POPs, the balance of risk is more favourable than with COCs (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Bone Health

The available evidence on the effect of OCs on bone health has limitations owing to factors such as: the lack of randomised controlled trials; different study designs; variations in the formulations of COCs used; different sites used for measuring bone mineral density (BMD), and confounders such as smoking habits, BMI, parity and previous exposure to hormones.

There are certain groups for whom it is important to know the consequences of hormonal contraception on bone health, for example adolescents and menopausal women. For the general population, use of COCs does not appear to negatively affect bone health and has not been shown to increase fracture risk (Lopez et al. 2014; Martins et al. 2006). It has however been suggested that COCs containing less than 30 μg of ethinylestradiol may have a negative impact on peak bone acquisition and that compared to never users, adolescents who use COCs containing 20 μg have lower bone mineral density (Nappi et al. 2012). In contrast, for peri-menopausal women, COC use may actually confer some benefits in terms of bone mineral density, even at low doses (Nappi et al. 2012), although the benefit has yet to be confirmed via randomised controlled trials. Use in the peri-menopause solely to assist bone health would need to be considered in the context of other age-related risks associated with COCs. Similarly, evidence is lacking a protective effect on bone loss in women at risk of osteoporosis e.g. women with dietary deficiency (Bergstrom et al. 2013).

Few studies have examined the effect of POPs on bone mineral density meaning that reviews evaluating the effect of contraception on fracture risk have failed to include the POP (Lopez et al. 2012, 2014). While there have been concerns about some non-oral progestogen-only methods reducing BMD (see Chap. 8), a negative effect with use of the POP is not expected (McCann and Potter 1994).

Glaucoma

In 2013 an increased risk of glaucoma associated with the use of oral contraceptives was reported via a range of media outlets (internet, press). These reports were based on findings from a cross sectional study presented at the annual meeting of the American Academy of Ophthalmology (2013). The reported findings suggested that self-reported glaucoma (not confirmed by diagnostics) was twice as likely amongst women who had used oral contraceptives for 3 years or more American Academy of Ophthalmology (2013).

Previous studies have differed in their findings regarding the risk of glaucoma, with earlier data from two UK cohorts suggesting no increased risk with ever use (RR 1.0 95 % CI 0.7–1.4) and RR 1.6 (95 % CI 0.9–2.0) respectively (Vessey et al. 1998). Another study suggested that although ever use of oral contraceptives did not appear to increase the risk of primary open-angle glaucoma, there was perhaps a modest increased risk with use of oral contraceptives for 5 or more years

(Pasquale and Kang 2011). The authors of this latter study however, did suggest the findings required further consideration (Pasquale and Kang 2011). A statement published by the Faculty of Sexual and Reproductive Healthcare in 2013 advised they were unable to comment on the findings reported at the 2013 annual meeting until the results had been published in a journal publication. The FSRH advised, that women need not stop their pill but that anyone who had particular concerns should seek further advice from their GP or optician (Faculty of Sexual and Reproductive Healthcare 2013).

Gastrointestinal Disorders

There are data to suggest a possible association between oral contraceptive use and the development of inflammatory bowel disease (IBD), in particular Crohn's disease (Cornish et al. 2008; Halfvarson et al. 2006; Khalili et al. 2013), although the limited available evidence does not suggest it affect disease flare-ups (Zapata et al. 2010). More research is required in this area to confirm the role of oral contraceptives in IBD development as studies have been limited by failure to control for family history and a lack of information about included formulations.

A European evidence-based consensus on reproduction in inflammatory bowel disease has highlighted that as a thrombophilic condition, use of oral contraceptives may increase the risk of thromboembolism in women with inflammatory bowel disease and therefore the decision to prescribe should be made on an individual basis (van der Woude et al. 2010). In the UK, medical eligibility criteria suggest the benefits of using oral contraceptives in women with IBD outweigh the risks (Faculty of Sexual and Reproductive Health Care 2009b). The CDC however suggest that the balance of benefits versus risks will depend on whether there are other risk factors for thromboembolism such as active/extensive disease or immobilisation (Centre for Disease Control 2010).

Teratogenicity

For some women, where a pregnancy is not planned, inadvertent use of oral contraceptives in early pregnancy may occur. Although pregnancy is listed as a contraindication to use of oral contraceptives within licensing information, a teratogenic effect has not been demonstrated (Waller et al. 2010). Concerns have been raised about fetal exposure to cyproterone acetate. Animal studies have revealed that feminisation of male fetuses may occur if cyproterone acetate is administered during the phase of embryogenesis at which differentiation of the external genitalia occurs. The SPC for Dianette (Bayer PLC 2014) advises that pregnancy must be excluded before treatment is begun, and while it acknowledges the fact that results of animal studies may not necessarily apply to humans, the

possibility that administration of Dianette to women after the 45th day of pregnancy could cause feminisation of male fetuses needs to be considered.

Breastfeeding

The World Health Organization (WHO) advises that to reduce the risk of negative maternal and infant outcomes, there should be at least 24 months between pregnancies; although there are also concerns about intervals of more than 5 years (Conde-Agudelo et al. 2007; World Health Organization 2005). Whilst postpartum contraception is therefore important, women who are breastfeeding may be concerned about the impact of hormonal contraceptives on breastfeeding both in terms of exposure of infants to hormones and on breastfeeding outcomes such as breast milk volume.

There is limited evidence on which to draw conclusions about the effect of hormonal contraception has on breastfeeding outcomes including duration, success, milk quantity and quality, and that which exists is often inadequate and inconsistent (Kapp and Curtis 2010; Truitt et al. 2003). A randomised controlled trial published in 2012 found no difference in breastfeeding duration or infant growth between women started on a COC or POP 2 weeks postpartum, although there were some study limitations and the authors themselves highlighted the need for a larger equivalence study to clarify their findings (Espey et al. 2012).

Despite the lack of good quality data, there is general consensus that prior to 6 weeks postpartum, use of combined hormonal contraceptives is considered inappropriate for women who are breastfeeding because of concerns about the impact on breast milk volume (World Health Organization 2010; Faculty of Sexual and Reproductive Healthcare 2009b; Centre for Disease Control 2010). In women who are fully or almost fully breastfeeding i.e. able to use lactational amenorrhoea method, the risks of prescribing COC are likely to outweigh any benefit (Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Advice however differs in relation to the eligibility of breastfeeding women to use POPs. In the UK and the US the use of POPs in breastfeeding women prior to 6 weeks is generally supported (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b): the WHO's medical eligibility criteria is slightly more cautious in the first 6 weeks in its interpretation of where it considers the balance of risk to lie- suggesting that the theoretical or proven risks still outweigh the benefits (World Health Organization 2010).

The WHO acknowledges that direct evidence does not generally support a negative effect of either the COC or the POP on infant health outcomes (World Health Organization 2009). However, they express concern about the limitations of the data (e.g. short duration of follow-up). The WHO's more restrictive view on the use of POPs prior to 6 weeks postpartum is due, they indicate, to theoretical concerns about

the impact of progestogens on infant brain development and the possible existence of negative unmeasured effects (World Health Organization 2009).

For postpartum non-breastfeeding women, as POPs are not thought to be associated with an increased risk of thrombosis, POPs can be used without restriction from delivery (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010). However because of the risk of thrombosis associated with COC use (see Chap. 6), each of these organisations advise a delay in initiating COCs until the risk of thrombosis associated with pregnancy and the postpartum period has reduced – the durations differ within each of the documents (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Interactions with Other Medicines

As mentioned earlier in this chapter, the efficacy of oral contraceptives has the potential to be reduced by enzyme-inducing medications (see Table 5.1). Oral contraceptives themselves also have the potential to impact on the efficacy of other drugs, for example COCs have been shown to increase the clearance of the antiepileptic medication lamotrigine, via the process of glucuronidation (Christensen et al. 2007; Sabers et al. 2001, 2003). The dose of lamotrigine may therefore need to be adjusted when starting or stopping COCs (GlaxoSmithKline UK 2014). It is important for health professionals to regularly check product information and other sources of information when considering co-prescribing medications with hormonal contraceptives.

Reported Adverse Effects

With regards adverse events/side effects related to OCs, establishing causation can be difficult due to the observational nature of studies and the number of other potential influencing factors. To establish causality, factors such as plausibility, dose-response effect, temporal relationships and any possible bias and confounding must be considered. While individual studies may suggest that certain pills may be better than other in terms of different side effects, collectively there is currently insufficient evidence from randomised controlled trials to suggest that any one pill or generation of progestogen is associated with a better side effect profile than others (Lawrie et al. 2011).

Irregular Bleeding and Cycle Control

Irregular bleeding or menstrual disturbances are common with POPs (Ahrendt et al. 2010; Faculty of Sexual and Reproductive Health Care 2009a). In the first 3 months around a third of women will experience a change in bleeding, with about 1 in 10 experiencing bleeding that is frequent i.e. more than five episodes of bleeding over a 90 day reference period (Faculty of Sexual and Reproductive Health Care 2009a). Longer-term, it is suggested that up to 40 % of women may experience erratic bleeding with use of the POP (Faculty of Sexual and Reproductive Health Care 2009a). While irregular bleeding can settle within the first few months of use (Faculty of Sexual and Reproductive Health Care 2009a; Lumsden et al. 2013), for some women bleeding patterns often remain irregular.

Although many studies have sought to investigate how best to prevent or treat the irregular bleeding, to date there is little evidence to suggest that any of the tested interventions work long-term (Abdel-Aleem et al. 2013). It is generally advised that women wait around 3 months to see if bleeding patterns settle before trying another method or switching to a different POP (Faculty of Sexual and Reproductive Healthcare 2009a). It is important to consider other factors that could cause irregular bleeding, for example sexually transmitted infections, pregnancy and abnormal cervical cytology and to exclude these either via a clinical history and/or examination (Faculty of Sexual and Reproductive Health Care 2009a).

Around 20 % of women using a COC will experience irregular bleeding in the first 3 months (Faculty of Sexual and Reproductive Health Care 2009a), which usually settles with time. Women will differ in their views as to what represents an acceptable bleeding pattern and it is difficult to compare between different preparations (Thorneycroft 1999) but COCs are considered generally to provide good cycle control. A Cochrane review reported that findings from comparative trials tended to suggest that COCs containing 20 μg of ethinylestradiol were associated with more bleeding disruptions than those with 30–35 μg (Gallo et al. 2013). However, these bleeding disruptions included lack of bleeding also and the authors called for more standardisation in the collection of bleeding data and highlighted there was insufficient evidence to exclude the role of progestogens in their findings (Gallo et al. 2013). Women using continuous or extended dosing regimens may experience a reduced number of bleeding days compared with cyclical regimens (Edelman et al. 2014).

Lawrie et al. (2011) suggested that on the basis of one double blind RCT of 456 women (Loudon et al. 1990), COCs containing third generation progestogens may offer favourable bleeding profiles to those containing second generation progestogens (RR 0.71, 95 % CI 0.55–0.91). However, when considering which pill to prescribe, the benefits of higher dose COCs and newer progestogens in terms of bleeding control should be considered in the context of their possible increased risk of thrombosis compared to those containing lower doses of ethinylestradiol or older progestogens (see Chap. 6).

Weight Changes

Two Cochrane reviews have sought to establish whether there is an association between oral contraceptive use and weight gain (Gallo et al. 2014; Lopez LM et al. 2013b). The Cochrane review examining combined hormonal contraceptives reported that from four trials which compared combined hormonal methods (3 COC trials and 1 combined transdermal patch) to either placebo or no intervention, no association with weight gain was found (Gallo et al. 2014). The authors did however caution that the findings are limited by the small number of studies and that given the wide variety of methods available, they could not completely exclude the possibility that an association may be present for some methods (Gallo et al. 2014).

The review also included a number of trials comparing combined methods to one another, but the authors reported that any differences were not substantial and that discontinuation rates did not tend to differ in these trials (Gallo et al. 2014). Claims that the anti-mineralocorticoid activity of drospirenone may counteract weight gain or fluid retention are largely unsubstantiated.

It has been reported that with use of progestogen-only contraceptives generally, after 12 months of use, the typical weight gain experienced is less than 2 kg (Lopez et al. 2013b). However, few data on the POP were included, which makes it difficult to directly apply the findings to this method. Although the evidence does not suggest a causal relationship between weight gain and oral contraceptive use, an effect cannot be entirely excluded due to the limitations of the available evidence.

Nausea

Gastrointestinal disorders such as nausea and vomiting are listed in the product information of different oral contraceptives as having occurred in varying frequencies within clinical trials. However, causation has not been established.

Headache

Headaches are a commonly listed undesirable effect possibly associated with use of oral contraceptives. A systematic review published in 2005 (Loder et al. 2005) examined the evidence as to whether the use of COCs resulted in or aggravated headaches. The review included a range of reasonable quality cohort studies and concluded that the available evidence did not appear to suggest a strong relationship between headaches and COC use (Loder et al. 2005). The review suggested that some women might possibly have a higher risk of developing headaches with COC use and that these women tended to be those with a strong personal or family history of problematic headaches (Loder et al. 2005). The authors noted that there did not

appear to be any evidence to suggest that the dose or type of progestogen would influence headache in COC users or that switching between COCs would help to treat headaches. It was postulated that, based on the belief headaches may be associated with estrogen withdrawal during the pill free interval, that shortening or manipulating this may provide some benefit (Loder et al. 2005).

A Cochrane review comparing continuous or extended COC use to cyclical use suggested that from few included studies which examined menstrual symptoms, those who used longer regimens tended to experience less frequent headaches (Edelman et al. 2014). Women experiencing headaches during their hormone free interval may potentially benefit from omitting or shortening it, either by using a regimen designed to be taken this way or by running packets together.

Evidence directly relating to the influence of progestogen-only methods on the development of headaches is lacking (MacGregor 2013). Use of the 75 μg desogestrel pill may confer some benefit to women with migraines (Huber et al. 2000; Merki-Feld et al. 2013a, b; Nappi et al. 2011), decreasing the frequency and intensity of episodes, although the data comes from small observational studies and more large prospective trials are required to confirm any potential observed benefit.

Mood Changes/Depression

Mood change is often cited as a reason for discontinuation of oral contraceptives (Davis et al. 2005) and whilst a causal association has not been demonstrated, the possibility of mood changes (both improved and worsened) can be highlighted to women.

A randomised controlled trial in which 76 adolescents with dysmenorrhoea were given either a COC or placebo for 3 months found that upon exiting the study there were few differences in the mean Centre for Epidemiologic Studies Depression Scale (CES-D) scores for the two groups (Davis et al. 2005). Similarly Duke and colleagues (2007) reported no significant difference in the odds of depression in users of oral contraceptives compared to non-users, although they did find that compared to women who used oral contraceptives for contraceptive purposes, women who used them for other reasons were at increased risk of experiencing depressive symptoms (RR 1.32, 95 % CI = 1.07–1.62). Analysis from a national longitudinal study of women aged 25–34 suggested that use of hormonal contraceptives (combined as well as progestogen-only), may be be protective against depressive symptoms with reported lower mean levels of concurrent depressive symptoms amongst hormonal contraceptive users than users of low efficacy contraception or no contraception (Keyes et al. 2013).

While Jofee et al. (2003) in their study investigating the impact of oral contraceptive use on premenstrual mood found that amongst 658 women using oral contraceptives, the only significant predictor of mood deterioration was previous

depression; Young and colleagues reported that women with depression do not appear to have worsening of their symptoms with use of combined hormonal contraceptives, indeed depression symptoms lessened (Young et al. 2007). Analysis from a national longitudinal study of women aged 25–34 suggested lower mean levels of concurrent depressive symptoms amongst hormonal contraceptive users (combined as well as progestogen-only) than non-users (Keyes et al. 2013).

For women with dysmenorrhoea COC use may help to improve premenstrual mood, although for most women it may have little impact (Joffe et al. 2003). Women with premenstrual syndrome (PMS) may wish to consider using the COC continuously rather than cyclically (Royal College of Obstetricians and Gynaecologists 2007b).

Large scale studies investigating any association between mood change, depression and oral contraceptive use, including studies which compare the influence of different pill types, are lacking. Therefore it is difficult to draw any conclusions about the effects of the different pill types on mood, including premenstrual syndrome and whether any pill is more effective than another. Medical eligibility criteria for contraceptive use do not suggest that there is any reason to restrict use of oral contraceptives in those who are depressed (Centre for Disease Control 2010; Faculty of Sexual and Reproductive Health Care 2009b; World Health Organization 2010).

Sexual Interest

Decreased libido is often reported to health professionals in clinical practice. Given that a decreased libido has the potential to impact on an individual's quality of life and relationship; it is perhaps no surprise that a number of studies have sought to investigate whether an association between OCs and libido exists. Undertaking such studies and drawing any clear conclusions is challenging given the subjective nature of the outcome, inter-individual variability and the number of possible biological, social and psychological factors that could impact, for example, the quality of the person's sexual relationship.

Reviews on the topic have tended to suggest no effect, whilst recognising the inherent difficulties associated with this research. Pastor and colleagues (2013) reported that while although a decline of free testosterone and an increase in sex hormone binding globulin was observed in those studies examining plasma levels; only 15 % of the 8422 COC users from the included studies, reported a decrease in sexual interest. The decrease in sexual interest tended to be amongst users of very low dose pills i.e. those containing 15 μg of ethinylestradiol (Pastor et al. 2013).

An earlier non-systematic review (Schaffir 2006) similarly suggested no effect for COCs and reported that, although there were limited studies on the topic, a major impact on sexual desire with use of POPs was unlikely.

Vaginal Discharge

The Summaries of Product Characteristics for many oral contraceptives list vaginal discharge as an undesirable effect noted within clinical trials. However, oral contraceptive use is not thought to alter vaginal flora or discharge considerably (Eschenbach et al. 2000). A change in vaginal discharge can be the result of sexually transmitted or non-sexually transmitted infection (e.g. vulvovaginal candidiasis (VVC) or bacterial vaginosis (BV)).

While it has been postulated that COCs may be associated with an increased risk of VVC because of the increased exposure to estrogen, an association has not been clearly demonstrated (Faculty of Sexual and Reproductive Healthcare 2012). It would not however be unreasonable to consider trying another form of contraception in a COC user who continues to experience recurrent VVC (Faculty of Sexual and Reproductive Healthcare 2012). With regards other causes of vaginal discharge COCs may reduce the risk of bacterial vaginosis (Calzolari et al. 2000; Riggs et al. 2007; Shoubnikova et al. 1997).

Fertility Return

When stopping contraception, a woman's chance of becoming pregnant will be influenced by a number of factors including her background fertility and that of her partner. There is some documented evidence to suggest that women who have been using oral contraceptives may take slightly longer to conceive compared with other methods for example barrier methods (Doll et al. 2001; Hassan and Killick 2004; Mikkelsen et al. 2013; Vessey et al. 1986) and intrauterine devices (Doll et al. 2001) but that this effect is transient. A large prospective study (Cronin et al. 2009) of drospirenone and other progestogen containing COCs reported no initial delay with 79.4 % of women pregnant after 1 year – this study did not undertake a direct comparison to other non-oral methods.

Data are often limited by a lack of ability to control for factors such as frequency and timing of intercourse, fertility of the partner, age, and smoking history. Overall, the evidence does not suggest that oral contraceptive use has an impact on long-term fertility. A review of available studies, published in 2011 (Mansour et al. 2011) suggested that overall pregnancy rates after stopping oral contraceptives are similar at 1 year to those stopping barrier methods or who have used no method. The 1 year pregnancy rates were reported to be approximately between 80 % and 95 % (Mansour et al. 2011).

In a trial of the desogestrel POP, the average time to first post-treatment ovulation was 17.5 days with all women ($n = 99$) having ovulated 30 days after treatment: Six women (approximately 6 % (6/99)) ovulated 7 days post-treatment (Korver et al. 2005). Therefore after stopping oral contraceptives, if pregnancy is

not desired, an alternative contraceptive method should be started immediately (Mansour et al. 2011; Faculty of Sexual and Reproductive Healthcare 2015, 2011a).

Factors to Consider When Prescribing Oral Contraceptives

Before prescribing contraception, potential benefits and risks should be identified through detailed history taking. These should be discussed with the patient and taken into account along with patient preferences, cultural and social factors. Key information to identify in the history should include:

- Medical conditions (past and present) including migraine with aura and thrombosis
- Family history of medical conditions including thrombosis
- Medication history (including prescription & non-prescription medicines, herbal remedies including St John's Wort and any other supplements)
- Menstrual history including attitude to amenorrhoea if relevant
- Contraceptive history including any previous problems
- Gynaecological history including cervical screening and HPV immunisation
- Any relevant surgical procedures
- Obstetric history and plans for future pregnancies
- Social history including smoking

There is no need for routine pelvic examination or ultrasound before initiating oral contraception. It is good practice to consider screening for sexually transmitted infection and cervical cytology where clinically appropriate and as resources allow. When prescribing a COC blood pressure monitoring is generally advised to exclude hypertension (Centre for Disease Control and Prevention 2013; Faculty of Sexual and Reproductive Healthcare 2011a; World Health Organisation 2004).

Quick Starting OCs

In some countries there has been a move toward the practice of quick starting oral contraceptives at any time in the menstrual cycle even in some instances, when pregnancy cannot be excluded, such as when prescribing oral emergency contraceptives (Faculty of Sexual and Reproductive Healthcare CEU 2010). The exception being co-cyprindiol pills which the UK Faculty of Sexual and Reproductive Healthcare advises are not started until pregnancy can definitely be excluded (Faculty of Sexual and Reproductive Healthcare 2010).

The objective of quick starting practice is to reduce barriers for women who may continue to be at risk if they have to wait until pregnancy can be excluded before starting oral contraceptives. The Centres for Disease Control and Prevention in the U.S. advise pregnancy testing in this circumstance, if a woman does not experience a withdrawal bleed in 3 weeks (Centre for Disease Control and Prevention 2013).

The UK's Faculty of Sexual and Reproductive Healthcare advises that if oral contraceptives are initiated when there has been a risk of pregnancy, that women be advised to test for pregnancy no sooner than 3 weeks after the last episode of unprotected sexual intercourse, in case women misinterpret bleeding patterns and in order to limit any potential exposure should emergency contraception fail (Faculty of Sexual and Reproductive Healthcare 2010).

Conclusions

Oral contraceptives are effective methods of contraception. However, their effectiveness is largely dependent on the user, and when pills are missed there is potential for an unintended pregnancy to occur. Whereas several COCs can be missed before efficacy is affected, when a POP is more than 3 h late, additional precautions are required if a pregnancy is to be avoided: the exception being the desogestrel pill which suppresses ovulation and can be taken up to 12 h late.

When used consistently and correctly and when prescribed appropriately, the risk/benefit profile of oral contraceptive use is likely to be favourable for the majority of women. There is no evidence that use will affect risk of all-cause mortality. There are certain conditions such as a history of cardiovascular disease, stroke, migraine with aura, hypertension, or smoking more than 15 cigarettes per day when aged over 35, which may tip the balance of risk unfavourably when considering prescribing a COC, and indeed in some instances present an unacceptable health risk. Where the risks are considered to outweigh the benefits, but the risk is not classified as unacceptable, the decision to prescribe is largely a matter of clinical judgement and/or the preference of the woman, taking into account potential non-contraceptive benefits and the availability/acceptability of other methods. Consulting with a specialist, either in contraception and/or the condition in question is advisable in such instances.

While COCs have some drawbacks in terms of their risk profile (for example cardiovascular risks), the same concerns do not appear to apply to POPs. Whilst it could perhaps be argued that women requesting oral contraceptives should therefore, in the first instance, be offered POPs in preference to COCs, it should be borne in mind that POPs may be less effective in 'real life' use as they generally require more rigid schedules to ensure protection is not lost if pills are taken late. In addition, POPs are often associated with less acceptable bleeding patterns than COCs.

COCs have a number of non-contraceptive benefits that have yet to be adequately demonstrated in POP users: alleviation of dysmenorrhoea, reduced menstrual bleeding and management of acne. Whilst a number of adverse events/side effects are reported by users of oral contraceptives, for example, weight gain, headaches, decreased interest in sex, there is often a lack of data to prove an association. Establishing a causal association is often difficult because of the limited data and the observational design of many studies.

Take Home Messages

- Oral contraceptives (COCs and POPs) are effective methods of contraception when used consistently and correctly.
- Efficacy can be affected by user compliance and factors that affect absorption or metabolism; for example vomiting, or use of enzyme inducing medications.
- Although there are some risks associated with use of COCs, when prescribed appropriately, they have a favourable benefit to risk profile for the majority of women
- COC use has been found to offer protection against ovarian and endometrial cancer, which lasts for several decades after stopping. Evidence is currently insufficient to allow recommendations to be made about their use primarily for cancer prevention.
- There are a number of other non-contraceptive benefits associated with COC use such as control of heavy menstrual bleeding, alleviation of dysmenorrhoea and acne improvement.
- Conditions likely to present a less favourable benefit to risk profile when COCs are used include a past or current history of cardiovascular disease, stroke or having certain risk factors for these conditions, such as migraine with aura or hypertension.
- POPs have a lower risk than COCs with regards cardiovascular health and there are few medical conditions that would limit a woman's eligibility to use POP.
- Current COC use may be associated with a small increase in risk of developing cervical cancer and possibly breast cancer. Any small increase in cancer risk reduces with time after stopping and women who use COCs have not been found to be at increased risk of death from cancer compared to those who have never used COCs.
- Weight gain, headaches and mood changes are often cited by women as concerns regarding side effects of COCs, but causal associations have not been established.
- Bleeding patterns may be irregular with use of POPs and there is little evidence of how best to manage irregular bleeding associated with use of POPs.

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Chapter 6
Oral Contraceptives and the Risk of Venous Thromboembolism

Susan Jick

Introduction

Oral Contraceptives (OC) were introduced in the 1960s and were a major advance in family planning technology for women. The first pill released in the United States, Enovid®, contained high doses of estrogen and progestin; specifically, mestranol and norethynodrel; four times more estrogen and ten times more progestin than today's OCs (Buttar and Seward 2009; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails). Because OCs were a new class of drug there was no existing knowledge or experience with their adverse risk profile, in particular in relation to the risk of cardiovascular disease (CVD). The first cases of cardiovascular events in OC users, including venous thromboembolism (VTE), myocardial infarction and stroke were observed soon after the pills were marketed (Records unit of the Research Advisory Service of the Royal College of General Practitioners 1967; Inman and Vessey 1968; Vessey and Doll 1968, 1969; Sartwell et al. 1969; Inman et al. 1970). It was thought at that time that the high doses of hormone were responsible (Records unit of the Research Advisory Service of the Royal College of General Practitioners 1967). In response to this concern, pills with lower doses of estrogen and different progestins were introduced to the market with the goal to reduce the CVD risk.

VTE is the most common of the three adverse CVD outcomes and thus is the focus of this chapter. Indeed the risk of VTE decreased with use of the OCs introduced in the 1980s; those with lower doses of estrogen (around 35–50 μg) and with the newer progestins levonorgestrel and norethindrone (BCDSP 1973; Stolley et al. 1975; Wharton and Blackburn 1988; Vessey et al. 1986). The risk of myocardial infarction and stroke have also decreased and will not be discussed

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further in this chapter as these outcomes are very rare in young healthy women and are thus difficult to study and not a major public health concern.

In the mid-1990s the discussion around OCs and VTE risk refocused on progestin type when concerns were raised that newer, so called third generation OCs, might increase the risk of VTE compared to OCs containing the older progestin levonorgestrel (Meade et al. 1980; Sitruk-Ware 2004; WHO 1995; Jick et al. 1995; Bloemenkamp et al. 1995; Lidegaard et al. 1998; Farmer et al. 1997; Spitzer et al. 1996; Jick et al. 2000; Kemmeren et al. 2001). Studies have since found that risks vary according to progestin formulation (Lidegaard et al. 2011; Vasilakis-Scaramozza and Jick 2001; Seaman et al. 2004; Vasilakis et al. 1999; Rubig 2003; Heineman and Dinger 2004). Below, the history of OC development and its relationship to the risk of VTE is described from the 1960s when the pill was first marketed until the present day, many years and many OC formulations later.

Oral Contraceptive Safety in the 1960s and 1970s

The first studies of oral contraceptives in relation to VTE were published in the late 1960s and early 1970s (Records unit of the Research Advisory Service of the Royal College of General Practitioners 1967; Inman and Vessey 1968; Vessey and Doll 1968, 1969; Sartwell et al. 1969; Inman et al. 1970). In 1967 the Royal College of General Practitioners (RCGP) published results of a case–control study of VTE in relation to OC use (Records unit of the Research Advisory Service of the Royal College of General Practitioners 1967). While this study was based on a small numbers of cases and controls, the results found that women who were taking OCs were at increased risk of VTE. Another study by Inman and Vessey found a strong association between OC use and fatal pulmonary embolism in previously healthy women (Inman and Vessey 1968). Vessey and Doll then published a more comprehensive study of OCs in relation to VTE in 1968 (Vessey and Doll 1968) which was updated in 1969 (Vessey and Doll 1969). These studies found that OC use was associated with an increased risk VTE of around 6–7 fold. The studies evaluated current use of OCs in idiopathic hospitalized and confirmed cases of VTE and compared OC use to women hospitalized for reasons other than VTE. These formal case-control studies quantified the magnitude of the risk of the then available OCs.

Sartwell et al. published another case-control study in 1969 (Sartwell et al. 1969) using similar case definition and methods that yielded similar results and further explored the effects of duration of use. These studies established both that OCs increase the risk of VTE and identified important risk factors and covariates for the outcome. Publications in the 1970s by Inman et al., the Boston Collaborative Drug Surveillance Program, and Stolley et al. added additional data and expanded on the known risk factors and biases present in studying this exposure-outcome relationship (Inman et al. 1970; BCDSP 1973; Stolley et al. 1975).

These early publications provided the framework for all future studies of OCs in relation to cardiovascular events. See Table 6.1 for a summary of these studies.

Table 6.1 Early studies of oral contraceptives in relation to venous thromboembolism

Authors	Citation	Title	Results	Exposure and case details
Records unit of the Research Advisory Service of the Royal College of General Practitioners	Collective Investigation 1967;13:267–79	Oral contraception and thromboembolic disease	17 exposed out of 147 cases vs 17 exposed out of 294 controls	OC exposure was stratified by current, recent and past use and compared to non-use. Cases were women 15–49 reported by their GP to have had a VTE
Inman WH, Vessey MP	BMJ 1968;2:193–9	Investigations of death from pulmonary, coronary, and cerebral thrombosis and embolism in women of child bearing age	95 confirmed PEs and 209 coronary thrombosis or MI; 2 controls per case. There was a strong association between use of OCs and death due to pulmonary embolism	OC exposure was use of an OC. Cases were women aged 20–44 in 1966 with idiopathic fatal thrombosis or pulmonary embolism identified from death certificates
Vessey MP, Doll R	Br Med J 1968;2 (5599):199–205	Investigation of relation between use of oral contraceptives and thromboembolic disease	42 cases of idiopathic VTE and 23 controls Risk of hospital VTE ~ 6–7 times greater in OC users than non-users	Current OC exposure was evaluated Cases were hospitalized with confirmed idiopathic VTE UK 1964–1966, subjects aged 16–40 years
Vessey MP, Doll R	Br Med J 1969;2 (5658):651–7	Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report	84 idiopathic VTE cases and 168 controls: RR 6.3 for OC use compared to nonuse	Current OC exposure was evaluated in idiopathic VTE cases from London hospitals 1964–1967 aged 16–40 years

(continued)

Table 6.1 (continued)

Authors	Citation	Title	Results	Exposure and case details
Sartwell PE et al.	Am J Epidemiol 1969:90:365–380	Thromboembolism and oral contraceptives: an epidemiologic case–control study	175 cases and matched controls. RR for VTE was 4.4 for current use compared to nonuse	Current OC use was evaluated Cases were idiopathic VTE in US hospitals aged 15–44. Matched to controls on age, race and hospital
Boston Collaborative Drug Surveillance Program	Lancet 1973;1 (7817):1399–404	Oral contraceptives and venous thromboembolic disease... Report from the BCDSP	43 Cases and 842 controls. Age standardized RR = 11 (95 % CI 5.2–25) for users compared to non-users	Current OC use was evaluated Cases were hospitalized idiopathic VTE in the US aged 20–44. Controls were women hospitalized for diagnoses not related to CVD or OC use
Stolley PD, Tonascia JA, Tockman MS, Sartwell PE et al	Am J Epidemiol 1975;102:197–208	Thrombosis with low-estrogen oral contraceptives	All cases (N = 457) and 1290 controls: RR = 1.8 for OC <100 μg and 2.1 for 100 μg OCs. Idiopathic cases only (N = 103) and 288 controls: RR = 4.7 and 10.1 for < 100 and 100 μg OCs	Current OC use was evaluated Cases were US hospitalized VTE. Matched to controls on age, hospital and race, aged 15–40. Idiopathic only, and separately, all cases were analyzed

PE pulmonary embolism, *RR* relative risk, *MI* myocardial infarction

For example, increasing age is strongly associated with an *increased* risk of VTE while OC *use declines* with increasing age. Thus the risk of VTE is highest in the age group of women with the lowest exposure. Therefore, age must be carefully controlled to prevent confounding. Calendar time is another important variable to control in all OC studies because OC use changes over time. OC use in cases of VTE must be compared to use in non-cases *at the same point in time* to avoid non-comparability. Similarly OC use differs in different regions of a country and the world, and women in different countries may have different risk factors for VTE and different OC use patterns, thus case women should be compared to women in the same geographic area to achieve valid results.

Other important risk factors that were identified in the early studies include smoking, obesity, and pre-existing cardiovascular disease. Pill use in women at high risk for thromboembolism thus became contraindicated and women with hypertension, a history of VTE or other cardiovascular disease, for example, became less likely to receive OCs. From this point forward it became important to exclude women with cardiovascular disease from studies of OCs and VTE, since they would be less likely to receive an OC than a healthy woman and their inclusion in a study would lead to biased results.

Early studies established that only current OC use was associated with increased risk of VTE and that the risk returned to baseline shortly after OC discontinuation (Sartwell et al. 1969). This has important implications for both study design and for women who are concerned about persistent effects of OCs. For woman taking the pill they should know that any increase in VTE risk conferred by the pill will return to baseline almost immediately after discontinuing the pill. For the researcher, studies of OCs should focus on current pill use.

Another important insight was that women who have other proximate causes for their VTE, such as recent surgery, pregnancy, injury, or trauma, should be excluded from studies of the relative effects of OCs on the risk of VTE (BCDSP 1973; Stolley et al. 1975). In the study by Stolley et al. (1975), it was demonstrated for example, that the inclusion of non-idiopathic cases greatly diluted the results such that the risk estimates were close to the null. Further investigation revealed that the risks in the non-idiopathic cases were around 1.0 while the risks in the idiopathic cases were elevated, consistent with previous studies. If restriction is not possible, then stratification by idiopathic (no other proximate cause or strong risk factors) versus non-idiopathic (recent other cause or strong risk factor present) case status, is essential to obtain valid results. This is because the risk conferred by the other causes will overwhelm any effect of an OC and therefore the distribution of OC use in non-idiopathic cases will tend to be similar to the OC use in the non-cases, leading to a bias of the true effect toward the null. Further, the risk in people with strong risk factors is biased away from receiving any OC or toward receiving OCs perceived to confer less risk. Differences in results of many published studies can be explained by differences in case definition (case validation and inclusion criteria), exposure definition (current only users or past users), and selection of reference group. See Table 6.1 for a summary of the early studies, their results and basic methodological characteristics.

Changes in OC Formulations Over Time: Second and Third Generation Pills

The 1980s and 1990s

The early findings that linked OC use to increased risk of thromboembolic events led to the development of newer OCs with lower doses of oestrogen in the 1980s.

The second round of OCs to come to market, so called second generation OCs, contained 50 μg or less estrogen, in combination with the progestins levonorgestrel or norethindrone. The goal of the new formulations was to reduce adverse cardiovascular events. At the same time, women with known risk factors were less frequently prescribed OCs and the rates of VTE consequently declined. That is, the risk was lower in the second generation compared to the high dose first generation OCs, and women at high risk were less frequently prescribed the pill. While new OCs were developed in the 1980s, few studies of OCs and VTE were published in this decade (Wharton and Blackburn 1988; Vessey et al. 1986; Meade et al. 1980). The results of these studies were similar to earlier studies and did not expand materially on the knowledge of the OC VTE risk.

Despite the lowered VTE risk, second generation OCs still conferred an increased risk of VTE compared to non-use of the pill, and thus newer "generations" of OCs with newer progestins were developed and marketed in attempt to further reduce the VTE risk. While the theory was that the new OC formulations, which were less androgenic (Sitruk-Ware 2004), would consequently confer lower cardiovascular risk, the reality did not meet the expectation. In fact the next, so called third generation OCs were found to increase rather than decrease the risk of VTE compared to the second generation pills (WHO 1995; Jick et al. 1995; Bloemenkamp et al. 1995; Lidegaard et al. 1998).

In the mid 1990s, research conducted by scientists at the World Health Organization found that women who received third generation OCs that contained either gestodene or desogestrel (new progestins), had higher risks of VTE compared to women who received second generation OCs which contained either levonorgestrel or norethindone (WHO 1995). The WHO study was published along with two independent research papers, each of which found that the new third generation OCs increased the risk of VTE by around two fold compared to the second generation pills (Jick et al. 1995; Bloemenkamp et al. 1995). There ensued several years of publications with varied results and debate over the true risk of third versus second generation OCs (Lidegaard et al. 1998, 2011; Farmer et al. 1997; Spitzer et al. 1996; Jick et al. 2000; Kemmeren et al. 2001). A summary of these studies is provided in Table 6.2.

Close examination of these studies reveals that variation in choice of comparison groups and case definitions between studies can explain the variations in the findings. The studies by the WHO, Jick, and Bloemenkamp all evaluated current OC use and included only or primarily idiopathic cases (the Bloemenkamp study had fewer exclusions than the other studies), and used a common referent (levonorgestrel OCs). Later studies, in contrast, included many or all VTE cases regardless of other proximate causes and strong risk factors. The strength of the associations for the third versus second generation OCs can be correlated with the number of exclusions applied. Those with the least exclusions for risk factors and other proximate causes yielded risks closest to 1.0. The risk estimates increased as the proportion of idiopathic cases increased. Studies by, Lidegaard, and Spitzer (Lidegaard et al. 1998; Spitzer et al. 1996) included many cases with other proximate causes of the VTE as well as co-morbidities that might bias the selection of the OC prescribed. The risk estimates in these studies were close to 1.0.

Table 6.2 Summary of third generation OC studies

Authors	Citation	Title	Results	Exposure and case details
WHO	Lancet 1995; 346:1582–1588	Effect of different progestagens in low oestrogen oral contraceptives on venous thrombo-embolic disease	Multiple results and comparisons presented but overall risk were around 2 fold for 3rd gen compared to levo OCs	Case-control study of current use, and non-use. Excluded non-idiopathic cases multi country 1989–93 aged 20–44
Jick H, Jick S, Gurewich V, Myers MW, Vasilakis C	Lancet 1995;346:1589–1593	Risk of idiopathic cardiovascular death and nonfatal venous thrombo-embolism in women using oral contraceptives with differing progestagen components	75 cases and 300 controls. OR = 2.2 for desogestrel compared to users of levo. OR = 2.1 for gestodene compared to users of levo. Cohort RR for 3rd gen vs levo = 1.9	Cohort study with nested case-control analysis. Current OC use evaluated, excluded non-idiopathic cases UK 1991–94 aged 15–44
Bloemenkamp KWM, Rsoendaal FR, Helmerhorst FM, Buller HR, Vandenbroucke JP	Lancet 1995; 346;1593–1596	Enhancement by factor V leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen	37 Deso cases, 20 levo cases OR 2.2	Case–control study of current OC use, excluded cases with prior VTE and recent pregnancy. Netherlands 1998–92, aged 15–49
Lidegaard O, Edstrom B, Kreiner S	Contraception 1998;57:291–301	Oral contraceptive and venous thromboembolism. A case-control study	117 cases 3rd gen, 30 2nd gen cases. OR 1.44	Case-control study of current, past and non OC use. Excluded only cases with prior VTE and MI. Denmark 1994–95 aged 15–44
Farmer RDT, Lawrenson RA, Thompson CR,	Lancet 1997;349:83–88	Population-based study of risk of venous thrombo-embolism	85 cases and 313 controls. 54 3rd gen cases, 29 2nd	Cohort study with nested case-control analysis.

(continued)

Table 6.2 (continued)

Authors	Citation	Title	Results	Exposure and case details
Kennedy JG, Hambleton IR		associated with various oral contraceptives	gen cases OR = 1.34. Cohort RR = 1.68	Current OC use evaluated and, excluded cases with other proximate causes but included cases with risk factors. UK 1991–95, aged 10–54
Spitzer WO, Lewis MA, Heinemann AJ, Thoroughgood M, MacRae KD	BMJ 1996;312:83–88	Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study	127 cases and 249 controls: 98 3rd gen vs 64 2nd gen cases OR 1.5	Case-control study of current use. Included all cases, none excluded. UK and Germany, 1992–1995 aged 16–44
Jick H, Kaye JK, Vasilakis-Scaramozza C, Jick S	BMJ 2000;321:1190–1195	Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis	54 3rd gen and 17 levo cases pre Oct. 1995 10 3rd gen and 25 Levo cases post 1995. ORs 2.2 and 2.8 respectively	Cohort study with nested case-control analysis. Current OC use evaluated, excluded non-idiopathic cases. UK 1993–1999 aged 15–39
Kemmeren JM, Algra A, Grobbee DE	BMJ 2001;323:131–4	Third generation oral contraceptives and risk of venous thrombosis: meta analysis	Concludes that risk of VTE is higher in users of third vs second generation OCs	Magnitude of risk depends on duration of use
Lidegaard O, Nielsin LH, Wessel CW et al.	BMJ 2011;343: d6423	Risk of venous thrombo-embolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001–9	939 3rd gen and 167 levo cases. Risk for 3rd gen OCs compared to levo was around 2	Cohort study of current OC use. Excluded women with prior thrombotic events, recent pregnancy, cancer and surgery, Denmark 2001–2009 aged 15–49

One theory that was proposed to explain the higher risk in third versus second generation OC users was that biased prescribing was responsible. This theory, however, was not supported by later results where third generation OC users were still at higher risk compared to second generation pill users after the publication of the first studies in 1995 (Jick et al. 2000; Lidegaard et al. 2011). If the early studies had been subject to the proposed biased prescribing, where less healthy women received the third generation pills because they were thought to be less harmful, then prescribing should have changed after the initial studies were published. If prescribing had been biased, that is influenced by perceived VTE risk and health of the OC user then, after the 1995 publications, the women with risk factors should have been preferentially prescribed second generation OCs. Thus if prescribing bias were the explanation for the results, this would have resulted in lower VTE risks in users of third generation OCs. In fact, later studies continued to find increased risks of VTE among users of third generation OCs (Jick et al. 2000; Lidegaard et al. 2011) suggesting that prescribing bias did not explain the results.

There continues to be some disagreement about the magnitude of the risk of third compared to second generation OCs, but over time general agreement has emerged that there is an increased risk for third compared to second generation OCs of around twofold more or less (Kemmeren et al. 2001). While use of third generation OCs declined ORs for VTE in third versus second generation OCs did not change, despite the reduced use and possibility of selective prescribing.

Cyproterone-Containing and Progestin-Only Oral Contraceptives

In the 1990s cyproterone-containing OCs were marketed. These OCs were also found to increase the risk of VTE compared to second generation OCs and in some countries they are no longer marketed for contraception (Lidegaard et al. 2011; Vasilakis-Scaramozza and Jick 2001; Seaman et al. 2004). These OCs are still marketed and licensed for contraception in the UK, NZ and other markets, but it is not a first line indication (acne is the indication). In practice these OCs may be prescribed to women with acne who also need contraception, but this is also decreasing as better treatments for acne become available.

There has been little controversy about the finding that cyproterone-containing OCs increase the risk of VTE. Conversely, progestin-only OCs (known as the progesterone-only pill (POP) in many countries – see Chap. 5) have been shown to confer no increase in risk of VTE when compared to non-users of OCs (Lidegaard et al. 2011; Vasilakis et al. 1999). Table 6.3 summarise the studies performed to investigate the risk of VTE with cyproterone-containing and progestin-only OCs.

Women who have contra- indications for combined oral contraceptive may be prescribed these progestin only pills. It should be noted however that the effectiveness of the progestin-only pills is lower than for combined OCs (see Chap. 5).

Table 6.3 Summary of cyproterone and progesterone-only OC studies of VTE

Authors	Citation	Title	Results
Cyproterone OCs			
Vasilakis-Scaramozza, Jick H	Lancet 2001;358:1427–9	Risk of VTE with cyproterone or levonorgestrel contraceptives	OR for cyproterone vs levo OCs was 3.9 (95 % CI 1.1–13.4) adjusted for BMI, smoking, polycystic ovaries, hirsutism, acne
Lidegaard O, Nielsin LH, Wessel CW et al. (Danish cohort study, 2001–9)	BMJ 2011;343: d6423	Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses	Risk was around twofold compared to levonorgestrel OCs and 4.1 (95 % CI 3.37–4.98) compared to non-use adjusted for age, year and level of education
Seaman HE, de Vries CS, Farmer RDT	Pharmocoepi and Drug Safety 2004;13:427–36	Venous thromboembolism associated with cyproterone acetate in combination with ethinylestradiol (Dianette): observational studies using the UK General Practice Research Data Base	RR was around 2.5 for Cyp OCs vs other OCs in women with and without acne, hirsutism, PCOS. No exclusions to case definition. OR for c-c analysis 1.71
Progesterone only OCs			
Vasilakis C et al.	Lancet 1999;354:1610–1611	Risk of idiopathic venous thromboembolism in users of progestagens alone	OR for contraceptive progestins vs no use was 1.3 (95 % CI 0.3–6.8)
Lidegaard O, Nielsin LH, Wessel CW et al. Danish cohort study, 2001–9	BMJ 2011;343: d6423	Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses	ORs <1.0 for different progestogens (norethisterone, desogestrel and levonorgestrel) adjusted for age, year and level of education

Arrival of the Next Generation of OCs: the 2000s and *Drospirenone OCs*

The 2000s saw a new generation of OCs come to market. There was hope, because of the antiandrogenic properties of drospirenone, that drospirenone-containing OC (Yaz® and Yasmin®) would be safer in relation to VTE and confer other benefits to women such as better control of pre-menstrual syndrome and acne (Sitruk-Ware 2004; Rubig 2003). The new OC formulation quickly became popular among young women in United States and Europe and use of the drug increased rapidly.

Unfortunately so did the reports of VTE. The earliest studies of VTE in users of drospirenone-containing OCs provided reassurance that the risk of the newer OC was similar to that of the older second generation OCs (Heineman and Dinger 2004; Dinger et al. 2007; Seeger et al. 2007; Dinger et al. 2010). However, later studies yielded risks ranging from around 1.5 to over 3.0, depending on the study methods (Lidegaard et al. 2009; van Hylckama Vliegl et al. 2009; Jick and Hernandez 2011; Parkin et al. 2011; Gronich et al. 2011).

A careful review of these studies reveals important differences in the case and exposure definitions. The first studies included all cases of VTE including those with prior VTE, cardiovascular disease and other proximate causes such as surgery, lower limb injury, and trauma (non-idiopathic cases) (Heineman and Dinger 2004; Dinger et al. 2007). As has been demonstrated, inclusion of these cases can bias and dilute any differences in effects between different OCs. These studies may have also included non-current OC users, but this information cannot be ascertained from the published literature. Later studies applied different degrees of exclusion to the case definitions and the risk of drospirenone compared to levonorgestrel pills increased with the increasing number of exclusions. The Seeger study (Seeger et al. 2007) included all VTE cases except for those with a prior VTE, and included all users of all OCs other than drospirenone OCs in the reference group including women who had taken third generation OCs. All these factors would explain the null result for drospirenone OCs.

The studies of Lidegaard and van Hylckama Vliegl (Lidegaard et al. 2009; van Hylckama Vliegl et al. 2009) excluded women with prior cancer and cardiovascular disease and recent pregnancy, and results yielded small increased risks in drospirenone OC users compared to levonorgestrel OCs. The studies of Parkin and Jick (Jick and Hernandez 2011; Parkin et al. 2011) excluded women with these factors in addition to other exclusions such as recent trauma, surgery, limb injury, and women with other chronic diseases. The effects were strongest in the latter two studies (Jick and Hernandez 2011; Parkin et al. 2011). It is important to recognize the subtle differences in case definition when assessing these studies and to understand how they impact the results. When attempting to assess the presence of adverse drug effects it is important to identify the healthiest population possible so that the presence and magnitude of risk can be established without concern for bias, confounding and effect modification. Studies restricted to idiopathic cases thus yield the most interpretable and informative results. To estimate the risk of VTE in women with risk factors and other proximate causes, a clinical trial may be the only way to obtain unbiased results and it is unlikely that such a study will ever be conducted. At this time there seems to be some acceptance that there is a higher risk of VTE conferred by drospirenone-containing OCs but the magnitude of the risk is not yet established (Table 6.4).

Table 6.4 Summary of drospirenone-containing OC studies of VTE

Authors	Citation	Title	Results	Exposure and case details
Heineman LA, Dinger J	Drug Saf 2004;27:1001–18	Safety of a new oral contraceptive containing drospirenone	12 VTEs on DRSP 11 on levo RR for DRSP vs levo = 1.0	Drospirenone vs levonorgestrel users. Timing of use not defined. All cases included regardless of prior history
Dinger JC, Heinemann LA, Kühl-Habich D	Contraception. 2007; 75(5):344–54	The safety of a drospirenone containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation	26 VTEs on DRSP 25 on Levo. 52 other. HR = 1.0	Drospirenone vs levonorgestrel timing of use not defined. All cases included regardless of prior history of VTE or other comorbidities
Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM	Obstet Gynecol. 2007;110(3):587–93	Risk of thromboembolism in women taking ethinylestradiol/ and other oral contraceptives	14 VTEs on DRSP, 30 on Levo current users, HR = 1.0	Drospirenone vs all other OCs. current OC users. Included all first time VTEs: no exclusions
Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C	BMJ. 2009; 339: b2890	Hormonal contraception and risk of venous thromboembolism: national follow-up study	2045 VTEs; 103 on DRSP, 201 on Levo, RR 1.64	Multiple comparisons including drospirenone vs levonorgestrel current OC users. Excluded some non-idiopathic cases
van Hylckama VA, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR	BMJ. 2009 13;339: b2921	The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study	1103 VTEs; current users 19 on DRSP 485 on Levo OR = 1.7	Drospirenone vs levonorgestrel current OC users. Excluded some non-idiopathic cases
Dinger J, Assman A,	J FamPlannReprod Health Care, 2010;36:123–9	Risk of venous thromboembolism and the use of	85 VTEs 25 on DRSP and 60 on	Drospirenone vs levonorgestrel timing of use

(continued)

Table 6.4 (continued)

Authors	Citation	Title	Results	Exposure and case details
Mohner S, Minh TD		dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study	Levo; DRSP vs Levo OR = 1.0	not defined. All cases included regardless of prior history of VTE or other comorbidities
Jick SS, Hernandez R	BMJ 2011;340: d2151	Risk of non-fatal venous thromboembolism in women using oral contraceptive containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data	121 VTEs on DRSP, 65 on Levo OR = 2.4	Drospireonone vs levonorgestrel current OC users. Excluded non-idiopathic cases
Parkin L, Sharples K, Hernandez R, Jick SS	BMJ 2011;340: d2139	Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on the UK General Practice Research Database	17 VTEs on DRSP, 44 on Levo OR = 3.3	Drospirenone vs levonorgestrel current OC users. Excluded non-idiopathic cases
Lidegaard O, Nielson LH, Skovlund CW, Skjeldestad FE, Lokkegaard E	BMJ 2011;343: d6423	Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study 2001–9	196 VTEs on DRSP, and 123 on Levo OR = 2.2	Multiple comparisons including drospirenone vs levonorgestrel current OC users. Some VTE non-idiopathic cases excluded
Gronich N, Lavi I, Rennert G	Can Med Assoc J 2011;183:E1319–25	Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-bases cohort study	99 VTEs on DRSP, N not reported for second generation OC OR =1.65	Women aged 12–50. Current OC use drospirenone vs second generation OCs. Included all first time VTEs: no exclusions

Recent Study of Currently Available OCs

In a large Danish cohort study using data from Danish national registries of women aged 15–49 in 1995–2009 (Lidegaard et al. 2011), authors identified 4,307 cases of first time VTE after excluding women at high risk for VTE (those with prior CVD, cancers and coagulation disorders) and cases that occurred post sterilization, or during pregnancy or postpartum. Current OC exposure was evaluated according to progestin type, timing of use, duration, dose of estrogen, and prior OC use, compared to non-exposure or to levonorgestrel-OC exposure. OCs containing desogestrel, gestodene, cyproterone and drospirenone all had increased risks of around twofold for VTE compared to levonorgestrel OCs. These results are consistent with studies that carefully selected idiopathic cases, defined exposure as current use, and compared the OC risk in relation to levonorgestrel OCs (WHO 1995; Jick et al. 1995, 2000; Bloemenkamp et al. 1995; Kemmeren et al. 2001; Lidegaard et al. 2009, 2011; Vasilakis-Scaramozza and Jick 2001; van Hylckama Vliegl et al. 2009; Jick and Hernandez 2011; Parkin et al. 2011; Gronich et al. 2011).

The use of the Danish data enabled the researchers to identify a large number of women in a well-defined population, to identify virtually all cases of VTE, and to ascertain complete information on OC exposure with a common reference group. These factors distinguish it from earlier studies that did not find differences in the effects of the various OCs (Lidegaard et al. 1998; Spitzer et al. 1996; Dinger et al. 2007, 2010; Seeger et al. 2007). However, it should be noted that the authors did include some cases with other proximate causes of VTE, such as women with recent surgery or lower limb injury. Inclusion of these non-idiopathic cases would tend to dilute the relative effects of the various contraceptives since other causes would likely overwhelm any incremental differences in risk. Thus it is possible that the true relative risks are higher than those presented in the Danish study. While only some non-idiopathic cases were excluded the authors did exclude many cases who were at high risk of VTE and whose medical history could have confounded the OC-VTE relation.

How to Evaluate Risks Between Various OC Formulations

In order to critically read and evaluate the epidemiological literature there are some basic methods with which one should be familiar. There are two main study designs in the area of observational research (non-intervention studies); case-control and cohort studies (Rothman et al. 2008). In case-control studies cases of an outcome (VTE in these studies) are identified and compared to controls (non-cases) with respect to an exposure (OCs in these studies). If there is more exposure in the cases than the controls then it is said that the exposure increases the risk of the outcome. In a cohort study, a group of people exposed to, for example OCs, is followed forward to identify occurrences of a new outcome such as VTE and a rate is

calculated. This rate is compared to the rate of VTE in people with no OC exposure. If the rate is higher in the exposed group compared to the unexposed group then it is said that the exposure increases the risk of the outcome under study.

In both study designs it is of utmost importance to ensure that the cases and controls or exposed and unexposed, are as similar as possible, so that other factors do not explain the difference in the exposure. So for example, the cases and controls or exposed and unexposed patients must all have the same age distribution so that one does not compare the rate of an outcome in non-comparable age groups since the rate of most outcomes varies greatly across different ages. The comparison of different studies of OCs and VTE must be made with careful consideration to the differences in study methods. The most important components to consider are the definition of exposure, the definition of outcome, and the selection of the comparison or referent group.

Exposure How is OC exposure defined? It has been shown that current OC use confers an increased risk of VTE, but that the risk diminishes quickly upon discontinuation of the pill. Thus the relevant exposure definition for studies of OCs in relation to VTE is current use. Also, there are many OC formulations. It is important to be sure that similar formulations are compared and studied.

Case definition The definition of the outcome must be clearly described and differences between studies should be identified. There are several important proximate causes of and risk factors for VTE. The most common causes of VTE in healthy young women (which describes most OC users), are recent pregnancy, surgery, lower limb injury, and major trauma. Important risk factors include a history of previous VTE, cardiovascular disease, renal failure, or auto immune disease. Thus it is important to exclude women with any of these proximate causes or strong risk factors from studies of drugs in relation to VTE. Inclusion of people with these important risk factors could bias the study result in either direction depending on the risk factor, the drug and the outcome. In the case of OCs and VTE, women with a history of VTE or cardiovascular disease would be unlikely to be prescribed an OC thus one could find a spurious protective effect of OC use in relation to a non-exposed referent if these women were included in a study. The inclusion of non-idiopathic cases (those with another proximate cause of the VTE) could bias the true result toward the null, since the incremental effect of either OC in women with other proximate causes (which could comprise a large proportion of all cases), is likely to be minimal.

Selection of the referent group In some published studies of drospirenone in relation to VTE, third generation OCs were included in the comparison group, some used levonorgestrel and others had a non-exposed referent. Each of these comparators confers a different risk for VTE, thus the relative risk of another OC, such as the drospirenone OC, will vary according to which OC it is compared. When compared to the lowest risk OC (a second generation pill) the *relative* risk is greater than when compared to a third generation OC, but not as great as when compared to non-users of OCs. Third-generation OCs have been shown to increase the risk of

VTE compared to levonorgestrel OCs, consequently, a comparator comprised of these OCs would lead to a lower relative risk of drospirenone OCs. Conversely, if the comparison group was made up of women who did not use any OC the effect measure, or relative risk, would be greater for drospirenone OC users. In other words, one must be aware of the referent group in each study to properly interpret the results. In epidemiology one must always ask: compared to what?

Regulatory Responses to the Risk of VTE with Oral Contraceptives

In 1995, before the three studies were published that found risks of around twofold for third generation compared to second generation OCs, the UK's Medicines Control Agency (MCA) sent a "Dear Doctor letter" to all GPs in the UK, warning of the increased risk of third compared to second generation OCs. The UK Committee on Safety of Medicines (CSM) recommended switching women from third generation pills to other OCs and warned that women should consult their Doctors "to see if a change of pill is necessary." (http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON019572; The pharma letter 1995) In the absence of published data to provide context, many women in the UK panicked and stopped taking the third generation pills. In the UK use of third generation OCs decreased by more than 80 % and because these pills were so widely used at that time, the supply of alternate pills was not sufficient to make up the deficit created by the pill's discontinuation and some women were left with no OC replacement. Data suggest that many unplanned pregnancies resulted from this unfortunate series of events (Furedi 1999). It is interesting to note that the UK CSM recommendation was later reversed. The UK "Pill Scare" is discussed further in Chap. 19 which addresses communicating the risks and benefits of women's medicines.

Regulatory action in other countries was not so dramatic and did not lead to mass discontinuation of the third generation pills or sudden material changes in OC prescribing. In Germany where the regulatory authorities had already recommended against taking third generation pills, the Federal Institute for Pharmaceutical and Medical Products issued a warning in October 1995 and prohibited prescribing of third generation pills to first time pill users under the age of 30. This action was reversed upon further review (BBC News Health U turn over pill scare). In the United States the authorities did not take immediate action. Norway followed the UK's actions and in France the Agence du Medicament sent out a 'communique de press' in October 1995 which summarized the results of the three studies, and said that they and the European Agency would review the evidence. In the meantime they warned against stopping current OCs. The EMEA did not take further action as they thought the studies were flawed (http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/12/WC500017336.pdf).

In the late 2000s after several studies found increased risks of VTE in drospirenone-containing pills, the Food and Drug Administration (FDA) in the United States added a warning to the label of drospirenone pills (http://www.fda.gov/drugs/drugsafety/ucm299305.htm). Similar warnings were added in Canada (http://www.bayer.ca/files/YASMIN-PT3-ENG-03FEB2014-169558.pdf?#), and other European countries (http://www.yazontrial.com/2010/04/yasmin-label-change-in-the-european-union-eu/).

The only pills to have been removed from the market in some countries due to regulatory action, rather than due to improvements in formulations, have been the cyproterone-containing pills. It is important to note that while some OCs have higher risks of VTE compared to others, the risk is low for all OCs and lower than the risk of VTE in pregnancy.

Clinical Considerations

Clinical issues for prescribing oral contraceptives are discussed in detail in Chap. 5. Some key clinical issues relating to the risk of VTE with OCs are summarised here as follows:

- Whilst the absolute risk of VTE with all OCs is very low, this is a well-recognised, serious and potentially fatal adverse effect of these medicines.
- Prescribers should take the relevant steps to identify women at increased risk of VTE (take a careful history from each woman) and undertake appropriate risk management.
- Prescribers should identify women who should not be prescribed a combined oral contraceptive (COC) due to the risk of VTE and prescribing should be in accordance with the relevant Medical Eligibility Criteria and international and local guidelines (see Chap. 5).
- For women who should not take an OC due to a higher risk of VTE, prescribers should find another suitable form of contraception.
- Women requesting oral contraceptives should be advised about the risk of VTE: explain it is rare, but may be serious or fatal if it occurs.
- Put the risks into context with the benefits of OCs and the higher risk of VTE in pregnancy.
- Explain that the increased risk of VTE with OCs is highest when the pill is first started and returns to baseline after the pill is stopped.
- OCs should not be stopped without first consulting a doctor (or other health professional) as the woman will then be at risk of becoming pregnant if no other form of contraception is used.
- Explain the risks factually and in terms women can understand.
- Prescribe the OC with the lowest risk of VTE i.e. a second generation pill (remember efficacy is similar between different brands of combined OCs).
- Inform women of the signs and symptoms of VTE (e.g. unilateral swollen leg or acute breathlessness) and encourage early presentation to medical services.

Conclusions

That OCs increase the risk of venous (and arterial) thrombosis has been well recognised and well researched since OCs were first marketed. Since the earliest reporting of the higher risk of VTE in women taking COCs, the doses and formulations of both the oestrogen and progestin components of COCs have changed, initially resulting in a decrease in the risk of thrombotic events and later leading to differences in the risk between COCs. There are also well recognized risks factors for VTE that should be considered before choosing to take COCs. A history of cardiovascular disease and obesity are two important risk factors, as are a family history of VTE and immobility. Presence of certain chronic diseases such as cancer, kidney disease and autoimmune diseases may also increase a woman's risk of VTE and thus OC use should be carefully considered in affected women.

Despite the increased risk of VTE in COCs users and the higher risk of drospirenone and third generation COCs, VTE is rare in healthy young women and the risks of VTE in pregnancy and postpartum are substantially higher than in OC users. Thus, preventing unintended pregnancies must remain a high priority and women should have multiple contraceptive options and be informed of each of their risks. Regardless of whether the thrombotic risk of third generation and drospirenone COCs compared to levonorgestrel COCs is increased by 1.5 or 3-fold, the absolute risk is still low.

Table 6.5 Summary of approximate VTE rates with combined oral contraceptive pills

Exposure category	**Rate of all VTE[a] per 10,000 women aged < 35**
Women **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a COC containing **levonorgestrel, norethisterone** or **norgestimate**	About 5–7 out of 10,000 women
Women using a COC containing **etonogestrel** or **norelgestromin**	About 6–12 out of 10,000 women
Women using a COC containing **drospirenone, gestodene** or **desogestrel**	About 9–12 out of 10,000 women
Women using a COC containing **chlormadinone, dienogest** or **nomegestrol**	Not yet known

Source: European Medicines Agency report 2013

[a]All VTE include VTEs in women with risk factors and other proximate causes such as recent surgery, pregnancy and trauma

Take Home Messages

- The risk of VTE in healthy young women (age 35 years or younger) is very low (see Table 6.5 above)
- Combined oral contraceptives (COCs) increase the risk of VTE and this risk varies according to the oestrogen dose and type of progestin (see Table 6.5 above).
- Second generation COCs have the lowest risk of VTE of all currently available COCs, increasing the risk (compared to no use) by about three-fold (see Table 6.5 above).
- Third generation and drosperinone COCs have a 1.5–3 fold higher risk of VTE than second generation pills (see Table 6.5 above).
- Despite the increased risk of VTE in COC users, the risk is still lower than in pregnancy and the post-partum period. In pregnancy the risk of VTE is 7–27 per 10,000 women.
- Other risk factors also increase the risk of VTE, including family history of VTE, cardiovascular disease, obesity and immobility.
- If there are no contraindications to COC use, doctors should prescribe a second generation pill initially
- Explain the risks (and benefits) of COCs factually and in terms each woman can understand
- Advise women about the signs and symptoms of VTE and that if these occur they should seek medical help immediately.
- Also explain that stopping OCs will result in loss of contraceptive protection and pregnancy may occur unless alternative contraceptive methods are used.
- The increased risk of VTE returns to baseline after cessation of therapy.

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Chapter 7
Emergency Contraception

Katarina Ilic

Introduction

Unintended pregnancy and particularly teenage pregnancy is a huge global problem. Of the estimated 210 million pregnancies a year, 38 % are unplanned and 22 % are terminated by an abortion (http://www.guttmacher.org/media/nr/abortww_nr.html, Kost and Henshaw 2014). In the US, about one million teenage girls, 11 % of all girls aged 15–19 (112 per 1,000) and 20 % of those who have had sexual intercourse (204 per 1,000) become pregnant each year. Teenage pregnancy rates are much higher in the United States (US) than many other developed countries – twice as high as in England and Wales, France and Canada; and nine times higher than in the Netherlands or Japan (http://kff.org/womens-health-policy/emergency-contraception/).

Emergency contraception (EC) is the use of hormonal emergency contraceptive pills (ECPs) or an intrauterine device after unprotected sexual intercourse (UPSI) to prevent an unintended pregnancy (Daniels et al. 2013). Emergency contraception (EC) has been studied and used for over 40 years. Although the abortion rate is high in many countries and despite the serious consequences of unintended pregnancy, the percentage of women who use EC has been reported as low. For example, in the US in the early 2000s, only 1.3 % of women who had an abortion reported taking EC to prevent pregnancy; and although 43 % of women knew EC was available, only 6 % of women had ever used EC (Kaiser 2003; Jones et al. 2002). In a survey conducted by the US Center for Disease Control and Prevention (CDC 2006–2008) (Daniels et al. 2013), 9.7 % of women aged 15–44 reported ever having used EC. Older women used emergency contraception less than younger women, with 5.0 % of women aged 30–44 having ever used it. Nearly 1 in 4 (23 %) sexually experienced women aged 20–24 never used emergency contraception, compared to

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16 % of women aged 25–29 and 14 % of women aged 15–19. A larger proportion of never-married women (19 %; almost 1 in 5) had never used emergency contraception compared to women who were cohabiting (14 %; 1 in 7 cohabiting women) or were currently or formerly married (5.7 %; 1 in 20 women). The percentage of women who had ever used emergency contraception at least once increased from 4 % in 2002 to 10 % in 2006–2008 (Mosher and Jones 2010).

Indications for Use of Emergency Contraception

Emergency contraception or post-coital contraception is a 'backup' method for contraceptive emergencies and is designed to prevent pregnancy after unplanned sexual intercourse or when a regular method of contraception fails. EC may be administered in the following situations: when contraception was not used; during exposure to suspected teratogens (cytotoxic drugs, viruses, live vaccines); after forced intercourse or rape, or in the event of contraception failure. Contraception failure may include the following situations (Katzman et al. 2010):

- Condom breakage, slippage, or incorrect use;
- Missed combined oral contraceptive pills (see Chap. 5);
- Taking the progestogen-only pill more than 3 h late (see Chap. 5);
- The start of combined hormonal contraception is delayed;
- The progestogen-only injection is given more than 2 weeks late;
- The transdermal contraceptive patch is detached for 24 h or longer during week 1, or detachment of the transdermal contraceptive patch for 72 h or longer during week 2 or 3;
- The vaginal contraceptive ring is expelled or removed for 3 h or longer during week 1, or removed for 72 h or longer during week 2 or 3;
- The vaginal ring is left in for more than 5 weeks in a row;
- When hormonal contraceptives are used with inducers of microsomal liver enzymes concomitantly or in the last month.

Types of Emergency Contraception

There are three types of emergency contraceptive pills: (i) combined, which contain estrogen and progestogen (Yuzpe method), (ii) progestogen-only emergency contraceptive pills (contain only levonorgestrel) and (iii) anti-progestin ECPs i.e. a progesterone receptor modulator (ulipristal-acetate) or mifepristone. Nowadays the Yuzpe method (combined contraceptive pills) has been mostly replaced by more effective and safer progestogen-only ECPs. Besides ECPs, a copper intrauterine contraceptive device – (IUD) may also be used for emergency contraception. Each of these methods will be described in this section.

Yuzpe Method

The Yuzpe method (a combination of estrogen and progestogen started within 72 h of sexual intercourse) has now been superseded by the progestogen-only hormonal regimen. This method was named after Dr. Albert Yuzpe from Canada who published the first studies demonstrating the method's safety and efficacy (Yuzpe et al. 1974). The levels of estrogen and progesterone in combined pills used for the Yuzpe method are higher than those included in daily combined oral contraceptive pills (see Chap. 5). The pills are administered in two doses with a 12 h interval, and are effective if the first dose is administered up to 72 h after unprotected intercourse (Westhoff 2003).

When ECP products are not available, combined progestogen and estrogen pills for regular contraception can be used as emergency contraception in two doses with a 12 h interval, with each dose consisting of 4–5 tablets depending on the brand. For example, for regular oral contraceptives containing ethinyl estradiol 120 μg and LNG 0.60 mg, four pills per dose would be required for emergency post-coital use, whilst for pills containing 100 μg/0.50 mg ethinyl estradiol/LNG, five pills per dose would be needed for emergency contraception (FDA 1997).

Levonorgestrel (LNG) Methods

Levonorgestrel (LNG) is a safer, more effective method of EC (see Effectiveness section below) and less frequently causes nausea and vomiting than the combined ECP (Rodriguez et al. 2013). In the US, the LNG ECP product Plan B®, was approved by the Food and Drug Administration (FDA) in 1999 and in other markets products such as Postinor® and Levonelle® were approved. These products are administered as two 0.75 mg LNG pills to be taken 12 h apart: the first dose should be administered as soon as possible after unprotected intercourse, (72 h at the latest) and the second dose 12 h after the first. A single 1.5 mg dose of levonorgestrel has been shown to be equally effective as the two dose regimen, while the adverse effects are similar (von Hertzen et al. 2002; Ngai et al. 2004; Johansson et al. 2002). Both the two-dose and single dose LNG ECP products are more effective when taken as early as possible after unprotected intercourse. Due to the benefits shown in studies, better compliance and simpler usage, levonorgestrel is increasingly dominating the market as a single-dose formulation of 1.5 mg.

Ulipristal Acetate

Ulipristal acetate (UPA) is a selective progesterone receptor modulator. It has been marketed for EC in Europe since 2009 and in the USA since 2010. UPA was shown

in two large randomized controlled trials (RCTs) (Creinin et al. 2006; Glasier et al. 2010) to be as effective as LNG for EC when administered within 72 h of unprotected sexual intercourse. Meta-analysis on the combined data from results of these two RCTs indicated significantly lower failure rate of UPA compared to LNG (1.36 % (22/1,617) vs. 2.15 % (35/1,625), $p = 0.046$). It has also been shown that the efficacy of UPA does not decrease if the time of administration after UPSI increases up to 120 h (Glasier et al. 2010; Moreau and Trussell 2012). UPA is approved in the US as a single dose of 30 mg, under the trade name Ella® or EllaOne®, which can be administered within 120 h of UPSI.

Mifepristone

Mifepristone is a progesterone receptor antagonist approved as a 600 mg dose for use in many countries for early first-trimester medical abortion and a 200 mg dose which has proven to be equally effective as an abortifacient (Schaff et al. 1999; Raymond et al. 2013). For emergency contraception, a WHO study confirmed that lower doses of mifepristone (50 and 10 mg) had similar efficacy to a 600 mg dose of mifepristone (WHO Task Force et al. 2000). However, because mifepristone is also used to induce medical abortion, and due to various social and political reasons thus far in some countries, it has only been approved for emergency contraception in China, Vietnam, Russia and Armenia in a dose 10–25 mg (Trussell and Raymond 2014; http://www.cecinfo.org/country-by-country-information).

Copper Intrauterine Contraceptive Device

IUDs are usually used as a primary contraceptive method and are considered appropriate for the majority of women, including nulliparous women and adolescents (see Chap. 8). However, an IUD may also be used as emergency contraception when hormonal contraception is contraindicated, when more than 5 days after sexual intercourse are passed, or when a women is taking medicines that interact with emergency contraceptive pills. The copper intrauterine contraceptive device (IUD) is the most effective form of emergency contraception (Wu et al. 2010). In the UK the Faculty of Sexual and Reproductive Health (FSRH) recommend it is offered to all women (FSRH Guidance 2012).

If the time of ovulation is estimated, an IUD can be inserted within 7 days following unprotected intercourse (FSRH Guidance 2012). WHO guidance states that an IUD may be inserted up to the 12th day of the menstrual cycle with no restrictions, or at any other time in the cycle if it is certain that the woman is not pregnant (WHO et al. 2011). Women may keep a copper IUD (ParaGard®) as a long-term contraceptive method for up to 10 years after placement.

Side effects of the copper-containing IUD when used for EC are uncommon and may include menstrual cramping or increased menstrual flow (Milsom et al. 1990; Larsson et al. 1993). In women with sexually transmitted infections, IUD insertion can cause pelvic infection in the first 3 weeks after insertion and infertility if left untreated (Farley et al. 1992). However, in healthy nulligravid women, use of an IUD is not associated with an increased risk of infertility (Hubacher et al. 2001) (see Chap. 8).

The availability of the copper IUD (Harper et al. 2008) for EC may be limited as it involves placement in a clinical setting by a trained healthcare professional. Interestingly, a survey among clinicians (n = 1,246; response rate 65 %) in a California State family planning program showed that although over 93 % of obstetrician–gynecologists were skilled in inserting the copper IUD, they were no more likely to have recommended it for emergency contraception than other physicians or advance practice clinicians (Harper et al. 2012).

Mechanism of Action of Emergency Contraceptives

Emergency contraceptive pills prevent pregnancy through various mechanisms (Gemzell-Danielsson and Marions 2004; Gemzell-Danielsson et al. 2014). Depending on the time they are taken, ECPs may inhibit or delay ovulation and/or block the migration of the sperm and fertilized egg. Several clinical studies showed that combined ECPs inhibit or delay ovulation, which is their most likely mechanism of action (Swahn et al. 1996; Rowlands et al. 1986; Croxatto et al. 2002).

Levonorgestrel emergency contraception has also been shown to inhibit or delay ovulation (Durand et al. 2001). The LNG ECP inhibits ovulation for 5–7 days, by which time any sperm in the reproductive tract will become non-viable (Croxatto et al. 2004). Administration of LNG ECPs immediately after unprotected intercourse and prior to ovulation has an effect on the ovulation process and the function of corpus luteum, the latter of which is required for retaining pregnancy (Müller et al. 2003; FSRH Guidance 2012). It has been shown that the administration of a two-dose regimen of levonorgestrel ECPs, during the medial luteal phase at the expected implantation time has no effect on morphology and development of the endometrium (Gemzell-Danielsson and Marions 2004). It has been demonstrated that LNG ECPs interfere with sperm motility by thickening cervical mucus (Kesseru et al. 1974, 1975). However, in vitro studies found that LNG in doses used for ECPs does not have direct effect on sperm function (Brito et al. 2005; Yeung et al. 2002).

Two studies estimating the effectiveness of LNG-ECPs provided evidence that this method of EC is unable to prevent ovulation (Novikova et al. 2007; Noé et al. 2011). In these studies the day of ovulation was calculated based on the blood level of hormones. In a pilot study (Novikova et al. 2007) 99 women received LNG 1.5 mg. Three women who had unprotected intercourse between one day before ovulation (‘day 1’) and ovulation day (‘day 0’) and took the ECP on day

2 after ovulation became pregnant despite taking the ECP (pregnancy rate, 3.0 %). However, in women who had unprotected intercourse on days −5 to −2 of the fertile period, and took ECP (LNG) before or on the day of ovulation, no pregnancies were occurred, although four pregnancies could have been expected (Novikova et al. 2007).

In another study, among 103 women who took LNG-ECP before ovulation (days −5 to −1), 16 pregnancies were expected and no pregnancy occurred ($p < 0.0001$) and among 45 women who took LNG-EC on the day of ovulation (day 0) or thereafter, 8 pregnancies occurred and 8.7 were expected ($p = 1.00$) (Noé et al. 2011).

Analysis of pooled data from three randomized trials of emergency contraception regimens has shown that ulipristal acetate prevents ovulation more effectively than LNG (Brache et al. 2013). When taken immediately before ovulation is to occur, UPA postpones follicular rupture. The likely mechanism of UPA for EC is inhibition or delay of ovulation. In addition, alterations to endometrium that may affect implantation, may also contribute to efficacy (ELLA Prescribing Information 6/2014).

If mifepristone is used in the follicular phase of the menstrual cycle, it can inhibit ovulation and significantly delay the onset of menstrual bleeding. If mifepristone is administered in the first half of the luteal phase, it inhibits progesterone receptors in the endometrium. In that way, mifepristone interferes with the secretory function of the endometrium, thus impairing implantation (Ashok et al. 2001). In the medial or late luteal phase of the menstrual cycle, it causes the regression of the corpus luteum in 50 % of women (Glasier 1997).

There is more than one mechanism of action for IUDs as post-coital contraceptives. IUDs change the cervical mucus, which can block the passage of sperm. In addition, IUDs cause an inflammatory reaction in the endometrium, and thus exhibit an anti-implantation effect after fertilization (FSRH Guidance 2012). IUDS may also prevent implantation of a fertilized egg (Leung et al. 2010).

Effectiveness of Emergency Contraceptives

The results of a RCT which compared combined ECP and LNG EC indicated that the pregnancy rate was 3.2 % (95 % CI 2.2–4.5) among women assigned the Yuzpe regimen and 1.1 % (0.6–2.0) among those assigned LNG. The crude relative risk of pregnancy for LNG compared with the Yuzpe regimen was 0.46 (0.16–1.32). The fraction of prevented pregnancies was 76 % in the Yuzpe group and 89 % in the LNG group (WHO 1998).

The efficacy and safety of a single 1.5 mg LNG dose and two doses of LNG 0.75 mg administered 12-h apart for emergency contraception was compared in a double-blind, randomized, multicenter, multinational study (WHO Study 97902). In total 2,381 healthy women with a mean age of 27 years, who needed emergency contraception within 72 h of unprotected intercourse were randomly allocated to

receive either a single 1.5 mg LNG dose (Plan B One-Step®) or two doses of 0.75 mg LNG 12-h apart (Plan B®). In the Plan B One-Step® group, 16 pregnancies occurred in 1,198 women and in the Plan B® group 20 pregnancies occurred in 1,183 women. Among women receiving Plan B One-Step®, 84 % of 100 expected pregnancies were prevented while 79 % of 95 expected pregnancies were prevented among those women taking Plan B®. The expected pregnancy rate of 8 % (with no contraceptive use) was reduced to approximately 1 % with Plan B One-Step®. The relative risk (RR) of pregnancy for LNG 1.5 mg compared with LNG 2×0.75 mg taken 12 h apart was 0.83 (CI: 0.46–1.50) in the full intention to treat (ITT) population and it was concluded that both LNG regimens are similarly effective (CDER Application number 21–998).

UPA (taken as a single 30 mg dose) is the most efficient oral emergency contraceptive with an estimated effectiveness of 62–85 % and can be used up to 5 days after unprotected sexual intercourse. In a randomized, multicenter, non-inferiority trial, 2,221 women were randomly assigned to receive a single oral dose of 30 mg UPA (n = 1,104) or 1.5 mg LNG (n = 1,117). After administering ECP (UPA, n = 844; LNG, n = 852) within 72 h of sexual intercourse, there were 15 pregnancies in the ulipristal acetate group (1.8 %, 95 % CI 1.0–3.0) and 22 in the levonorgestrel group (2.6 %, 1.7–3.9) giving an odds ratio (OR) of 0.68 (95 % CI 0.35–1.31). In 203 women who received emergency contraception between 72 and 120 h after sexual intercourse, there were three pregnancies, all of which were in the levonorgestrel group (Glasier et al. 2010).

The effectiveness of mifepristone administered 72 h to 5 days after unprotected intercourse was studied in women for whom an IUD was not an option. The results of the study showed that the risk of pregnancy was 0.65 % with this method. By using probability of conception it was concluded that 85 % of expected pregnancies were prevented (Ashok et al. 2001). Randomized clinical studies have led to the conclusion that a single 10 mg dose of mifepristone is equally effective as the EC regimen consisting of levonorgestrel alone while the incidence of nausea and vomiting is lower (Westhoff 2003).

In a Cochrane review on interventions for emergency contraception, a meta-analysis was performed which included 55,666 women participating in controlled clinical trials (86/100 trials were conducted in China) and requesting EC following a single act of UPSI (Cheng et al. 2012). This indicated that low-dose mifepristone (<25 mg) was less effective than mid-dose mifepristone (25–50 mg) (25 trials; RR 0.73; 95 % CI 0.55 –0.97). However, both mid and low-dose mifepristone were significantly more effective than LNG. If only high-quality trials were included in this meta-analysis, there were no statistically significant differences in effectiveness between mid and low dose mifepristone (6 trials; RR 0.75; 95 % CI 0.50–1.10), while difference in effectiveness between mifepristone (mid and low dose) and LNG was marginal (4 trials; RR 0.70; 95 % CI 0.49–1.01) (Cheng et al. 2012). When compared with the Yuzpe regimen, the use of mifepristone is associated with a lower incidence of nausea and vomiting, but some users may experience delay of subsequent menstruation secondary to delayed follicular development and ovulation, which may sometimes be a cause for concern (Glasier et al. 1992).

Copper Intrauterine Contraceptive Device

When inserted within 5 days of unprotected sexual intercourse, a copper IUD reduces a woman's risk of pregnancy to 1 in 1,000 (Wu et al. 2010). To compare this figure with data for other methods of emergency contraception, for every 1,000 women who used an ECP after UPSI, at least 20 users of LNG or 14 users of UPA would face an unintended pregnancy (von Hertzen et al. 2002; Cheng et al. 2008).

Factors Affecting the Effectiveness of Emergency Contraception Pills

The efficacy and effectiveness of ECPs may be reduced due to delay in starting treatment, drug interactions, vomiting, and further acts of intercourse. There has also been discussion about the effect of body mass index (BMI) and weight on effectiveness of ECPs, but in July 2014 the European Medicine Agency (EMA) announced that the available data do not support reduced effectiveness of emergency contraceptives with increased body weight (EMA/440549/2014). All these issues will be discussed further in this section.

Time to Administration/Treatment Delay

The frequently used term 'morning after pill' is misleading, because combined ECPs and LNG are effective if taken up to 72 h after unprotected sexual intercourse (Piaggio et al. 1999) while UPA is effective if taken up to 120 h after unprotected sexual intercourse (Davis and Dun 2000). However, ECPs is appropriate term as there is some evidence that earlier administration of ECP increases efficacy. A early RCT which included 1998 women at 21 centers worldwide, of whom 997 were assigned the Yuzpe regimen and 1001 the LNG regimen, showed that the efficacy of both the Yuzpe and LNG method declined significantly ($p = 0.01$) after 49–72 h, compared to administration in the 0–24 h interval since unprotected coitus. Within each of these strata, the Yuzpe regimen was associated with a higher pregnancy rate than the levonorgestrel regimen (Task Force on Postovulatory Methods of Fertility Regulation 1998).

Data from an extensive randomized clinical study showed that the risk of pregnancy is lower than 1 % if a combined ECP or a LNG regimen is used within 12 h, compared to 3 % if the same regimen is used 61–72 h after unprotected intercourse (Westhoff 2003). This lead to the conclusion that both these methods of emergency contraception are more effective if administered as early as possible after unprotected intercourse. Combined ECPs and LNG remain moderately effective after 72–120 h, but the efficacy decreases as the time interval increases. While

LNG can be administered between 72 and 120 h, it is less effective, and is not currently labeled for use after 72 h.

A pooled analysis of four WHO trials examined the effect on pregnancy rates when the LNG ECP was delayed (Piaggio et al. 2011). In this analysis no reduction in effectiveness was shown with delayed administration up to 96 h, but there were limitations which must be considered when interpreting this finding. For example, in some studies it was unclear what the level of risk of pregnancy was for each woman and her partner for each episode of unprotected intercourse. Thus no observed drop in effectiveness could have been due to other factors. Given the evidence which is now available on mechanism of action of the LNG ECP (see section above) it seems likely that efficacy is reduced with time and guidance documents on the ECP support early administration (FSRH Guidance 2012).

Drug Interactions

Interactions may decrease the efficacy of hormonal contraceptives, by accelerating the metabolism of ethinyl estradiol and progesterone. An IUD is regarded as a good option for emergency contraception for women who take other medications that can cause interactions and decrease the efficacy of ECPs.

No specific drug-drug interaction studies for the Yuzpe regimen or LNG method alone have been conducted. Most information available concerning drug-drug interactions with the Yuzpe regimen or LNG method is extrapolated from the oral contraceptive literature. Ethinyl estradiol is metabolized by the cytochrome P450 (CYP) 3A4 enzyme pathway. Drugs known to induce CYP3A4 (e.g. phenytoin, primidone, barbiturates, carbamazepine, ethosuximide, topiramate, methosuximide, rifampin, griseofulvin, protease inhibitors and non-nucleoside reverse transcription inhibitors) can lead to decreased plasma ethinyl estradiol levels and may cause failure of emergency contraception (FSRH Guidance 2012). Use of St. John's Wort (Hypericum perforatum) may lead to interactions with oral contraceptives as this also induces CYP 3A4 (Hall et al. 2003). Women on liver enzyme-inducing drugs or who have stopped using them ($\leq$28 days ago) who require EC should be offered a copper IUD as efficacy is not affected by drugs.

Levonorgestrel also undergoes hepatic metabolism and is subject to increased clearance by microsomal liver enzyme induction. The label of Plan B One-step® (1.5 mg levonorgestrel) states potential changes in the progestin level in the plasma if the drug is used together with HIV protease inhibitors, or with non-nucleoside inhibitors of reverse transcriptase (FDA 2009). It is recommended that women taking liver enzyme inducing medicines take an increased dose of LNG. For example, if LNG 0.75 mg pills are used, a 2.25 mg dose (three tablets) should be taken up to 72 h after unprotected intercourse. This 50 % dosage increase is based on clinical practice and is not stated on the registration label. If single 1.5 mg doses of LNG are used, it is recommended that women taking liver enzyme inducing drugs who are ineligible or who do not wish an intrauterine method should take a single 3 mg dose (100 % dose

increase; i.e. two Levonelle® tablets) (outside product license) up to 72 h after unprotected intercourse. There are no published studies on any possible adverse effects of increased ECPs doses (FSRH Guidance 2012).

In June 2014, the FDA Center for Drug Evaluation and Research (CDER) approved Safety Labeling Changes for Ella® (30 mg ulipristal acetate) to state that as a CYP3A4 inducer, rifampin decreases the plasma concentration of Ella significantly. Coadministration of Ella should be avoided with drugs or herbal products that induce CYP3A4 (rifampin, phenytoin, carbamazepine, oxcarbamazepine, griseofulvin, barbiturates, bosentan, felbamate, topiramate, St. John's wort) as that may decrease effectiveness of Ella (ELLA Prescribing Information 6/2014).

Furthermore, CYP3A4 inhibitors (e.g. itraconazole, erythromycin, HIV protease inhibitors and grapefruit juice) may increase plasma levels of UPA (FSRH Guidance 2012). The Ella® (30 mg ulipristal acetate) product label states that inhibitors of CYP3A4, such as itraconasol and ketonasol, can cause the increase of UPA concentration in the plasma. Medications which increase gastrointestinal pH (proton pump inhibitors, H_2 antagonists, antacids) may reduce the plasma levels of ulipristal acetate and thus are not recommended for simultaneous use (FDA 2010).

Body Mass Index

Data from a meta-analysis of two RCTs comparing the efficacy of UPA with LNG (Glasier et al. 2010) indicated that the risk of pregnancy was greater for overweight (BMI = 25–29.9 kg/m^2) and obese women (BMI $\geq$30 kg/m^2) compared with normal or underweight women (BMI < 25 kg/m^2) whichever ECP was taken. However, for obese women, the risk was lower for UPA users (OR, 2.62; 95 % CI, 0.89–7.00; ns) than for those taking LNG (OR, 4.41; 95 % CI, 2.05–9.44, p = .0002). For both ECs in these studies, pregnancy risk was related to the cycle day of intercourse. Women who had intercourse the day before the estimated day of ovulation had a fourfold increased risk of pregnancy (OR, 4.42; 95 % CI, 2.33–8.20; p < .0001) compared with women having sex outside the fertile window.

However, the EMA recently concluded that the available data on BMI are limited and not robust enough (EMA/440549/2014). For emergency contraceptives containing LNG, the EMA considered the results from a meta-analysis of three WHO studies which primarily included African and Asian women and data from a meta-analysis of two published studies which primarily included Caucasian women (EMA/440549/2014). The conclusion was that these studies did not show a trend for reduced efficacy with increasing body weight and therefore emergency contraceptives can be used to prevent an unintended pregnancy in women of any weight or body mass index.

Vomiting

Vomiting may reduce the efficacy of ECPs due to decreased absorption. If vomiting occurs within 3 h after the administration of ELLA (ELLA Prescribing Information 6/2014) or within 2 h after the administration of Plan B One Step (Plan B One Step, Prescribing Information 7/2009) it is recommended that the dose should be repeated.

Further Acts of Intercourse

Women who had further acts of intercourse after taking an ECP had higher pregnancy rates than women without further intercourse (Yuzpe regimen 5.3 % [19/360] vs. 1.9 % [12/619]; LNG 1.6 % [6/372] vs. 0.8 % [5/602]) (WHO 1998). Data from a meta-analysis of two randomized controlled trials comparing the efficacy of ulipristal acetate (which may delay ovulation for some days) with levonorgestrel have shown that women who had further intercourse after they took ECPs had significantly higher likelihood to get pregnant compared to women who did not have further intercourse (OR, 95 % CI: LNG 7.3 [3.4–15.1]; UPA 5.6 [2.4–12.5]). For both methods, women who had unprotected intercourse after using EC were more likely to get pregnant than those who did not (Glasier et al. 2011).

Safety of Emergency Contraception

Contraindications for Emergency Contraception

The only absolute contraindication for the use of any emergency contraceptive is established or suspected pregnancy. In addition, for LNG/UPA prescribing information also states that contraindications to use include hypersensitivity to LNG/UPA or any of the other components (Plan B One Step, Prescribing Information 7/2009; ELLA Prescribing Information 6/2014).

Although there has been limited inclusion of under-18 s in the clinical trials of UPA, young age is not listed as a contraindication. Use of a copper IUD for emergency contraception (EC) carries the same contraindications as routine IUD insertion (see Chap. 8). Risk of sexually transmitted infections (STIs), previous ectopic pregnancy, young age and nulliparity are not contraindications to use.

Adverse Effects

The most frequent side effects of Yuzpe method and LNG are nausea and vomiting, abdominal pain, headache, dizziness, breast tenderness and fatigue. Nausea (23.1 vs. 50.5 %) and vomiting (5.6 vs. 18.8 %) as well as dizziness (16.7 vs. 11.2) and fatigue (28.5 vs. 16.9) are significantly less frequent with the levonorgestrel regimen than with the Yuzpe regimen ($p < 0.01$) (WHO 1998). If these effects occur, it is usually soon after the administration of ECPs and may last for 24 h.

The levonorgestrel ECP can cause changes in the menstrual cycle; however the changes experienced are transient and resolve in the next cycle (Gainer et al. 2006). In a study conducted by the WHO, 16 % of women had bleeding unrelated to expected menstruation within 7 days of ECP treatment. Menstrual bleeding occurred several days before or after the expected menstruation in 50 % of women (FSRH Guidance 2012). From post-marketing surveillance, skin and subcutaneous tissue disorders like rash, urticaria, and pruritus or face oedema have been reported but were very rare (Levonelle SPC 2014).

After use of UPA the most commonly (>10 %) reported adverse effects were headache (18 % overall), nausea (12 % overall), abdominal pain and upper abdominal pain (12 % overall) (ELLA Prescribing Information 6/2014). In addition, UPA delayed onset of menstruation by a mean of 2.1–2.8 days (Richardson and Maltz 2012).

Table 7.1 summarises data from worldwide spontaneous reports to Vigibase™, (the WHO global database) for emergency contraceptive pills (Ilic 2013):

The data in Table 7.1 indicate that the most frequently reported adverse events (besides unintended pregnancy) for ECPs were: menometrorrhagia, metrorrhagia and nausea (combined ECPs), irregular menstruation and nausea (LNG and UPA). VigiBase™ was established in 1968 and includes more than eight million reports at the present time (August 2014) from more than 100 countries and is the largest collection of spontaneous reporting drug safety information (http://www.umc-products.com/DynPage.aspx?id=73471&mn1=1108). The total number of reports for ethinylestradiol/ LNG, LNG and UPA reflects the time these ECPs have been on the market around the world. Thus UPA may be expected to have significantly fewer reports as it has only been approved since August 2010. Because of under reporting and lack of data on patients exposure (denominator is not known) in VigiBase™ the incidence of Adverse Drug Reactions (ADR) cannot be calculated (Ilic 2013).

Mifepristone causes similar side effects to other emergency contraceptives, including changes in menstrual bleeding patterns (Ashok et al. 2001). A disruption in the timing of the next menstrual period was the most frequently reported adverse effect for mifepristone (39 % and 42 %) in two studies (Webb et al. 1992; Glasier et al. 1992). The authors of one study reported a lower frequency of nausea (37 % vs. 70 %) and vomiting (3 % vs. 22 %) with mifepristone compared with the Yuzpe regimen. Breast tenderness occurred in a similar percentage of women in both groups (18 %) (Webb et al. 1992). In another study (Glasier et al. 1992) a similar pattern of adverse effects were identified.

Table 7.1 The most frequently reported adverse reactions of emergency contraceptive pills. Reports to VigiBase™ until Dec 31, 2011 (Ilic 2013)

Ethinylestradiol/LNG (14,515)[a]	**Levonorgestrel (4,578)**[a]	**Ulipristal EC (36)**[a]
Unintended pregnancy (1,369)	Menstruation irregular (1,952)	Unintended pregnancy (29)
Menometrorrhagia (1,179)	Unintended pregnancy (548)	Abortion induced (12)
Metrorrhagia (1,103)	Nausea (407)	Drug ineffective (8)
Nausea (998)	Pelvic pain (394)	Pregnancy after post coital contraception (4)
Headache (887)	Vomiting (286)	Maternal exposure during pregnancy (2)
DVT (801)	Drug ineffective (273)	Therapeutic response decreased (2)
Pulmonary embolism (742)	Menstruation delayed (240)	Abdominal pain (1)
Abdominal pain (491)	Abdominal pain (221)	Cardiovascular disorder (1)
Vomiting (350)	Dizziness (193)	Dizziness (1)
Amenorrhoea (296)	Headache (193)	Hypotension (1)
Total No. 23,441	**Total No. (8,139)**	**Total No. (66)**

[a]Numbers in the brackets represent total number of the reports in descending order of frequency
DVT-Deep Venous Thrombosis

The use of post-coital intrauterine devices may be associated with potential complications such as cramps, bleeding, infections and uterine perforation, although perforation is a rare event (see Chap. 8).

Risk in Pregnancy and Breastfeeding

The available evidence suggests that pregnancies occurring after LNG ECP failure were not associated with any major congenital malformations, pregnancy complications or other adverse pregnancy outcomes. A urine pregnancy test is generally not required before use of LNG EC. There is no evidence that LNG is teratogenic (Plan B Step One, Prescribing Information 7/2009).

Although there are no adequate and well controlled studies in pregnant women, Ella® belongs to FDA Pregnancy Category X (see Chap. 4) based on the results from animal data. The product information for Ella® states that pregnancy should be excluded before prescribing and if pregnancy cannot be excluded on the basis of history/physical examination, pregnancy testing should be performed (Ella Prescribing Information 2014).

Congenital malformations, perinatal complications and delivery circumstances were investigated in a prospective comparative cohort study including 332 pregnant women who had used LNG-EC during the conception cycle, matched to a group of 332 pregnant women without exposure to LNG. In the LNG EC group there were 31 pregnant women who miscarried within 14 weeks of gestation compared with 28 women in the comparison group and four malformations were found in each group. Between the two groups there were no statistically significant differences in the incidence of miscarriage or malformation or in the neonatal outcome. In the study group, both birth weight (3,416 vs. 3,345 g, $p = 0.040$) and the sex ratio of birth (boys/girls, 1.14 vs. 0.90, $p = 0.153$) were higher than in the comparison group (Zhang et al. 2009).

There are no restrictions on the use of LNG pills by breastfeeding women according to the WHO Medical Eligibility Criteria. Ulipristal acetate and its active metabolite were detected in breast milk of lactating women 5 days after administration of Ella® but the effect of this exposure on newborn infants has not been studied; thus risk to the breast-fed child cannot be excluded (Ella Prescribing Information 2014). Breastfeeding should be avoided for 1 week after use of EllaOne® (ELLA Prescribing Information 6/2014). To stimulate lactation during this time, it is advised that women express and discard the breast milk (FSRHC 2013).

Overall Risk Benefit of Emergency Contraception Pills

Reducing abortion rates is a priority worldwide. Given the consequences of unintended pregnancy, including the risks of medical and surgical abortion, there are no situations where the risks outweigh the benefits of being able to prevent inadvertent pregnancy. Levonorgestrel ECPs have been used for more than a decade, their safety profile is well characterized and they are safe for use by all women including adolescents. Even if they are accidentally taken by a woman who is already pregnant, there is no evidence that the fetus is harmed or that the course of pregnancy is disturbed (WHO 2010a, b). Although no serious risks have been reported in women who used LNG ECP repeatedly, repeated use of post-coital hormonal contraception is not recommended (Halpern et al. 2010). In a study of 332 pregnant women who used progesterone ECPs, no congenital malformations or any perinatal/delivery complications were found (Zhang et al. 2009).

Use of the LNG EC does not increase the risk of ectopic pregnancy (Plan B One Step Prescribing Information 2009; Kozinszky et al. 2011) but if pregnancy does occur an ectopic pregnancy should be considered. Women with a history of ectopic pregnancy, cardiovascular disease, migraine and liver disease can use the LNG ECP. Women who are allergic to levonorgestrel or any other tablet component should use emergency contraceptives with caution (FSRH Guidance 2012).

There are no data on the minimum time interval between two successive uses of the LNG ECP, but it is known that no additional treatment is needed 12 h after the administration of emergency contraception (FSRH Guidance 2012). Prescribing information for LNG EC recommends caution for women with impaired liver function, hereditary galactose intolerance, or glucose and galactose malabsorption (as the product contains lactose as excipient) (Plan B One-Step, Prescribing Information 2009). In women with serious malabsorption syndromes such as Crohn's disease, the efficacy of oral emergency contraceptives may be decreased.

Ulipristal acetate is not recommended in women with severe hepatic impairment or with asthma poorly controlled by oral glucocorticoids (Ella Prescribing Information 6/2014). The label for ulipristal acetate (30 mg) states that repeated use of UPA within the same menstrual cycle is not recommended as the safety and efficacy of repeated use has not been evaluated. In a clinical study, single doses equivalent to up to four times the dose of UPA in Ella® were administered to a limited number of subjects without any adverse reactions (Ella Prescribing Information 6/2014; Trussell and Raymond 2014).

Use of EC pills does not contraindicate the continued use of regular contraception (Prescribing Information for Plan B One Step and ELLA) although additional precautions may be required when starting or continuing regular contraception following use of EC pills (CEU Guidance Quick Starting Contraception 2010). LNG can be used more than once in a cycle or for recent indication even if there has been another episode of UPSI outside the treatment window (>120 h). Use of UPA

more than once per cycle or if there has been another episode of UPSI outside the treatment window (>120 h) is currently not supported (CEU Guidance 2010).

Availability of Emergency Contraception

In 148 countries at least one ECP brand is registered; in 58 countries ECP are included in their Essential Medicines Lists; but 46 countries have no ECP brands registered. In 73 countries access to EC is without prescription (in 17 countries ECP are available over the counter (OTC) and in 56 ECP are behind the counter – i.e. available from a pharmacist without a prescription) (http://www.cecinfo.org/country-by-country-information). In the US, LNG ECPs remains prescription only for those under age 17, despite recommendations to eliminate age restrictions from FDA experts (Wood et al. 2012).

Levonorgestrel's long history of safe and effective use and low incidence of side effects has allowed reclassification of LNG by regulatory agencies in many countries as a non-prescription emergency contraceptive. In the US, LNG EC met the criteria to be available OTC, which include: no potential for overdose or addiction, very low toxicity, uniform dosage, no major drug interactions or contraindications, poses no danger to an existing pregnancy, and the user can determine her own need for the product (www.cecinfo.org). However, even with increased availability, EC users still require timely and adequate information and a toll free number and a website could provide information to potential users 24 h a day. Other risk minimization measures proposed for OTC availability of EC include a phone number and website included on outside package and interior labeling, and ECPs dispensed by pharmacists certified every year on emergency contraception use (Ilic 2013).

Although over-the-counter (OTC) availability of LNG EC is more convenient for women and provides rapid access to EC when necessary, a systematic review of 23 published articles which included data from RCTs, cohort studies, and community interventions failed to demonstrate a reduction in unintended pregnancy or abortion rates with increased access (Raymond et al. 2007). The quality of the studies included in this systematic review varied. In only one study, increased access to ECPs was associated with greater use (Raymond et al. 2006). Six studies suggested that intervention increased promptness of emergency contraceptive pill use, though this effect was not seen in one large RCT (n = 1,948) (Raymond et al. 2007).

A meta-analysis performed by Polis et al. in 2007 included eight RCTs representing 6,389 patients in the United States, China and India. Advance provision (in which women receive a supply of emergency contraception before unprotected sex) "did not decrease pregnancy rates compared to standard access (OR 1.0; 95 % CI: 0.78–1.29) in studies for which 12 month follow-up data were included;

OR 0.91; 95 % CI: 0.69–1.19 in studies for which 6 month follow-up data were included; OR 0.49; 95 % CI: 0.09–2.74 in a study with 3 month follow up data), despite increased EC use (single use: OR 2.52; 95 % CI 1.72–3.70; multiple use: OR 4.13; 95 % CI 1.77–9.63) and faster use (weighted mean difference (WMD) −14.6 h; 95 % CI −16.77–12.4 h)". Advance provision did not lead to increased rates of sexually transmitted infections (OR 0.99, 95 % CI 0.73–1.34), unprotected intercourse, nor changes in contraceptive methods (Polis et al. 2007).

Women who must wait for physician appointments could have significant delays in access to the EC, which in turn may compromise the efficacy of the ECP. Because pharmacies are available in rural areas and open on weekends and for more hours than physicians' offices, pharmacies present unique access points for ECPs. In many countries pharmacists are allowed to dispense LNG to women; the age restriction varies from 15 or older years (Finland), 16 years or older (Bulgaria) 17 years of older (US, Serbia), but in some countries there is no age restriction (Austria, Belgium, Netherland, Ireland, Slovenia, Denmark, France, India).

Although pharmacists have front-line contact with EC users and it is expected that they are familiar with the guidelines for EC use, one study conducted in the UK found that they did not provide sufficient counselling to women in need for ECP for various reasons – for example, the pharmacy does not have private space for conversation, workload in pharmacies, pharmacists' religious beliefs (Cooper et al. 2008) or lack of knowledge (Van Riper and Hellerstedt 2005). Pharmacists may also miss the opportunity for counseling and to refer women to test for sexually transmitted infections (STI) (Habel and Leichliter 2012). In addition, healthcare providers should educate women who are not in stable relationships to use condoms in order to reduce the risk of STIs.

Levonorgestrel is safe and effective if it used within 72 h of unprotected intercourse and should be available as behind the counter contraceptive in all the countries. Pharmacists must improve their knowledge about ECPs through continuous education and pharmacies must have private space for consulting users of EC.

Legal, Ethical and Regulatory Aspects of Access to Emergency Contraception

Different legal, political, and other factors caused by the interpretation of abortion laws and lack of knowledge may cause obstacles to the introduction of EC into some countries. Additionally, access to EC may be influenced by religious factors (Tadiar and Robinson 1996). Catholic bishops around the world have opposed access to emergency contraception, stating EC is an abortifacient, encourages promiscuity and may even cause ectopic pregnancy (http://www.catholicsforchoice.org/documents/EmergencyContraceptionCatholicsinFavor.pdf).

At times, the bishops have been successful, however more often, policymakers armed with medical information, have supported access and increased availability of EC in many countries. The issues surrounding availability of EC in the USA are discussed in some detail in Chap. 16 – "Political and Religious Perspectives on Prescribing Women's Medicines".

In 2002, a Judicial Review in the English High Court ruled that pregnancy begins at implantation not with fertilization. As emergency contraception is a method of contraception not abortion, emergency contraception can continue to be lawfully supplied (Judicial Review of Emergency Contraception 2002). In countries where it is considered that pregnancy begins with implantation – such as the UK, Germany and New Zealand (Tadiar and Robinson 1996) – emergency contraception is lawfully supplied as a method of contraception (not abortion). This includes dispensation of ECPs over the counter in pharmacies. However, pharmacists with religious, moral or conscientious objections to EC could also limit the wider use of EC, by either refusing to dispense it, or by giving biased advice (Cooper et al. 2008).

Conclusions

Emergency contraception provides women a last chance to prevent pregnancy after unprotected intercourse and in most countries current options for EC include a copper IUD or hormonal emergency contraception pills (ECPs) containing either levonorgestrel (LNG) or ulipristate acetate (UPA). However, although both unplanned pregnancy rates and abortion rates are high in many countries, the use of emergency contraception is low.

In this chapter the mechanism of action, effectiveness and safety of all methods of currently available EC is reviewed. An IUD is the most effective form of EC and may be inserted within 5 days of unprotected intercourse. The LNG ECP is approved for use up to 72 h after unprotected intercourse and UPA is approved in many countries for up to 5 days after unprotected intercourse. Women should be advised to take the LNG ECP as soon as possible after unprotected intercourse or contraceptive failure. If more than 72 h has elapsed after sexual intercourse, UPA or a copper IUD are the preferred method of EC.

LNG has been used for several decades and it is safe for use by all women including adolescents. Thus it is available in many countries as an OTC or BTC emergency contraceptive. UPA has been used only in recent years and its safety profile is not as well characterized. To date, it is available only with a prescription in some countries and is not yet available in other countries.

Take Home Messages

- The decision which method of EC to use depends on several factors, such as the number and timing of episodes of UPSI, drug interactions and individual choice.
- LNG ECPs greatly decrease the chances of pregnancy if taken within 72 h of UPSI.
- If more than 72 h have elapsed after sexual intercourse, UPA or a copper IUD are preferred methods of EC.
- Mechanism of action studies show that ECPs do not cause abortion.
- In countries where it is considered that pregnancy begins with implantation emergency contraception is lawfully supplied as a method of contraception.
- The LNG ECP is a safe and well tolerated treatment with very few contraindications for use.
- EC users should be told to perform a pregnancy test if the menstrual period does not begin within 3 weeks of taking ECP, or if it is delayed by a week or more, as well as before taking UPA if pregnancy cannot be excluded on the basis of history/physical examination.
- ECP use may be repeated if needed, but women should be advised to use a regular method of contraception.
- Healthcare providers must provide information about adequate use of EC and regular contraception.

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Chapter 8
Contraceptive Devices for Women: Implants, Intrauterine Devices and Other Products

Julie Craik and Sam Rowlands

Introduction

The purpose of this chapter is to examine the health benefits, risks and side effects associated with contraceptive devices, specifically progestogen-only implants and intrauterine contraceptive methods. The combined transdermal patch, combined vaginal ring and progestogen-only ring will also be covered briefly. It is outside the scope of this chapter to cover other contraceptive methods such as contraceptive injectables, barrier methods and devices for the purposes of sterilisation. Additionally, new contraceptives are continually being developed (Bahamondes and Bahamondes 2014) but such methods will not be dealt with in this chapter.

The devices covered in this chapter are commonly referred to as long-acting reversible contraceptives (LARCs) as they are administered less frequently than once a month; the exception being the combined transdermal patch. Unlike short-acting methods, such as condoms and oral contraceptives, which are heavily dependent on user adherence for efficacy, once initiated, intrauterine methods and progestogen-only implants provide contraceptive cover for a number of years, without any particular action being required on the part of the user. Consequently their failure rates are very low.

Despite this, globally these methods are often under-utilised, with wide country variation (United Nations et al. 2013). For example a worldwide review of intrauterine contraception use showed that in Asia overall approximately 18 % of

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women aged 15–44 who are married or in a union used intrauterine devices (Buhling et al. 2014). The figures for North America and Oceania were 4.8 % and 1.1 % respectively (Buhling et al. 2014). Women's choice of contraceptive will be driven by socioeconomic, environmental, cultural and individual factors; women's knowledge of the method; ease of use; health professionals' attitudes towards the method and concerns about safety and side effects (Belfield 2005).

In addressing the risks and benefits associated with these contraceptive devices, data are cited from different pharmacovigilance reporting systems. Conclusions about the safety of medicines cannot be made on the basis of these data and a listed reaction is not proof of causality. Case numbers from spontaneous reporting datasets cannot be used to estimate the prevalence of such events as such systems have no baseline data about the number of exposures. They have been included, in the same way as case reports, solely to illustrate that examples of such events exist.

It should be noted that not all the methods mentioned in this chapter are available in all countries. For example the transdermal patch is available in many European countries, the USA and Canada; it is not licensed for use in the New Zealand. Also, levonorgestrel implants are not licensed in the UK.

Progestogen-Only Implants

Norplant® was the first implant marketed for contraception. It comprised six small capsules, inserted into the arm in a fan formation, which released levonorgestrel. Norplant® was withdrawn from the UK and US markets in the 1990s in response to concerns about side effects and difficulties with removal: globally the product stopped being marketed in 2008 (Rowlands 2010a).

Subsequent devices were developed and the contraceptive implants available today consist of one or two flexible rods filled with etonogestrel (68 mg) or levonorgestrel (75 mg) (see Table 8.1).

The two rod levonorgestrel implants should be inserted in a v-shape with a 30 degree arc. The rate at which etonogestrel is released into the circulation from the implant decreases with time. In the first 5–6 weeks the release rate is

Table 8.1 Summary of progestogen-only implants available

Name of implant	Progestogen	Number of rods	Length of rod (cm)	Dose per rod (mg)	Licensed duration of use (years)
Implanon®	Etonogestrel	1	4	68	3
Implanon NXT®/ Nexplanon®[a]	Etonogestrel	1	4	68	3
Jadelle®	Levonorgestrel	2	4.3	75	5
Sino-implant(II)®	Levonorgestrel	2	4	75	4

[a]In the UK, Implanon NXT® is marketed as Nexplanon® and will be referred to thus hereafter

approximately 60–70 μg/day: by the end of year 3 it is approximately 25–30 μg/day (Merck Sharp & Dohme Limited 2013). The release rate of levonorgestrel steadily decreases over time up until year three and then remains relatively steady in years four and five (Sivin et al. 2002).

Implanon® and Nexplanon® are bioequivalent (Schnabel et al. 2012): the main differences between the two products are their inserters and the addition of barium sulfate to Nexplanon®, which makes it radiopaque. The two rod levonorgestrel implants contain the same dose of levonorgestrel, however, the Sino-implant (II) is licensed for a shorter duration of use.

Progestogen-only implants provide contraceptive protection via a variety of mechanisms; ovulation suppression, thickening of cervical mucus and possibly endometrial changes (Croxatto 2002). The extent to which ovulation is suppressed varies between the implants, with it more consistently suppressed for up to 3 years in those who use the etonogestrel implant (Croxatto 2002). For Implanon® and Nexplanon®, the effects of the etonogestrel on cervical mucus and endometrium are therefore perhaps of less clinical importance than for levonorgestrel implants.

Efficacy and Unintended Pregnancies

Data from clinical trials suggest that progestogen-only implants are highly effective methods of contraception with a Cochrane review quoting pregnancy rates of 0.13 and 0 per 100 women for the levonorgestrel and etonogestrel implants respectively (Power et al. 2007). The probability of pregnancy in the first year of Sino-implant (II) use has been reported as being up to 0.1 % and cumulatively up to 2.1 % at 5 years (Steiner et al. 2010). It is therefore rare for etonogestrel or levonorgestrel implants to truly 'fail'. That said, cases of unintended pregnancy with contraceptive implants in situ have been reported and it is likely that pregnancy rates from trials under-represent the number of failures that will occur in real life when external factors such as insertion difficulties and drug interactions come into play.

In 2005 a case series (Harrison-Woolrych and Hill 2005) from Australia was published following reports of unintended pregnancies arising with use of the etonogestrel implant. While not a direct failing of the implant itself, unrecognised non-insertion of the implant led to a number of unintended pregnancies. This will be covered later in this chapter. Additionally, this case series identified that a number of failures occurred as a result of concomitant use of enzyme inducing drugs (Harrison-Woolrych and Hill 2005). Other reports of failures possibly as a consequence of drug interactions are documented (Patni et al. 2006; Lakhi and Govind 2010; McCarty et al. 2011; Matiluko et al. 2007; Haukkamaa 1986; Gbolade 2010): product information warns that efficacy may be reduced with concomitant use of drugs which induce hepatic enzymes, specifically cytochrome P450, for example carbamazepine or rifampacin (Merck Sharp and Dohme Limited 2013). In 2014, the Medicines and Healthcare Regulatory Agency (MHRA) in the UK produced a Drug Safety Update (Medicines and Healthcare Products Regulatory Agency 2014)

which highlighted that in the last quarter of 2013 the MHRA had received two reports of unintended pregnancies occurring in women using the etonogestrel implant possibly as a consequence of using St John's Wort.

It is recommended that women using enzyme inducing drugs concomitantly with the etonogestrel implant should switch to a method such as a copper intrauterine device (Cu-IUD) whose efficacy is considered to be unaffected by these medicines (Faculty of Sexual and Reproductive Healthcare 2011a). Alternatively, a short-term option would be to use an additional contraceptive method, for example condoms, while taking the enzyme-inducing drugs and for 28 days afterwards (Faculty of Sexual and Reproductive Healthcare 2011a).

In the UK, by November 2013, the MHRA had approximately 1,344 pregnancies on file for Implanon®, 1,076 of which are listed specifically under the heading Unintended Pregnancies (Medicines and Healthcare Products Regulatory Agency 2013). In 2011, a Danish Pharmacovigilance Update suggested 28 cases of unintended pregnancy in women using the etonogestrel implant had been reported since its introduction in 1999 (Danish Medicines Agency 2011).

As a result of reported cases of non-insertion, clinicians have placed emphasis on palpation of the rod in the arm after insertion by both clinician and patient. Despite this, cases continue to occur, some resulting in litigation. Additional training has been shown not to be the answer to problems relating to human factors; applicator design is likely to be a more fruitful approach to risk management (Rowlands et al. 2010).

In the UK, the Faculty of Sexual and Reproductive Healthcare (FSRH) advises the removal of the implant should pregnancy occur with an implant in situ, unless the woman is going to have a termination and wants to continue the method afterwards (Faculty of Sexual and Reproductive Healthcare 2014).

Pregnancies documented with an implant in situ may also arise from an implant being inserted around the time of conception or from a woman not adhering to any stipulated requirements for additional precautions when starting the method.

Weight and Body Mass Index (BMI) Issues for Progestogen-Only Implants

Studies have found an inverse relationship between hormone concentrations and weight, or BMI, which has caused concern that contraceptive implants may be less effective or effective for a shorter duration of time for women who are classified as obese, than for women of 'normal' weight/BMI. A pharmacokinetic study (Mornar et al. 2012) found that in the first 6 months following insertion of Implanon®, women classified as obese, had plasma levels of etonogestrel up to 63 % lower than levels reported for normal weight women, although the difference was not statistically significant. The authors noted that the findings may be subject to confounding as a result of racial differences between the two groups (obese and normal weight) (Mornar et al. 2012).

A small case series (Ciangura et al. 2012) of three morbidly obese women (BMI 49.2–64.7 kg/m^2) undergoing bariatric surgery similarly reported serum etonogestrel levels far lower than might be expected in women of normal weight. The authors indicated the need for further research, but suggested that in obese women undergoing bariatric surgery, levels of etonogestrel sufficient to suppress ovulation may only be present for up to 8 months (Ciangura et al. 2012). Such findings (and from only three women), however, do not necessarily confirm a reduced contraceptive effect as, even if reduced plasma levels resulted in less ovarian suppression, the secondary effects of the implant may still offer sufficient contraceptive protection.

In terms of calculating failure rates according to body weight or BMI, the data are quite limited. With a growing epidemic of obesity in many countries, more studies are required as clinical trials to date have often failed to include women weighing more than 130 % of their ideal body weight and few trials have included women weighing over 100 kg for the full duration of implant use.

In two studies of the levonorgestrel implant, pregnancies were reported in women weighing over 70 kg at the time of their levonorgestrel implant insertion: 131/1198 (Sivin et al. 1998b) and 134/511 (Sivin et al. 1998a) women weighed 70 kg or over at baseline. In the smaller study (Sivin et al. 1998a) of 511 women, pregnancies occurred in women weighing over 79 kg. A cumulative failure rate at five years of 4.2 per 100 women was calculated for women weighing over 70kg (Sivin et al. 1998a). Product information for Jadelle® suggests that women over 60 kg may wish to consider replacing the device at 4 years (New Zealand Consumer Medicine Information 2013a). In a large cohort study in which implant (etonogestrel) users who were overweight or obese were compared to women of 'normal' weight and to women using intrauterine devices, no reduction in efficacy was observed with the implant as a result of high body mass index (Xu et al. 2012).

Longer Term Risks and Benefits

As indicated in Chaps. 5 and 6, few long-term epidemiological studies have included sufficient numbers of women using progestogen-only methods to be able to reach definitive conclusions about the associated risks or benefits in relation to cardiovascular health, cerebrovascular disease and cancer. Data for progestogen-only implants in particular are lacking. The available evidence for other progestogen-only methods generally suggests no increased risk of thrombosis, myocardial infarction (MI) or stroke (Lidegaard et al. 2012a, b; Mantha et al. 2012; Chakhtoura et al. 2011). For women with multiple risk factors for cardiovascular disease, published medical eligibility criteria for contraceptive use indicate that the benefits of using progestogen-only implants generally outweigh any risks (Faculty of Sexual and Reproductive Healthcare 2009a; Centre for Disease Control and Prevention 2010; World Health Organization 2010). The risk of breast cancer associated with use of the progestogen-only implant is

undetermined due to small sample sizes in studies that have examined this, but no increased risk has been observed (Strom et al. 2004).

Non-contraceptive Benefits of Progestogen-Only Implants

As primary dysmenorrhoea is associated with menstruation, contraceptive devices that suppress ovulation may be expected to alleviate ovulatory pain. An integrated analysis (Mansour et al. 2008a) of bleeding patterns from eleven clinical trials of the etonogestrel implant noted that five of these trials reported on dysmenorrhoea. At the time of removal, dysmenorrhoea was noted to have improved in 77 % of those who reported it at baseline (Mansour et al. 2008a). For some women however, dysmenorrhoea may occur or worsen with use of the etonogestrel implant (Croxatto 2000; Mansour et al. 2008a).

European Guidelines (European Society for Human Reproduction and Embryology 2013), advise that the levonorgestrel intrauterine system (LNG-IUS), the progestogen-only injectable (depot medroxyprogesterone acetate) and combined oral contraceptives can be considered for the management of dysmenorrhoea secondary to endometriosis. Few studies have looked at the use of the progestogen-only implant in managing dysmenorrhoea secondary to pelvic pathology but there is some data to suggest a possible benefit (Walch et al. 2009; Yisa et al. 2005; Ponpuckdee and Taneepanichskul 2005). In a pilot study of 41 women with histologically confirmed endometriosis randomised to either the progestogen-only implant or the progestogen-only injectable (depot medroxyprogesterone acetate), endometriosis associated pain was reduced in both groups and their therapeutic effects comparable (Walch et al. 2009). However, the etonogestrel implant is not currently listed in European guidelines as a suggested treatment strategy (European Society for Human Reproduction and Embryology 2013).

Other Risks

Bent/Fractured Implants

Although reports of bent and/or fractured implants are uncommon in the literature, there are several examples of case reports and health professional correspondence detailing experiences of this phenomenon in relation to the etonogestrel implant (Doshi 2011; Bentley 2013; Torres et al. 2013; Pickard and Bacon 2002; Agrawal and Robinson 2003). Although details of the specifics are not documented, a total of 149 cases of broken devices, 11 damaged devices and 5 device kinks are listed in UK reporting systems for the etonogestrel implant (Medicines and Healthcare Products Regulatory Agency 2013). The implications of implant fractures in terms of efficacy are largely unknown: correspondence from Rekers reports that a damaged etonogestrel implant is unlikely to affect contraceptive efficacy of these

single rod implants as, compared to those that are undamaged, the in vitro release rate is only slightly increased (Rekers 2013). No cases of bent or fractured Jadelle® implants are on file with the licence holder (personal communication).

Bone Health

It is well recognised that use of the progestogen-only injectable is associated with a reduction in bone mineral density (BMD) which usually recovers upon cessation (Faculty of Sexual and Reproductive Healthcare 2008; National Institute for Health and Care Excellence 2005; Lopez et al. 2012). Less is known about the impact of the progestogen-only implant, but it is suggested that on the basis of the available evidence there is not thought to be a clinically significant adverse effect (Faculty of Sexual and Reproductive Healthcare 2014).

Beerthuizen et al. (2000) compared users of the etonogestrel implant to users of a non-hormonal intrauterine device over a 2 year period to study the effects of the implant on bone mineral density. From baseline, the observed changes in the implant group were reported not to be different to those experienced by intrauterine device users (Beerthuizen et al. 2000). However, in other observational studies, a statistically significant loss of bone mineral density compared to pre-insertion values was observed in the distal radius, but not the ultra-distal radius, in the small number of etonogestrel and levonorgestrel implant users who continued their method for up to 36 months (Monteiro-Dantas et al. 2007); losses were also observed after 18 months of use (Bahamondes et al. 2006a). A cross-sectional study reported statistically significant changes in bone mineral density in the ulna and distal radius in women using the etonogestrel implant compared to women using non-hormonal contraceptives (Pongsatha et al. 2010).

In summary, although studies of progestogen-only implants have noted some statistically significant decreases in bone mineral density (Beerthuizen et al. 2000; Monteiro-Dantas et al. 2007; Bahamondes et al. 2006a; Pongsatha et al. 2010) the decreases may not be of clinical significance as bone mineral density is only a surrogate endpoint for fractures. As yet, the risk of fractures associated with progestogen-only implants is undetermined.

Ectopic Pregnancy

The fact that progestogen-only implants are such effective methods of contraception means that the absolute risk of pregnancy, ectopic or intrauterine, is low. Post-marketing surveillance of Norplant® reported an ectopic pregnancy rate of 0.30 per 1,000 woman years of use in women using Norplant® compared with 2.66 per 1000 woman years amongst those not using any contraception (International Collaborative Post-Marketing Surveillance of Norplant 2006). Other studies have similarly reported low ectopic pregnancy rates for Norplant® and Jadelle® (Sivin et al. 1998b).

However, when a pregnancy does occur while using a progestogen-only implant, it may be more likely to be ectopic. In post-marketing surveillance, around 11 % of those pregnancies that occurred when using Norplant® were ectopic compared with 0.6 % of women using no method (International Collaborative Post-Marketing Surveillance of Norplant 2006). A published review of clinical trials and marketing data suggested that ectopic pregnancies accounted for around 5 % of all reported pregnancies whilst using Implanon® (Graesslin and Korver 2008). Case reports of ectopic pregnancy have also been documented following concomitant use of drugs that may affect the efficacy of progestogen-only implants such as anti-retrovirals (Patni et al. 2006; McCarty et al. 2011). In the UK, there are 57 ectopic pregnancies on file which could relate to use of the etonogestrel implant (Medicines and Healthcare Products Regulatory Agency 2013). If a pregnancy does occur with a progestogen-only implant in situ, the possibility of an ectopic pregnancy should be considered.

Expulsion

Spontaneous expulsion of an implant after correct insertion is close to impossible (Fraser 2006). A review of clinical trials on all types of implant gave an expulsion rate of between 0 and 0.6 % (Brache et al. 2002). Expulsions were reported to occur within the first 4 months after insertion in 70 % of cases (Brache et al. 2002). Implanon® trials showed an expulsion rate of zero (Mascarenhas 1998). However, there are several post-marketing case reports of expulsion/extrusion of Implanon®/ Implanon NXT® (Gwinnell 2007; Chaudry 2013; Mansour 2013). It appears to be a slow process of erosion culminating in partial expulsion.

Discontinuation rates due to implant expulsions are low (Division of Human Resource Development Research1993) and in a case series expulsions accounted for only 3/218 unintended pregnancies with Implanon® use (Harrison-Woolrych and Hill 2005). Sixteen cases of expulsion/extrusion are on file in the UK in relation to the etonogestrel implant (Medicines and Healthcare Products Regulatory Agency 2013): it is not possible however to determine whether these are actual expulsions or whether non-insertion may account for some of these.

Infection/Implant Site Reactions

Implant site reactions, pain and infection have been noted in clinical trials of implantable contraceptives (Klavon and Grubb 1990; Dunson et al. 1995). In a review of Implanon® trials, swelling at the insertion site occurred in 0.5 % of insertions, redness in 0.3 % and pain in 1.9 % of cases (Mascarenhas 1998). A study of Nexplanon® showed an incidence of swelling or redness of 4.7 % (Mansour et al. 2010). Post-insertion wound infection is not reported in trials of Implanon®/ Nexplanon®.

A case of lipoatrophy around the site of Implanon® insertion was reported in a 40 year old woman, which resolved 6 months after removal (Lindsay 2010). A response from Schering Plough Ltd, indicated that whilst a relationship between the implant and the lipoatrophy was possible, there was insufficient evidence to establish causality and that other possible factors may have played a role (Mohlala and Falowo 2010). A case of lipoatrophy has also been reported in a young woman who presented for removal of her Norplant device (Chadha-Gupta and Moss 2007). In the UK at the end of 2013, two reports of lipoatrophy were listed on the drug analysis print for the etonogestrel implant (Medicines and Healthcare Products Regulatory Agency 2013).

Insertion and Removal Difficulties: Non and Deep Insertion and Nerve Damage

Whilst it is important to understand the benefits and risks associated with the use of progestogen-only implants, there are a number of safety issues relating to the device itself and the procedures required to be undertaken to insert or remove the device. Harm/risk related to the insertion and removal of contraceptive implants can generally be divided into three categories: non-insertion, deep insertion and nerve injury (Rowlands 2010a).

The risk of non-insertion is of course that a woman leaves the clinical setting without a reliable contraceptive method in situ and is therefore at increased risk of an unintended pregnancy and the potential negative consequences this may have for her. Failings, due to human factors (Dekker 2011), leave clinicians open to the possibility of litigation (Rowlands 2010a). During the first 3 years of marketing of the etonogestrel implant in Australia, over 200 unintended pregnancies were reported (Harrison-Woolrych and Hill 2005). Of the 127 cases, after excluding those who were deemed to be pregnant at the time of insertion and those for whom there was insufficient information to deduce a reason, 66 % (n = 84) were attributed to failed insertions (Harrison-Woolrych and Hill 2005). Similarly in France, around 30/77 unintended pregnancies over a 17 month period were considered to be the result of an insertion technique error (Bensouda-Grimaldi et al. 2005).

In the UK, the Medical Defence Union (MDU) published advice to general practitioners (GPs) inserting contraceptive implants in 2011 indicating that the organisation had been notified of 29 claims in relation to use of the etonogestrel implant: most related to pregnancy failure and concerns about insertion failings (MDU 2011). An overview of legal implications of contraceptive implants, including further examples of litigation, has been published (Rowlands 2010a).

A new inserter has been developed with Nexplanon® in part to eliminate the risk of insertion errors. The risk of non-insertion may be less with implants such as the Sino-implant (II), that require to be manually inserted into a trocar, as the health professional has to observe the implant throughout the insertion process (Rowlands et al. 2010). In their article assessing the risks associated with the insertion and removal of contraceptive implants, Rowlands et al. (2010) postulate that, as it is

highly unlikely the preloaded applicator systems have been supplied with an absent implant, the problems with Implanon® non-insertion are generally a result of human factors: most likely that the applicator is removed with the implant still in situ. Palpating the arm to check for the implant(s) and documenting the implant's presence has been proposed as a way of minimising the possibility of an unidentified non-insertion.

In terms of siting an implant, the arm has the advantage over other sites, in that the subcutaneous tissue is thinner thereby easing the insertion process: the disadvantage is that vital structures are nearer the surface (Rowlands et al. 2010). Progestogen-only implants are licensed for insertion in the sub-dermal plane; however there are several reports in the literature of impalpable implants which upon further investigation are found to be located far deeper than expected, which can present health professionals with difficulties at the time of removal (Singh et al. 2006). In a single centre in France, a retrospective case series identified 28 women for whom their etonogestrel implant had to be removed in an operating theatre: over a third of women (11/28) were found to have an implant deep to the fascia; one had to retain her implant as it could not be located, and three were found near or touching the brachial artery (Vidin et al. 2007).

Following correct insertion of a contraceptive implant, significant migration appears to be a relatively uncommon occurrence: of 87 women followed prospectively for 1 year, migration did not occur in 45 % of these women (Ismail et al. 2006). In the remaining 55 % for whom some degree of migration occurred, migration was predominantly caudally, and in all but one case, migration was less than 2 cm- no deep implant migration was noted (Ismail et al. 2006). The view, certainly in the case of Implanon®, would seem to be that deep insertions are more likely to be the result of poor insertion technique (Rowlands et al. 2010; Singh et al. 2006; Walling 2005).

Weight may play a role in difficult insertions and removals. It has been suggested that where women have scant subcutaneous tissue, deep insertion may be more likely to occur (Mansour et al. 2008b) and that weight gain following insertion may make palpation difficult (Navani and Robinson 2005). Whereas other devices are not visible on X-ray, the addition of 15 mg of barium sulfate means that a non-palpable Nexplanon® could be located via X-ray or computed tomography scan, although visualisation via ultrasound should still be the first course of action. Removal problems with Jadelle® (Norplant II) occur less often than with Norplant® (Sivin et al. 1998b). In New Zealand, up until June 2013, 21 reports of location or removal difficulties with Jadelle and three reports with Implanon® were on file with the Centre for Adverse Reactions Monitoring (New Zealand Medicines and Medical Devices Safety Authority (2013b)).

With incorrect insertion and impalpable implants, the potential arises for the third type of harm – nerve injury. In 2012, a case was reported in which an impalpable Implanon® was located on the deep surface of the fascia beside the medial cutaneous nerve of the forearm (Brown and Britton 2012). The woman had been experiencing forearm pain and hypoesthesia for 2 years following insertion of Implanon®, which subsequently resolved after removal (Brown and Britton 2012).

Table 8.2 Neurological adverse events from UK spontaneous reporting, 1999–2013 for etonogestrel single agent products

Adverse reaction	Number of cases reported
Implant site paraesthesia	3
Nerve injury (not classified)	1
Peripheral nerve injuries	7
Paraesthesias and dysaesthesias	42
Mononeuropathies	2
Sensory abnormalities	31

In 2011, two cases of median nerve injury were reported (one a 10 % laceration, the other an incomplete but significant high median nerve injury), arising from exploratory procedures to locate an impalpable Implanon® (Gillies et al. 2011). The authors (Gillies et al. 2011) noted that both cases were potentially preventable, had the clinician followed advice to image impalpable implants prior to attempting removal. Other reports of medial cutaneous nerve damage can be found, as can cases of ulnar nerve damage, ulnar lesions and contusion following removal of progestogen-only implants (New Zealand Medicines and Medical Devices Safety Authority 2013b; Bragg et al. 2006; Osman et al. 2005). Two cases of possible compression of the musculocutaneous nerve with Norplant® have been reported (Hueston and Locke 1995).

Table 8.2 highlights the number of adverse reactions reported to the UK's Medicines and Healthcare products Regulatory Agency (MHRA) (Medicines and Healthcare Products Regulatory Agency 2013) relating to etonogestrel implants (during the period Nov 1999– Nov 2013) which may possibly be as a result of nerve damage. While they cannot be used to predict the frequency of such events occurring, these reports would seem to reflect the types of case reports available in the published literature.

Vascular Injury

Injuries to vascular structures are extremely rare. In a French case, an Implanon® was inserted into the brachial artery causing thrombus formation (Mourtialon et al. 2008). In a German case, an Implanon® was inserted and then was not palpable (Ernst 2004). Ultrasound and magnetic resonance imaging (MRI) failed to locate the rod; MRI scanning was extended to the heart. Echocardiography of the heart, pulmonary artery angiography and phlebography of lung veins and superior vena cava were also done and did not locate the implant. Quantitative blood etonogestrel levels were positive confirming the implant was in the body. A cardiothoracic specialist concluded that the implant might be lodged in a branch of the pulmonary artery, possibly up to a peripheral branch of a lung segment and that it was unlikely to cause serious problems. The assumption was that the implant had embolised in the venous circulation from a vein in the arm.

Avoidance of Injury

Placing the implant superficially, away from the neurovascular bundle in the upper arm is important in minimising risk of injury to vital structures. Clinicians inserting and removing implants should receive training approved in their country. Skills should be maintained with regular updating.

Sometimes implants are impalpable; these deeply located implants are more complex to remove. Ultrasound-guided removal is recommended which should only be performed by clinicians with particular expertise.

Side Effects of Progestogen-Only Implants

Bleeding Disturbances

A change in bleeding pattern is a common side effect associated with the use of progestogen-only implants, and often a stated reason for dissatisfaction with and/or discontinuation of these methods (Sivin et al. 1998b; Mansour et al. 2008a; Harvey et al. 2009; Lakha and Glasier 2006; Funk et al. 2005; Darney et al. 2009; Grunloh et al. 2013; Zheng et al. 1999; Short et al. 2014). Bleeding patterns are broadly similar for all progestogen-only implants, although less frequent bleeding and a higher incidence of amenorrhoea have been noted amongst Implanon® users compared to Norplant® users (Zheng et al. 1999). Irregularity is the most commonly experienced bleeding pattern with contraceptive implants, with bleeding that is frequent and/or prolonged appearing to be the most unacceptable to women (Mansour et al. 2008a; Biswas et al. 1996). A review of bleeding patterns from 11 trials of Implanon® suggested that while bleeding patterns may improve amongst those who find the bleeding unfavourable in the first few months of use, for others the bleeding patterns are likely to remain unacceptable (Mansour et al. 2008a).

A variety of interventions such as administration of antiprogestogen, estrogen supplementation and additional progestogen have been tried to improve the bleeding patterns associated with progestogen-only methods and may offer short-term benefits, but evidence to support routine use of any of these interventions or use in the longer term is lacking (Abdel-Aleem et al. 2013a).

Breast Pain/Acne/Weight Gain and Headaches

Breast pain has been reported by around 10 % of women in clinical trials of progestogen-only implants, although it accounted for less than 1 % of women who discontinued the method for this reason (Darney et al. 2009).

Acne has been reported by women as a side effect of implant use (Darney et al. 2009; Yildizbas et al. 2007; Flores et al. 2005). Product information for the etonogestrel implant indicates that acne was a very commonly (>1/10 women) reported undesirable

effect in clinical trials and it is cited as a reason for method discontinuation (Sivin et al. 1998b; Darney et al. 2009; Grunloh et al. 2013; Urbancsek 1998). As with bleeding, it is difficult to predict what will occur in an individual woman.

In clinical trials, women have reported weight gain as a reason for discontinuing progestogen-only implants (Funk et al. 2005; Urbancsek 1998). A 5-year trial of Jadelle reported that amongst those who continued to use the method, the average weight gain per year was 0.7 kg (Sivin et al. 1998b). However, there were variations with some women losing weight and others gaining much more within the first year of use. It has been reported that compared with users of the non-hormonal copper intrauterine device, etonogestrel implant users are more likely to report perceived weight gain (Nault et al. 2013).

Because the progestogen-only implant is not thought to be associated with an increased risk of stroke, medical eligibility criteria generally support initiating progestogen-only implants in women with migraine, including migraine with aura (Faculty of Sexual and Reproductive Healthcare 2009a; Centre for Disease Control and Prevention 2010; World Health Organization 2010). However, headaches are a commonly reported side effect in trials of progestogen-only implants and a reason for method discontinuation – although there is little available evidence investigating the role of progestogen-only contraceptives in headache development and a causal relationship has not been established (Faculty of Sexual and Reproductive Healthcare 2014; National Institute for Health and Care Excellence 2005). An integrated analysis of 11 clinical trials reported that headache was a side effect reported by 5 % or more of subjects with around 1.6 % of women discontinuing their method due to headaches (Darney et al. 2009). In another study, 7.5 % of women who asked to stop their etonogestrel implant early did so because of headaches (Grunloh et al. 2013).

Hair Loss

One of the possibly related undesirable side effects noted within the product licensing information of levonorgestrel and etonogestrel implants is hair loss/alopecia: the Summary of Product Characteristics (SPC) for the etonogestrel implant suggests it has been reported in 1–10 % of women in clinical trials (Merck Sharpe and Dohme Limited 2013). The MHRA (Medicines and Healthcare Products Regulatory Agency 2013) in the UK, has 66 reports of alopecia/alopecia areata/alopecia totalis listed in its drug analysis prints for the etonogestrel implant. A study investigating continuation rates of LARCs and characteristics of those discontinuing, reported that 3.2 % (3/94) of women who stopped the etonogestrel implant before 6 months of use did so because of hair loss (Grunloh et al. 2013). Despite these reports, evidence confirming an association is lacking and further research is needed.

Reduced Sexual Interest

Decreased libido is again commonly noted (>1 % <10 %) as a possibly related undesirable effect of progestogen implant use. As mentioned in Chap. 5 in relation to oral contraceptives, establishing causality is difficult given the many other factors that could influence sexual interest and there is a lack of studies investigating this. Di Carlo et al. (2014) conducted a preliminary study into the impact of Nexplanon® on sexual function and quality of life via validated questionnaires in a small group of healthy Italian women and did not find any adverse effects (Di Carlo et al. 2014).

Ovarian Cysts

It is not uncommon for women using progestogen-only implants to have persistent ovarian follicles or cysts and these become more common with increasing duration of use (Hidalgo et al. 2006). Ovarian cysts have been reported to occur more frequently amongst users of progestogen-only implants than amongst users of a copper intrauterine device (Cu-IUD) (Hidalgo et al. 2006). Treatment of ovarian cysts in progestogen-only implant users is not usually required and spontaneous resolution is common (Hidalgo et al. 2006).

Return of Fertility After Use of Progestogen-Only Implants

Women may be concerned about the impact long-acting methods of contraception have on their future fertility. Cumulative conception rates of 80.3 per 100 women at 1 year and 88.3 % per 100 women at 2 years have been documented in women stopping Jadelle® for the purposes of pregnancy planning (Buckshee et al. 1995). Within 1 month of discontinuation, 20 % of women had conceived and duration of use did not appear to be a factor in return of fertility when comparing 2 or more years of use to less than 2 years of use (Buckshee et al. 1995). Those over the age of 30 took on average 6 months to become pregnant following stopping for the purposes of pregnancy, versus 3.8 months for those under the age of 30 (Buckshee et al. 1995). Similar pregnancy rates at 12 months have been noted in other studies for Norplant® and Jadelle® (Diaz et al. 1987; Sivin et al. 1992).

Following removal of the etonogestrel implant, ovulation returns quickly. In one study approximately 91 % of women reported return of 'normal' menses within 3 months of the implant being removed and of those who reported non-use of contraception (pregnancy intentions unknown), around 14 % had become pregnant within 90 days (Croxatto et al. 1999). Similar findings were reported by Funk et al. (2005) who noted that of the 282 women who were evaluated 3 months after their Implanon® was removed, 88 % reported that their normal menses had

resumed: nearly a quarter (11/46) of women who did not use any subsequent contraception became pregnant between 7 and 131 days following removal. Guidance in the UK suggests women be informed that there is no evidence of a delay in return to fertility (National Institute for Health and Care Excellence 2014) and that effective contraceptives are required following removal, if a woman wishes to avoid an unintended pregnancy (Faculty of Sexual and Reproductive Healthcare 2014).

Section Summary: Progestogen-Only Implants
Progestogen-only implants are highly effective, long-acting, reversible methods of contraception. Women commonly experience irregular bleeding with use of these methods – often resulting in discontinuation. Unfortunately, there is little evidence for how best to treat such events long-term.

Adverse events such as stroke, MI or venous thromboembolism (VTE) are not thought to be associated with use of contraceptive implants and although data on use are lacking in high risk groups, progestogen-only implants are generally considered a highly effective option for women with risk factors or a history of these conditions.

While there is little evidence in terms of breast cancer risk, as with other progestogen-only methods, any observed increased risk with use is likely to be small. However, use in women with current breast cancer is not advised.

With use of contraceptive implants, many of the risks experienced are not a result of the implant itself, rather as a consequence of human factors associated with insertion and removal of the device and therefore there is scope for such risks to be reduced.

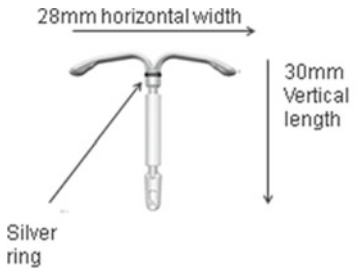
Intrauterine Devices

Before the development of oral contraceptives, contraceptive implants and injectables, women's contraceptive options were limited to barrier methods such as condoms and diaphragms, and to non-hormonal intrauterine devices. The non-hormonal intrauterine devices have been available in many forms and some such as the Dalkon Shield have been subject to much controversy (Sivin 1993). Modern day intrauterine methods are classified as non-hormonal or hormonal.

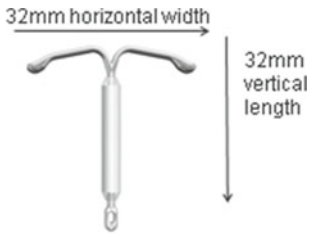
Copper-intrauterine devices (Cu-IUDs) are non-hormonal devices which were introduced onto the market in the late 1960s. The copper content varies between the different types and sizes available but they are mostly T-Shaped devices. An intrauterine ball (IUB) is currently under investigation: the IUB takes on a 3-dimensional spherical form (Baram et al. 2014), whereas the currently marketed devices take on a 2-dimensional shape in the uterus.

In the UK and some other countries such as the US, the currently available hormonal intrauterine devices contain either 52 mg of levonorgestrel (LNG-IUSs)

(Mirena®, Levonova®) or 13.5 mg of levonorgestrel (Jaydess®, Skyla®), hereafter referred to as LNG-IUS and 13.5 mg LNG-IUS respectively. The daily release rate for the LNG-IUS is 20 μg (Bayer PLC 2013); for the 13.5 mg LNG-IUS release starts at 14 μg/day reducing to 5 μg/day at 3 years (Bayer PLC 2014). The 13.5 mg LNG-IUS can be distinguished from the LNG-IUS by the presence of a silver ring just below the side arms which shows up on both X-ray and ultrasound scan (see diagram below).



Jaydess® -13.5mg LNG-IUS



Mirena® - 52mg LNG-IUS

Whereas the LNG-IUS is licensed for contraceptive cover for 5 years, the 13.5 mg LNG-IUS is only licensed for 3 years. The 13.5 mg LNG-IUS is currently only licensed for contraception (Bayer PLC 2014) and not for the treatment of heavy menstrual bleeding or indeed endometrial protection, which, in the UK, the LNG-IUS is (Bayer PLC 2013).

Effectiveness of IUDs

The contraceptive effect of intrauterine contraceptives is achieved via a variety of mechanisms. While endometrial changes that occur with use of both hormonal and non-hormonal intrauterine devices are likely to have an effect on implantation, the primary mechanism of action for both methods is interference with the process of fertilisation (Ortiz and Croxatto 2007).

Cu-IUDs and LNG-IUSs are highly effective methods of contraception with very low failure rates; over 5 years less than 20 in 1,000 and 10 in 1,000 unintended pregnancies respectively would be expected (National Institute for Health and Care Excellence 2005). While pregnancy with one of these methods in situ is rare, there is a greater risk of an adverse pregnancy outcome (e.g. ectopic pregnancy or preterm delivery) if a pregnancy does occur with an IUD in situ. This risk may not be completely negated by early removal of the device but appears to offer more favourable outcomes than retention (Brahmi et al. 2012).

Cu-IUDs, depending on their copper content, are recommended for use for between 5 and 10 years. Studies have demonstrated their efficacy beyond this and in some countries, for example in the UK, the FSRH advises that a Cu-IUD,

providing it has a copper load of over 300 mm^2, may be able to be used for longer than 10 years, on the proviso that the woman is over the age of 40 at the time the device is inserted (Faculty of Sexual and Reproductive Healthcare 2010). At 7 years, the cumulative pregnancy rates with a LNG-IUS in situ are only slightly higher than at 5 years (up to 1.1 and up to 1 per 100 women years respectively (Diaz et al. 1993; Cox et al. 2002; Sivin et al. 1991; Andersson et al. 1994; Nilsson et al. 1983), although some studies (Diaz et al. 1993; Sivin et al. 1991) may have included devices containing more levonorgestrel than in the currently marketed device. However, in the UK, it is recommended that if a woman is over the age of 45 she can consider using the LNG-IUS for longer than 5 years for contraceptive purposes (National Institute for Health and Care Excellence 2005; Faculty of Sexual and Reproductive Healthcare 2010). For the 13.5 mg LNG-IUS, the reported cumulative contraceptive failure rate from an randomised controlled trial (RCT) conducted over 3 years was 0.9 % (Nelson et al. 2013).

As it is a non-hormonal method, the efficacy of the Cu-IUD would not be expected to be affected by concomitant drug use. A report (Zerner et al. 1981) in which pregnancies were documented in Cu-IUD users, using concomitant immunosuppressive drugs led to concerns about reduced efficacy when using these types of medications. There is however no evidence from large studies to substantiate an effect. Product information for the LNG-IUS suggests that its efficacy in the presence of enzyme inducing drugs has not been studied, but is not thought to be a concern due to its predominantely local mechanisms of action (Bayer PLC 2013, 2014). A small observational series noted low failure rate when the LNG-IUS was used with enzyme inducing drugs (Bounds and Guillebaud 2002): the authors indicated that if any increased risk of pregnancy existed, it would be considered to fall within acceptable limits and the LNG-IUS was therefore an appropriate option for women using such drugs (Bounds and Guillebaud 2002). Women using enzyme inducing drugs, who are using other forms of contraception, may be advised to switch to an intrauterine method (Faculty of Sexual and Reproductive Healthcare 2011a).

Benefits of Intrauterine Devices

Reduced Dysmenorrhoea

Women with primary or secondary dysmenorrhoea may benefit from use of the LNG-IUS (Faculty of Sexual and Reproductive Healthcare 2015; Bounds and Guillebaud 2002). Dysmenorrhoea and bleeding have been shown to be significantly reduced with use of the LNG-IUS compared with use of a Cu-IUD (Nilsson et al. 1982) and that severity of dysmenorrhoea may also be improved (Lindh and Milsom 2013; Kelekci et al. 2012; Nilsson et al. 1982). Pain/cramping have however been reported as reasons for discontinuation of both methods. In one large cohort study, analysis of reasons for method discontinuation showed that

around 28 % of LNG-IUS discontinuers and 35 % of Cu-IUD discontinuers reported that pain/cramping was their primary reason for having requested removal before 6 months of use (Grunloh et al. 2013).

Dysmenorrhoea secondary to endometriosis or adenomyosis has been shown to be reduced with use of the LNG-IUS (Tanmahasamut et al. 2012; Lockhat et al. 2005; Crosignani et al. 1997; Petta et al. 2005; Tekin et al. 2011; Cho et al. 2008; Sheng et al. 2009; Fedele et al. 1997; Ozdegirmenci et al. 2011) and is a recommended treatment option (European Society for Human Reproduction and Embryology 2013). The LNG-IUS may also help in reducing the recurrence of dysmenorrhoea following surgical interventions for endometriosis (Abou-Setta et al. 2006).

Endometrial Protection

One of the licensed indications of the LNG-IUS in the UK is protection from endometrial hyperplasia during estrogen replacement therapy (Bayer PLC 2013). A systematic review reported that compared with oral and vaginal administration of progestogen, in women using estrogen replacement therapy, the LNG-IUS is at least as effective in preventing endometrial proliferation and consequentially endometrial pathology (Wan and Holland 2011).

Studies have also sought to investigate its role in the treatment of endometrial hyperplasia. The findings are somewhat limited by a lack of randomised controlled trials (RCTs). A systematic review and meta-analysis of observational studies suggested that the LNG-IUS was no more or less effective than oral progestogens at inducing simple hyperplasia disease regression compared to oral progestogens, but would appear to induce disease regression at a higher rate for both complex hyperplasia (pooled rate of 92 vs 66 % respectively $p < 0.01$) and for atypical hyperplasia (90 vs 69 %; $p = 0.03$) (Gallos et al. 2010). A subsequently published comparative cohort study of 344 women with non-atypical complex hyperplasia or with atypical hyperplasia, similarly reported more favourable outcomes with treatment of the LNG-IUS compared with oral progestogens (Gallos et al. 2013).

A systematic review of RCTs, however, concluded that for both non-atypical and atypical hyperplasia the evidence is insufficient to recommend the LNG-IUS as an equivalent treatment to high dose progestogens or hysterectomy (Wan and Holland 2011) and a Cochrane review concluded that more randomised controlled trials are required to establish the efficacy of the LNG-IUS in the treatment of women with atypical hyperplasia (Luo et al. 2013). For women using tamoxifen, use of an LNG-IUS may also help to reduce the formation of endometrial polyps and hyperplasia (Wan and Holland 2011; Chin et al. 2009).

Whilst a non-hormonal device, use of a Cu-IUD has been associated with a reduced risk of endometrial cancer (Hubacher and Grimes 2002; Beining et al. 2008) and cervical cancer (Castellsague et al. 2011). One theory on the cause of these protective effects is that the chronic low-grade inflammatory

response to Cu-IUDs results in reduced mitotic activity and reduced oestrogen receptor concentrations.

Reduced Bleeding

The LNG-IUS is licensed for contraception and/or treatment of heavy menstrual bleeding (Bayer PLC 2013) and a recommended treatment option (National Institute for Health and Care Excellence 2007). The effectiveness of the LNG-IUS in reducing menstrual blood loss as a treatment of heavy menstrual bleeding is well documented. A systematic review of 26 RCTs reported that across the studies investigating the use of the LNG-IUS, there was a 71–95 % reduction in menstrual bleeding in women whose uterine bleeding was abnormal as a presumed consequence of endometrial dysfunction (Matteson et al. 2013). The authors recommended the use of the LNG-IUS for the management of such bleeding, over other effective treatments such as combined oral contraceptives, non-steroidal anti-inflammatory drugs and luteal phase progestogens (Matteson et al. 2013). In the US, it has been suggested that the LNG-IUS may be the most cost effective intervention for those who wish to preserve fertility (Ganz et al. 2013).

In comparison to surgical interventions, a Cochrane review (Lethaby et al. 2005) reported that the LNG-IUS is associated with a smaller reduction in blood loss than endometrial ablation, more progestogenic side effects than transcervical resection of the endometrium (TCRE) and, based on the findings from one Finnish study, fewer costs than hysterectomy. Quality of life and satisfaction appeared to be comparable (Lethaby et al. 2005). A subsequent RCT reported that at 5 years, when compared to LNG-IUS users, those who had undergone thermal balloon ablation had significantly higher menstrual blood loss (45.5 % vs 0.0 % $p < .001$) and were more likely to have gone on to have a hysterectomy (Silva-Filho et al. 2013). An LNG-IUS is less invasive and associated with fewer major risks than hysterectomy, although women may be more likely to require additional interventions (Matteson et al. 2013). A cost effectiveness analysis in the UK using a Markov model suggested that the LNG-IUS is less cost effective than hysterectomy (Roberts et al. 2011). However, the authors noted that the findings may be at odds with an approach that is individualised to the woman and promotes choice (Roberts et al. 2011).

While trials comparing two lower dose LNG-IUS methods (13.5mg and 19.5mg respectively) with the 52 mg LNG-IUS have shown reduced bleeding over time with all three methods, the proportion of women benefitting from this is smaller with the lower doses of LNG (Gemzell-Danielsson et al. 2012). Women with iron deficiency anaemia, as a consequence of heavy menstrual bleeding, may benefit from use of the LNG-IUS but more studies are required (Lowe and Prata 2013).

Risks of Intrauterine Devices

Breast Cancer

As with other progestogen-only contraceptive methods, there is a paucity of evidence in relation to breast cancer and the LNG-IUS (Curtis et al. 2007). A large post-marketing surveillance study from Finland found no difference in the risk of breast cancer in users of the LNG-IUS compared to the general population in women aged 30–54 years (Backman et al. 2005). Similarly no increased risk of breast cancer was observed amongst ever users or current users of the Cu-IUD or LNG-IUS in a retrospective, population-based, case-control study powered to exclude a 1.5-fold risk of breast cancer in women under 50 years of age (Dinger et al. 2011). One case-control study which utilised registry data reported that use of the LNG-IUS was associated with an increased risk of breast cancer in newly postmenopausal Finnish women when used on its own or in conjunction with estradiol (Lyytinen et al. 2010). The authors noted that this finding was unexpected and it may be that the findings are the result of bias and confounding.

Little is known about the impact of LNG-IUS use on breast cancer recurrence. However use is generally not advised in women who have breast cancer or those with a past history of breast cancer (Centre for Disease Control and Prevention 2010; Faculty of Sexual and Reproductive Healthcare 2009a; World Health Organization 2010).

VTE and Cardiovascular Disease

Whilst limited, the available data, as with other progestogen-only methods (Chakhtoura et al. 2011), do not suggest a woman's risk of VTE is increased by use of the LNG-IUS (Lidegaard et al. 2012a; Mantha et al. 2012). Subgroup analysis data from a meta-analysis of the eight included observational studies reported that, from the two studies that included information on the LNG-IUS, the relative risk of VTE was not statistically significant (0.61 (95 % CI 0.24–1.53)) (Mantha et al. 2012).

Bone Mineral Density

There is no known association between use of the LNG-IUS and reduced bone mineral density. Comparative studies of the LNG-IUS and Cu-IUD have not reported any significant differences between users of the two methods (Bahamondes et al. 2006b, 2010).

Ectopic Pregnancy

A previous history of ectopic pregnancy is a risk factor for further ectopic pregnancies: medical eligibility criteria for contraceptive use do not however suggest that a previous ectopic pregnancy is a condition that restricts use of intrauterine contraceptives (Centre for Disease Control and Prevention 2010; Faculty of Sexual and Reproductive Healthcare 2009a; World Health Organization 2010). As with the progestogen-only implant, the absolute risk of ectopic pregnancy is low because a woman's overall risk of pregnancy is markedly reduced by the use of intrauterine contraception (Xiong et al. 1995; Skjeldestad 1997; Ory 1981; Rossing et al. 1993; World Health Organization 1985). The UK National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care Excellence 2005) reports that with 5 years of use, the overall risk of ectopic pregnancy for those using intrauterine contraceptives is less than 1 in 1,000. An absolute ectopic pregnancy rate of 0.10 per 100 woman-years (95 % CI 0.02–0.29) has been reported for the 13.5 mg LNG-IUS (Nelson et al. 2013). No studies have been sufficiently powered to compare ectopic pregnancy rates between the 13.5 and 52 mg LNG devices.

However, if a woman does experience a pregnancy with an intrauterine method in situ, the proportion of ectopic pregnancies may be increased (Xiong et al. 1995). In a cross-sectional study of 17,360 users of the LNG-IUS, of the 64 pregnancies that occurred with a LNG-IUS in situ, over half (53 %) were ectopic (Backman et al. 2004). A cohort study reported around 39 % of pregnancies that occurred with an LNG-IUS in situ were ectopic compared with around 18 % of those with a Cu-IUD (Heinemann et al. 2013a). Similarly, in phase II and phase III trials of the 13.5 mg LNG-IUS, up to 50 % of the occurring pregnancies were ectopic but the numbers of women becoming pregnant in these studies was small ($n = 2$ and $n = 7$ respectively) (Nelson et al. 2013; Gemzell-Danielsson et al. 2012). It is therefore advised that ectopic pregnancy be excluded in women who become pregnant with an intrauterine contraceptive method in situ and that women themselves are informed about the possibility of ectopic pregnancy and associated symptoms for example unilateral abdominal pain and vaginal bleeding (Bayer PLC 2013, 2014; Faculty of Sexual and Reproductive Healthcare 2015).

Expulsion

Expulsion of an intrauterine contraceptive method usually occurs in the first few months following insertion and alongside menstruation (National Institute for Health and Care Excellence 2005; World Health Organization 1987). Such events leave a woman vulnerable to an unintended pregnancy, therefore women should be informed about how to check for signs of expulsion and what to do if expulsion is suspected (National Institute for Health and Care Excellence 2005; Faculty of Sexual and Reproductive Healthcare 2015). However, it is reported that at 5 years of use, less than 5 % of women will have experienced an expulsion (National

Institute for Health and Care Excellence 2005). The rate of expulsion does not appear to be influenced by the timing within the menstrual cycle that a Cu-IUD is fitted; no evidence is available for the LNG-IUS (Whiteman et al. 2013). However, when and how an intrauterine method is inserted post-partum and post-abortion does appear to exert some influence on the rate of expulsion. Expulsion rates following insertion of an IUD immediately following a vaginal delivery are higher than if the method is inserted during caesarean section (Goldstuck and Steyn 2013; Kapp and Curtis 2009). Waiting until more than 6 weeks post vaginal delivery appears to be associated with fewer expulsions than if the device is inserted in the first 48 h post-delivery (Kapp and Curtis 2009; Grimes et al. 2010a). Similar findings have been reported for post-abortion insertion (Grimes et al. 2010b).

Generally the type of framed Cu-IUD has not been found to influence the rate of expulsion (Kulier et al. 2007). The impact of modifying the frameless IUD inserter on early problems with expulsion is not known (O'Brien and Marfleet 2005). A Cochrane review of RCTs reported that the LNG-IUS has a higher rate of expulsion than Cu-IUDs containing more than 250 mm^2 (French et al. 2004), although the reverse has also been documented (Aoun et al. 2014).

During 3 years of use, the cumulative risk of partial or complete expulsion associated with the 13.5 mg LNG-IUS was under 5 % (Nelson et al. 2013).

Pelvic Inflammatory Disease

There have long been concerns that use of intrauterine methods increases a woman's risk of developing pelvic inflammatory disease (PID). As pelvic inflammatory disease is largely the result of a bacterial infection ascending from the cervix into the upper reproductive tract, the concern is predominantly that insertion of an intrauterine device may facilitate this process. The evidence supporting this concern is lacking (Farley et al. 1992; Grimes 2000) and generally much of the available evidence in this area is subject to limitations, confounding, and bias (Hubacher et al. 2013).

The insertion procedure and a woman's background risk of sexually transmitted infections (STIs) are the most likely contributing factors to the development of PID in intrauterine device users (Farley et al. 1992). In the first 20 days following insertion, the risk of PID is increased sixfold but remains low thereafter (Farley et al. 1992). The risk of PID is lower amongst women who have an IUD inserted in the absence of chlamydia or gonorrhoea; the risk for women with an STI appears similar, regardless of whether an intrauterine contraceptive device is inserted or not (Grimes 2000). NICE reports that PID may occur in fewer than 1 in 100 in women who are at low risk of sexually transmitted infections (National Institute for Health and Care Excellence 2005). Even in young women for whom their age means they are at increased risk of sexually transmitted infections and consequently PID, the benefits of IUD use are felt to outweigh any potential or theoretical risk (Centre for Disease Control and Prevention 2010; Faculty of Sexual and Reproductive Healthcare 2009a; World Health Organization 2010; Carr and Espey 2013).

However, in the presence of purulent cervicitis from chlamydia or gonorrhoea, or in symptomatic women awaiting test results, insertion of an intrauterine contraceptive device should be delayed (Centre for Disease Control and Prevention 2010; Faculty of Sexual and Reproductive Healthcare 2009a; World Health Organization 2010).

While background risk of STIs appears to be an influencing factor for developing PID, the type of Cu-IUD does not (Farley et al. 1992). There is conflicting evidence as to whether the LNG-IUS is associated with a lower risk than the Cu-IUD (Grimes 2000). A multicentre RCT which compared the copper IUD (Nova T) to the LNG-IUS (20 μg/daily) found that the cumulative rate of PID amongst women using the LNG-IUS was lower at 36 months than with the Cu-IUD (0.5 and 2.0 respectively) (Toivonen et al. 1991) whereas similar rates of PID were found in other studies comparing Cu-IUDs to hormonal IUDs (Sivin et al. 1991). In these two studies use of Cu-IUDs was not found to be associated with a higher rate of discontinuation due to PID than the LNG-IUS (Sivin et al. 1991; Toivonen et al. 1991). A systematic review concluded that incidence of PID amongst Cu-IUD users differs little to that experienced by women initiating other methods of contraception such as the LNG-IUS, the progestogen-only injectable or combined oral methods of contraception (Steenland et al. 2013).

For women who do develop PID with an intrauterine contraceptive device in situ, there appears to be no clear advantage in terms of clinical outcomes to having it removed for treatment (Tepper et al. 2013).

Perforation

Uterine perforations are a rare, yet potentially life threatening complication of intrauterine contraceptive use, which nearly always occur at the time of insertion but can often be asymptomatic (National Institute for Health and Care Excellence 2005; Kaislasuo et al. 2012; Harrison-Woolrych et al. 2003; Caliskan et al. 2003) and are sometimes not identified until months or years after insertion (Harrison-Woolrych et al. 2003; van Grootheest et al. 2011; Kaislasuo et al. 2013). An intrauterine device is not thought to 'migrate' through the uterine wall. However, less commonly an intrauterine device may penetrate into the myometrium: this is termed partial perforation (Zakin et al. 1981).

Perforation rates of less than 1 in every 1,000 intrauterine contraceptive device insertions are quoted (National Institute for Health and Care Excellence 2005), although rates observed in controlled clinical trials may be lower than those from real life situations and higher incidences have been documented, including in large cohort studies (Harrison-Woolrych et al. 2003; Caliskan et al. 2003). In the UK MHRA spontaneous reporting database, under levonorgestrel single agent products, there are 105 uterine perforations listed. Whilst the LNG-IUS is one of a number of single agent products listed, it would seem most likely that these reports relate to this product.

Rates of perforation with any IUD may in part be influenced by the maintenance of the skill of the operator. In a large prospective observational cohort study of a

copper IUD, doctors who had inserted fewer than 10 IUDs during the 10 year study period, (73 % of the sample) had significantly higher reported perforation rates than those who had inserted between 10 and 99 (Harrison-Woolrych et al. 2003).

Perforation typically occurs into the utero-rectal pouch with an anteverted uterus or vesicouterine pouch if retroverted (Zakin et al. 1981). It can also occur through the fundus particularly if the uterus is in an axial position. Usually the device, once translocated into the abdominal cavity, is free. Devices in the abdominal cavity may become adherent to omentum. There are very rare reports of perforation beyond the uterus into the bowel (Sarkar 2000; Rowlands 2010b).

The effect of breastfeeding or insertion during the postpartum period on perforation rates has been debated for over 25 years. A systematic review of poor to fair quality trials suggested that there is no increased risk of complications such as perforation when intrauterine methods are inserted in the postpartum period (Kapp and Curtis 2009). A number of studies suggest that uterine perforations with an intrauterine contraceptive method appear to be more common when a woman is breastfeeding (Kaislasuo et al. 2012; Harrison-Woolrych et al. 2003; Andersson et al. 1998; Heinemann et al. 2013b, 2014). However, that said, Medical Eligibility Criteria (Centre for Disease Control and Prevention 2010; Faculty of Sexual and Reproductive Healthcare 2009a; World Health Organization 2010) do not currently warn that the risk of perforation is increased by insertion in the postpartum period or amongst breastfeeding women. The type of Cu-IUD does not appear to be an influencing factor in perforation rates (O'Brien and Marfleet 2005).

The crude incidence for complete or partial perforation has been very low (0–0.03 %) in clinical trials of low dose levonorgestrel intrauterine devices (Nelson et al. 2013; Gemzell-Danielsson et al. 2012).

Sepsis

Whilst a very rare occurrence, cases of invasive group A streptococcus have been reported following insertion of intrauterine contraceptive methods (Venkataramanasetty et al. 2009; Saleh et al. 2011; Gisser et al. 2002; Cho and Fernando 2013). Although asymptomatic women do not need to be screened for group A streptococcus prior to IUD insertion, women found to be carrying the organism in the vagina should be treated (Faculty of Sexual and Reproductive Healthcare 2015).

Vasovagal Syncope

Vasovagal syncope can occur after cervical dilatation and instrumentation of the uterus. Such events usually resolve quickly and rarely do such events require more than basic resuscitation measures. However, where bradycardia persists, further interventions may be required. The risk of this adverse event associated with IUD insertion is a reason for clinics to have resuscitation facilities on hand.

Removal Difficulties

Intrauterine devices are sometimes difficult to remove. There are various reasons for this. Some IUDs become embedded in the myometrium; such cases need careful assessment (Zakin et al. 1981). Postmenopausal women may need estrogen treatment to counteract atrophic changes before removal is possible. Intrauterine devices should not be left in situ in postmenopausal women because of the risk of pyometra.

Occasionally the threads break off from the vertical stem of the device. There are also some threadless devices. There are millions of women who have had stainless steel ring IUDs inserted in China. When these need removal a hook or alligator forceps will be needed (Cheung 2010; Penney et al. 2006).

Side Effects of Intrauterine Devices

Both Cu-IUDs and the LNG-IUS are associated with adverse effects and these will be described in this section. Despite containing a lower dose of progestogen than the LNG-IUS, the 13.5mg LNG-IUS has a similar side effect profile to that of the LNG-IUS (Gemzell-Danielsson et al. 2012). Where evidence to the contrary is available this will be specified.

Acne, Breast Tenderness, Headache, Libido and Mood Changes

As with other hormonal methods, product information for the LNG-IUS lists a number of systemic side effects commonly ($\geq$1/100 to $<$1/10) noted in clinical trials, including acne, breast tenderness, headache, libido and mood change. Hormonal side effects may result in higher removal rates than with use of Cu-IUDs (Chi 1991). There is relatively little comparative data from which to draw conclusions, however at 5 years when compared to non-hormonal IUDs, their side effect profiles have not been found to differ significantly (French et al. 2000). Use of intrauterine methods of contraception does not appear to negatively affect libido (Enzlin et al. 2012; Martin-Loeches et al. 2003; Bastianelli et al. 2011; Li et al. 2004).

Altered Bleeding Patterns

Initially, following insertion of an intrauterine device, bleeding patterns are often irregular, frequent or prolonged (Suvisaari and Lahteenmaki 1996). These patterns appear to improve with time (Suvisaari and Lahteenmaki 1996; Datey et al. 1995). However, for some women irregular bleeding will continue (Suvisaari and Lahteenmaki 1996; Hubacher et al. 2009), with one study reporting that irregular

bleeding was still present in around 20 % of women at 12 months of use (Suvisaari and Lahteenmaki 1996).

After using the LNG-IUS for 12 months or more, women are more likely to move towards infrequent bleeding or amenorrhoea (Suvisaari and Lahteenmaki 1996). This is not the case with use of Cu-IUDs. With the lower dose 13.5mg LNG-IUS the proportion of women experiencing amenorrhoea may be less than with the 52 mg LNG-IUS (Gemzell-Danielsson et al. 2012).

For both Cu-IUDs and the LNG-IUS, altered menstrual bleeding patterns are a reason often given for method discontinuation (National Institute for Health and Care Excellence 2005; Cox et al. 2002; Wong et al. 2009). A study designed to investigate characteristics associated with discontinuation and reasons for discontinuation of LARC methods reported that at 6 months, of those who discontinued their LNG-IUS before 6 months, 10 % (n = 14) reported doing so because of irregular or prolonged bleeding. The corresponding figure for those who had discontinued their Cu-IUD was 19.2 % (n = 10). Interestingly, amenorrhoea is a common reason for discontinuation of the LNG-IUS; some women appear to seek regular reassurance that they are not pregnant.

In terms of managing such bleeding, non-steroidal anti-inflammatory drugs (NSAIDs), may offer some benefit to women using Cu-IUDs (Godfrey et al. 2013). Long-term strategies to manage problematic bleeding associated with the LNG-IUS are lacking (Abdel-Aleem et al. 2013a). Guidance in the UK suggests trying a combined oral contraceptive for women experiencing unscheduled bleeding with the LNG-IUS (Faculty of Sexual and Reproductive Healthcare 2009b).

Ovarian Cysts

Ovarian cysts are documented in the Summary of Product Characteristics for the LNG-IUS (Bayer PLC 2013) and 13.5 mg LNG-IUS (Bayer PLC 2014) as commonly (>1/100 to <1/10) /very commonly (>1/10) reported in clinical trials. In a comparative trial, compared with the LNG-IUS, significantly fewer ovarian cysts were observed in women using lower dose levonorgestrel intrauterine systems (Gemzell-Danielsson et al. 2012).

Such cysts are not thought to present a clinical problem as they often resolve of their own accord. In a study of women with heavy menstrual bleeding, a higher incidence of ovarian cysts was found in those using an LNG-IUS compared to those who had undergone a hysterectomy (17.5 % vs 3 %) (21.5 % vs 8 %) at 6 and 12 months respectively (Inki et al. 2002): the cysts observed in women using the LNG-IUS tended to be small, asymptomatic, and 94 % resolved spontaneously. In a 5 year RCT comparing the LNG-IUS to a Cu-IUD, a non-significant increased risk of ovarian cyst formation was observed with use of the LNG-IUS: 1.5 (95 % CI, 0.51–4.4). Discontinuation rates for enlarged follicles were similar for the LNG-IUS and Cu-IUD: 0.09 and 0.07 per 100 women respectively (Andersson et al. 1994).

Weight Gain

Weight gain has been noted as a side effect in trials of Cu-IUDs and the LNG-IUS (Andersson et al. 1994; Sheng et al. 2009). However as a non-hormonal device, no effect on weight would be expected with the Cu-IUD and any observed gain is unlikely to be the result of this method of contraception. In trials comparing the LNG-IUS to the Cu-IUD no significant differences in documented (Dal'Ava et al. 2012) or perceived weight change (Nault et al. 2013) has been shown. Body composition has similarly not been found to be significantly different following 12 months of use, although LNG-IUS users demonstrated a significant increase in fat mass and loss of lean mass, whilst Cu-IUD users demonstrated a non-significant loss of fat mass and gain of lean mass (Dal'Ava et al. 2012). There is little evidence to suggest that use of progestogen-only contraceptives is associated with weight gain (Lopez et al. 2013a).

Return of Fertility After Use of Intrauterine Devices

Concerns about the effect on fertility has been cited as a reason for wariness in relation to long-acting contraceptives (Glasier et al. 2008). A cohort study (Doll et al. 2001) of nulliparous married women in Scotland and England reported that, even when controlling for potential confounding such as age and gynaecological history, there appeared to be an association between increased duration of IUD use and decreased fertility. Women who had used their device for 78 months or more had less favourable fertility patterns at 12 months after stopping than those who had used it for less than 42 months (28 % had delivered compared with 46 %) (Doll et al. 2001).

However, findings from other studies would generally suggest that women can largely be reassured that there does not appear to be a delay in return to fertility following use of intrauterine methods (Wilson 1989; Mansour et al. 2011) or an increase in the risk of tubal occlusion and infertility (Vessey et al. 1983; Hov et al. 2007). A non-systematic review of the literature has suggested that 1 year after stopping use of intrauterine methods, similar rates of pregnancies would be expected for these women as for those who had used no contraception or who had stopped using condoms (Mansour et al. 2011). Guidance indicates that women can be informed that after stopping their method that there is no delay (National Institute for Health and Care Excellence 2005; Faculty of Sexual and Reproductive Healthcare 2015).

Use of Intrauterine Devices by Young and/or Nulliparous Women

Provision of intrauterine methods to young or nulliparous women is often resisted due to misconceptions amongst healthcare providers as to the safety of these

methods (Tyler et al. 2012). Although there is some evidence to suggest expulsion rates may be higher in young women (Deans and Grimes 2009), there is no reason to deny a young person an intrauterine method on the basis of age or parity alone; in fact, medical eligibility criteria indicate that parity (parous or nulliparous) does not place any restriction on the use of intrauterine methods (Centre for Disease Control and Prevention 2010; Faculty of Sexual and Reproductive Healthcare 2009a; World Health Organization 2010). Although nulliparity is not listed as a contraindication to use, the licence for the 13.5 mg LNG-IUS suggests that it should not be first choice for nulliparous women (Bayer PLC 2014).

Section Summary: Intrauterine Devices

Intrauterine methods of contraception confer similar protection against pregnancy as sterilisation and are therefore highly effective. The LNG-IUS is licensed for use as a contraceptive for up to 5 years; the 13.5mg LNG-IUS can be used for up to 3 years. Depending on the device, Cu-IUDs can be used for between 5 and 10 years. In some circumstances intrauterine devices may be used for longer, for example when women are over the age of 45 years at the time they have their LNG-IUS inserted. Such use however, would be outside the terms of the product licence.

Studies to date have not demonstrated an association between use of intrauterine methods and cancer, indeed they may offer women some protection against endometrial cancer. Concerns about pelvic inflammatory disease and infertility appear to be largely unfounded; the risk is mediated in part by a woman's background risk of sexually transmitted infections, and after the first few weeks following insertion, a woman's risk is generally no higher than it would have been before insertion. Uterine perforations can occur during IUD insertion, but rarely do. There does not appear to be any way to ameliorate this risk, therefore women should be advised about thread checking and signs/symptoms that may be indicative of uterine perforation.

An ectopic pregnancy is a potentially life threatening event. Women who use intrauterine contraceptives are largely protected from ectopic pregnancy by the very fact they are using such an effective method of contraception. However, health professionals should be aware, that if these methods fail, the chance of the pregnancy being ectopic is higher than for women not using contraception. There is no reason why nulliparous women cannot safely use intrauterine contraceptive methods if they choose to, although the licence for the 13.5 mg LNG-IUS advises it should not be first choice for nulliparous women.

Combined Hormonal Patch and Vaginal Ring

In addition to combined oral contraceptives (COCs), which were discussed in Chap. 5, a combined vaginal ring (Nuvaring®) and a combined transdermal patch (Evra®, Evra 3®, Ortho Evra®) are available to women in many countries for example the United States, Canada, Australia, and throughout Europe. Whereas the combined vaginal ring is available in New Zealand, the transdermal patch is not.

The combined vaginal ring contains 2.7 mg of ethinylestradiol and 11.7 mg etonogestrel which are released at a rate of 0.015 and 0.120 mg per 24 h respectively (Merck Sharpe and Dohme 2014).

The active hormones within the transdermal patch are ethinylestradiol and norelgestromin. The total content and release rates vary slightly depending on whether it is OrthoEvra or Evra but both currently marketed products release approximately 35 μg of ethinylestradiol a day (Janssen-Cilag 2014; Janssen Pharmaceuticals 2014). The daily release rate of norelgestromin from OrthoEvra is quoted as 150 μg (Janssen Pharmaceuticals 2014); in the UK for Evra it is quoted as 203 μg (Janssen-Cilag 2014).

In the UK, the licensed advice, according to the Summary of Product Characteristics, is that the contraceptive ring is inserted into the vagina and worn for 3 weeks (Merck Sharpe and Dohme Limited 2014). It is then removed for 1 week following which a new ring is inserted. The contraceptive patch requires a new patch to be applied and replaced weekly for 3 weeks, followed by a 7-day hormone free interval (Janssen-Cilag 2014). Extended regimens e.g. omitting the ring-or patch-free interval can be used but would be outside the terms of the product licence (Faculty of Sexual and Reproductive Healthcare 2011b).

Effectiveness of the Vaginal Ring and Patch

The effectiveness of the combined vaginal ring and patch have each been shown to be comparable with that of COCs (Lopez et al. 2013b). Oral methods undergo extensive first pass metabolism and therefore their efficacy is affected by factors that affect absorption such as vomiting or severe diarrhoea, whereas the ring and patch are not. However, as with oral methods, the effectiveness of the patch and ring has the potential to be affected by drugs that induce microsomal/hepatic enzymes such as certain antiepileptic, human immunodeficiency virus (HIV) and herbal medications/products (Merck Sharpe and Dohme Limited 2014; Janssen-Cilag 2014).

Eligibility Criteria for the Patch and Ring

The majority of the available epidemiological evidence for combined hormonal contraceptives relates to oral contraceptives. There is less available data for the ring

and the patch. However, the WHO, US and UK Medical Eligibility Criteria for Contraceptive Use (MEC) (Centre for Disease Control and Prevention 2010; Faculty of Sexual and Reproductive Healthcare 2009a; World Health Organization 2010) generally apply the same restrictions to these methods as to COCs and therefore the same cautions and considerations should broadly be applied to these methods as to COCs. Likewise, although direct evidence is scant, if the risks are assumed to be similar, it would be reasonable to assume that the beneficial effects may also extend to these methods.

Safety Profile

As with COCs, cycle control with these two combined hormonal methods is good (Lopez et al. 2013b). The side effect profiles are generally similar to those experienced with the COC (Lopez et al. 2013b), although there are some notable differences. A Cochrane review noted that compared with COC use, those who used the ethinylestradiol/etonogestrel vaginal ring were less likely to experience nausea, acne, irritability, depression and mood changes and were less likely to discontinue their method due to adverse events than COC users (Lopez et al. 2013b). Ring users were however more likely to report vaginal irritation and discharge than COC users (Lopez et al. 2013b), which could in theory be in part a consequence of their route of administration.

However, norelgestromin/ethinylestradiol patch users were more likely to experience breast discomfort, dysmenorrhea, nausea, and vomiting and compared to COC users were significantly more likely to discontinue due to adverse events (Lopez et al. 2013b).

In 2006 the application for the EVRA (norelgestromin/estradiol) patch was declined in NZ because of an unfavourable risk: benefit assessment, with concerns noted about the high incidence of estrogenic side effects (Medsafe. Extract from 78th MAAC minutes. 2006). In the US, product information for OrthoEvra states that the estrogen exposure is 60 % higher than if taking an oral contraceptive containing 35 μg of ethinylestradiol (Janssen Pharmaceuticals 2014).

Risk of Venous Thromboembolism

As with COCs, one of the biggest safety concerns, in relation to the use of these combined hormonal devices is the risk of thrombosis (see Chap. 6). The ring and patch contain ‘newer’ generation progestogens and, as discussed in Chaps. 5 and 6, there has been much interest in the impact these progestogens have on mediating thrombosis and cardiovascular risk. While some studies have suggested that, in comparison to COCs containing ‘older’ progestogens such as levonorgestrel and norethisterone, the transdermal patch presents a generally similar level of

venous thromboembolism (VTE) risk (Jick et al. 2006, 2007, 2010), others have suggested that the risk is greater (Lidegaard et al. 2012a; Cole et al. 2007; Dore et al. 2010; European Medicines Agency 2014).

While there is less available data for the combined vaginal ring, reported findings regarding risk of VTE are also conflicting (Lidegaard et al. 2012a; Sidney et al. 2013). No studies to date have suggested a decreased risk for either the patch or the ring compared with oral contraceptive pills and therefore despite the ring being lower dose, there is no apparent benefit in terms of VTE risk in the use of a non-oral method.

The European Medicines Agency (European Medicines Agency 2014) published findings of a review in 2013 which stated that certain progestogens (including those in the patch and ring) are associated with an increased risk of thrombosis compared to others. However, the absolute risk of VTE they report is generally very low with combined hormonal contraceptive methods containing less than 50 μg of ethinylestradiol (5–12 per 10,000 women depending on the progestogen used- see Chaps. 6 and 14) and the conclusion is that for most women the benefits of combined hormonal contraceptives outweigh the risks when prescribed appropriately (European Medicines Agency 2014).

Vaginal Ring for Lactating Women

A progesterone releasing ring is available for breastfeeding women in Latin America. It is inserted once every 3 months for as long as breastfeeding continues, helping to prolong amenorrhoea and reduce the number of bleeding/spotting episodes (Nath and Sitruk-Ware 2010). Amongst breastfeeding women it has been shown, at 1 year, to compare favourably with the IUD use in terms of efficacy (Sivin et al. 1997). Over the 3 month period, the flexible silicone ring releases progesterone at an average rate of 10 mg/day (Nath and Sitruk-Ware 2010). No adverse effect on breastfeeding outcomes or infant growth has been shown with the use of this method (Nath and Sitruk-Ware 2010). Vaginal complaints may be more common with use of the progesterone releasing ring as compared with the IUD (Nath and Sitruk-Ware 2010; Sivin et al. 1997).

Section Summary: Combined Hormonal Patch and Vaginal Ring
There are a number of currently marketed hormonal contraceptive devices and many more under development. Long-term data from epidemiological studies on combined contraceptive devices such as the transdermal patch and vaginal ring are lacking. However, studies which have looked at VTE risk do not suggest any potential benefit to non-oral routes. The risks associated with

(continued)

use of these combined contraceptive devices are taken to be the same as for combined oral contraceptives with similar prescribing restrictions applied.

The transdermal patch and vaginal ring have been approved for use in several major markets including the UK and the USA, which indicates that the benefit to risk assessment was considered favourable for the licensed indications. In other words, the benefits of contraceptive protection provided by these devices outweighed the risks of adverse events. However it should be noted that the evidence to support approval is derived mainly from clinical trials and longer term studies of post-marketing use are required. It should also be noted that the combined contraceptive patch EVRA® has not been approved in all markets.

Take Home Messages

- Progestogen-only implants and intrauterine contraceptive devices are highly effective methods of contraception.
- Progestogen-only implants and intrauterine devices are generally very safe.
- Many of the risks associated with use of the progestogen-only implant are a consequence of the insertion and removal procedure, not the device itself; therefore there is scope for reducing these risks.
- The most commonly experienced side effect of progestogen-only devices is irregular vaginal bleeding
- Perforation of the uterus is a recognised but rare complication of intrauterine device insertion; there is no obvious way of significantly reducing the incidence.
- Use of intrauterine contraceptive devices does not need to be restricted to parous or older women.
- Further research is needed with regard to efficacy in women of heavier weight and the safety of progestogen-only methods in high risk populations.
- Initially, following insertion of intrauterine methods of contraception women may experience changes to their regular bleeding patterns- with time, absent or infrequent bleeding is likely with the use of the LNG-IUS.
- In many countries, newer hormonal contraceptive devices are now available, including a transdermal patch and a vaginal ring
- Although in some countries the transdermal patch has not been licensed, currently available medical eligibility criteria consider that contraceptive devices releasing estrogen and progestogen directly through skin or mucous membrane are considered to have similar risk and benefit profiles as combined oral contraceptives.

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Chapter 9
Human Papilloma Virus Vaccines

Margaret Stanley

Introduction

Papillomaviruses are small double stranded DNA viruses infecting the squamous epithelia (skin and internal mucosae) of both animals and man. Human papilloma viruses (HPVs) are not classified as serotypes but as genotypes on the basis of the DNA sequence of the major coat protein L1. HPVs are a very large branch of the papillomavirus family with the DNA of more than 130 HPV types, many of which have been fully sequenced, having been isolated from tissue biopsies (de Villiers 2013). Despite the daunting number of HPVs they fall basically into two groups: those that infect skin, or cutaneous surfaces, and those that infect the internal wet squamous mucosal surfaces, particularly the genital tract. Within these groups there are low-risk types (LRHPV), which generate benign lesions, in other words warts, and high-risk or oncogenic types (HRHPV), that are associated with cancers and their precursor lesions.

Burden of Disease Attributed to Genital HPVs

Approximately 40 HPV types regularly or sporadically infect the mucosal epithelial surfaces of the lower genital tract causing both warts and cancers. The LRHPV types, HPV6 and 11 cause more than 90 % of external genital warts with minor types (HPV42,44) and some HRHPVs contributing to the remaining 10 % (Lacey et al. 2006). HPV associated malignant disease in the genital tract is dominated by HPV16 and HPV18 which, with their close relatives, 31, 33, 35, 52, 58, 39, 45, 59, 56, 66 and 51, are the cause of virtually all cervical cancer and the majority of the

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high grade cervical cancer precursor lesions CIN2/3 (cervical intra-epithelial neoplasia grades 2 and 3) (Bosch et al. 2008). Thus 99 % or more of biopsies of invasive cervical cancer worldwide, and approximately 80 % of CIN 2/3 contain HRHPV DNA sequences. HPV16 dominates, and is present in at least 50 % of cancers irrespective of geographical location, followed by HPV18, 7–20 %. However invasive cervical cancer is not the only malignant disease associated with HRHPV infection, HPV DNA sequences are found in most anal and tonsil carcinomas, and a proportion of vulvar, vaginal, penile and head and neck cancers. HPV16 again is the dominant oncogenic type (Parkin and Bray 2006; Gillison et al. 2012). Overall, the global malignant burden attributable to HPV infection is calculated to be 5.2 % of all cancers (Ferlay et al. 2010).

Benign disease caused by the mucosal LRHPVs is not trivial. Genital warts are the most common viral sexually transmitted disease, they are highly infectious, refractory to therapy, result in significant morbidity and are a health economic burden (Woodhall et al. 2009). In immunocompromised patients, such as those with HIV they can form large polypoid growths requiring surgical intervention and be a clinical management problem (Denny et al. 2012). A maternal history of genital warts (Silverberg et al. 2003) is associated with a 231-fold risk for recurrent respiratory papillomatosis (RRP) an uncommon but potentially devastating disease, characterized by the growth of wart-like benign neoplasms throughout the aerodigestive tract that often requires repeated surgeries (Derkay and Darrow 2000).

HPV Vaccines: Rationale

Traditionally prophylactic vaccines that generate virus specific neutralising antibody have represented a cost effective means to control viral diseases. HPV should, in theory, be no exception but the exquisite host and tissue tropism and complex biology of the papillomaviruses differentiates them from most other viruses against which vaccination has proved successful. The HPV life cycle is exclusively intra-epithelial and only a fully differentiated squamous epithelium supports the complete infectious cycle and the production of infectious particles (Doorbar et al. 2012). There is no detectable viraemia, virus particles are shed from mucosal surfaces far from lymphatics and vascular channels and, not surprisingly, systemic cellular and humoral immune responses to HPV antigens are poor (Stanley 2008). Serum neutralizing antibody to the major capsid protein L1 is generated in genital HPV infections but neutralizing antibody titres are very low and only about 50–70 % of infected individuals sero-convert (Carter et al. 2000). Furthermore the degree of protection and the duration afforded by antibody in natural infections is not known. Re-infection with the same HPV genotype and reactivation of latent virus is thought to occur, even in seropositive individuals, so would vaccines that generate neutralising antibody protect against HPV infection and disease?

The evidence from animal papillomavirus infections, including some of the earliest published works from Shope, the founding father of papillomavirus

research, showed very clearly that neutralizing antibody was protective (Shope 1937). In Shope's experiments if rabbits were infected systemically with the cotton tail rabbit papillomavirus (CRPV) by direct injection of virus into the muscle or bloodstream, papillomas did not arise on the skin of the animals but neutralizing antibody was generated and the animals were completely resistant to viral challenge by abrasion of the skin, the route of infection by papillomaviruses. This and other data suggested very strongly that generating neutralizing antibody to virus coat protein would be an effective prophylactic vaccine strategy. Neutralising antibodies are directed against the L1 coat or capsid protein and the generation of this antibody requires the protein to be in the tertiary or native form. Since these viruses cannot be grown in bulk in tissue culture and viral particles particularly of the oncogenic types are sparse in lesions, the generation of native, or properly folded L1 protein, was challenging. The challenge was met by the demonstration that if the L1 gene was expressed via a viral or yeast vector, the L1 protein was produced in large amounts and self-assembled into a macromolecular structure, a virus-like particle (VLP) an empty capsid that is geometrically and antigenically almost identical to the native virion (Zhou et al. 1991; Kirnbauer et al. 1992). These VLPs were shown to generate neutralizing antibody in the animal models and immunized animals were protected against high-level virus challenge (Suzich et al. 1995; Breitburd et al. 1995).

Licensed Prophylactic HPV Vaccines

The currently licensed prophylactic HPV vaccines are subunit vaccines comprised of virus-like particles (VLPs) formed of the L1 protein. Vaccine HPV VLPs are made using sophisticated recombinant technologies in which the L1 gene of specific HPV types is recombined into the host genome of the yeast *Saccharomyces cerevisiae* or the insect virus baculovirus and the L1 protein expressed via these recombinant vectors. The chemistry of the expressed protein is such that it spontaneously assembles into VLPs that are morphologically and antigenically similar to the wild-type virus particle illustrated in Fig. 9.1. However, VLPs lack DNA and are non-infectious and non-oncogenic (Stanley et al. 2006). There are two prophylactic HPV L1 VLP vaccines. These are Cervarix®, a bivalent HPV (bHPV) 16/18 product from GlaxoSmithKline Biologicals Rixensart, Belgium and Gardasil® (also known as Silgard), a quadrivalent HPV (qHPV) 6, 11, 16, 18 product from MSD, Whitehouse Station, New Jersey, USA. These products are licensed in more than 160 countries.

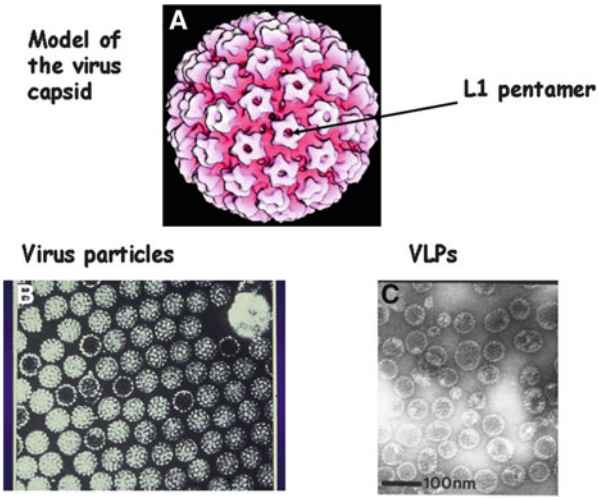

Fig. 9.1 *Panel A*: A model of the papillomavirus coat or capsid. There are two coat proteins L1 and L2. The rosette like surface structures (*arrowed*) are pentamers each consisting of five molecules of L1, one molecule of L2 fits into the central dimple of each pentamer. *Panel B*: Papillomavirus particles, both full (contain DNA) and empty particles can be seen. *Panel C*: HPV 16 L1 virus like particles, VLPs, made by expressing the HPV 16 L1 gene in baculovirus. The L1 protein so expressed spontaneously assembles into empty capsids or VLPs that are morphologically similar to the empty virus particles seen in panel B. From Stanley et al. 2006 with permission

Vaccine Efficacy

Both vaccines have undergone large, randomised, placebo controlled, double blind phase III trials (RCTs) in young women, 15–26 years old. For a detailed review see Schiller (Schiller et al. 2012) and also details in Table 9.1 and mentioned below.

These trials were designed primarily to demonstrate efficacy in preventing high grade cervical intraepithelial neoplasms (CIN2/3) and Adenocarcinoma in situ, (AIS) caused by infection related to the vaccine HPV types (both vaccines) or vaginal intra-epithelial neoplasia (VaIN) and vulval intra-epithelial neoplasms (VIN) and external genital warts (qHPV vaccine). Two phase III studies evaluated the qHPV vaccine (Future I and Future II) and two evaluated the bHPV vaccine (Patricia and the Costa Rica vaccine trial (CVT)). The Future I and II and Patricia trials were company sponsored multi-centre trials in Europe, the Americas and Asia Pacific. The CVT was a US Government sponsored community based trial in Guanacaste Province, Costa Rica; the primary endpoint in this trial was 12 month HPV 16/18 persistent infection, a prerequisite for development of CIN. The qHPV vaccine has also undergone trials in 16–23 year old men to determine efficacy against external genital warts in heterosexual men (Giuliano et al. 2011) and anal intraepithelial neoplasia in men who have sex with men (Palefsky et al. 2011).

Table 9.1 Phase III randomised control trials (RCTs) end of study: per protocol efficacy populations

Vaccine	Quadrivalent	Bivalent
Women 15–26 years		
Mean follow up	42 months	42 months
Prophylactic efficacy	% 95 % CI	% 95 % CI
HPV16/18 CIN[a]2	100 (95,100)	95 (88,98)
HPV16/18 CIN3	97 (88,100)	92 (67,91)
HPV 16/18 AIS[b]	100 (31,100)	100 (−8,100)
HPV16/18 VIN3[c]/VaIN3[d]	100 (83,100)	Not reported
HPV6/11/16/18 VIN1/VaIN1	100 (86,100)	Not a target
HPV6/11/16/18 EGL[e]	99 (97,100)	Not a target
Women 25–45 years		
6/11/16/18 PI[f]/CIN/VIN/VaIN	89 (78,95)	
Men 16–23 years		
HPV 16/18/6/11 EGL (MSW[g])	90 (69,98)	No studies
HPV 16/18/6/11/AIN[h] (MSM)[i]	78 (40,93)	No studies

Notes
[a]CIN cervical intra-epithelial neoplasia
[b]AIS adenocarcinoma in situ of the cervix
[c]VIN vulval intra-epithelial neoplasia
[d]VaIN vaginal intra-epithelial neoplasia
[e]EGL external genital lesions
[f]PI persistent infection
[g]MSW men who have sex with women
[h]AIN anal intra-epithelial neoplasia
[i]MSM men who have sex with men

Quadrivalent vaccine: Data for CIN2/3 and AIS are a combined analysis of four randomised clinical trials (Kjaer et al. 2009). 20,583 women aged 16–23 years with a lifetime history of not more than 4–5 sex partners and negative for HPV 16 and/or 18 infection from month 0 though to 1 month post the 3rd immunisation were randomised to receive vaccine or placebo. The primary composite endpoint was the combined incidence of HPV 16/18 related CIN2/3, AIS or cervical cancer. Case definition was a diagnosis by the pathology panel of CIN2, CIN 3, AIS or invasive cervical cancer. Data for HPV 6/11/16/18 related anogenital disease from 5,455 women 16–24 years randomised to receive vaccine or placebo PCR and seronegative for vaccine type HPV at month 0 through to month 7. Coprimary composite endpoints were the incidence of HPV 6/11/16/18 related external genital warts vulval and vaginal intraepithelial neoplasia and invasive cancer
Bivalent vaccine: The data are from the pivotal Phase III randomised control trial PATRICIA (Lehtinen et al. 2012) n = 7,338 vaccine group n = 7,305 placebo. The according to protocol cohort are women 15–25 years HPV 16 and 18 sero-negative and PCR negative at baseline and at month 6, with less than 6 lifetime sexual partners (Lehtinen et al. 2012). The primary endpoint was the incidence of HPV 16/18 related CIN2/3

End of study analyses of the pivotal phase III trials in young women have now been published and are summarised in Table 9.1. The design of the RCTs differs significantly for both vaccines in terms of population demographics, baseline inclusion criteria for case assignment, serological and DNA detection methods (Schiller et al. 2012). However both vaccines have shown very high efficacy –

greater than 94 % – against HPV 16/18 caused high grade CIN2/3 – the endpoint accepted as the ethically acceptable proxy for vaccine efficacy against cervical cancer (Pagliusi and Teresa Aguado 2004). In the according to protocol (ATP) cohort i.e., women 15–26 years old, HPV DNA negative by Polymerase Chain Reaction and sero-negative for vaccine type HPVs at trial entry and after completion of the three dose immunisation regime, efficacy against intra-epithelial cervical disease of all grades caused by the HPV types in the vaccines was greater than 90 % (Kjaer et al. 2009; Lehtinen et al. 2012) and is maintained for at least a decade (Roteli-Martins et al. 2012b; Rowhani-Rahbar et al. 2009).

Implementation and Effectiveness

HPV vaccines are prophylactic, not therapeutic, preventing not treating infection and they are not effective in individuals with already established infections. Genital HPV infection is usually sexually transmitted and the most important risk period for acquisition of a genital HPV is soon after the onset of sexual activity (Winer et al. 2008). The average age of sexual debut varies widely between societies but to be assured that the vaccine recipients receive protection, young adolescents in the 9–14 year age group should be targeted. Immunisation before puberty with HPV vaccines is immunologically optimal and antibody responses 2× greater are achieved in 9–13 year old adolescents compared to 15–23 year old women (Giuliano et al. 2007; Reisinger et al. 2007). The recommendations for HPV vaccination in most countries – both in the developing and developed world – recognise this and are remarkably uniform in targeting 12–14 year olds as the primary group for immunisation (Dorleans et al. 2010; Garland et al. 2011). Catch up programmes are recommended in some countries but there is variability in the age of the catch up populations (Dorleans et al. 2010).

Vaccine Impact

At the time of writing HPV vaccination has been incorporated into the National Immunisation Programme in 62 countries covering all continents and evidence of the impact on disease and infection is becoming available. Some of the most striking effectiveness data come from Australia which commenced an HPV immunisation programme in April 2007 targeted to girls aged 12–13 years with a catch up programme over 2 years for 13–26 year old young women. The programme was funded by the Federal Government but delivered by the States and Territories through schools and for the older girls via clinics and GP practices. The quadrivalent vaccine was used and coverage rates (for the full three dose regime) of approximately 75 % were achieved for the school programme (up to 17 years) with lower rates in the older girls (Garland et al. 2011).

Disease Impact

Genital warts, more than 90 % of which are caused by HPV 6 and 11, have a short natural history with lesions appearing within 3–6 months of infection. To assess vaccine impact on genital wart incidence, patients attending eight sexual health centres for the first time between 2004 and 2011 (n = 8,770) in major Australian cities were surveyed (Read et al. 2011). Those with a diagnosis of new genital warts (n = 7,686) were stratified by age group (<21 years, 21–30, > 30 years) at the time of presentation (Ali et al. 2013). Over the post-vaccination period July 2007 to mid-2011, the incidence of genital warts fell by 92.6 % in women under 21 years, 72.6 % in women under 30 years but there was no decline in those over 30 years. In men who have sex with women (MSW) aged <21 years incidence of genital warts fell by 81.8 %, by 51.1 % in those 21–30 years and 15 % in those >30 years. No decline was observed in bisexual or homosexual men.

Denmark introduced vaccination for 12 year old girls in December 2009 and this was preceded by a catch up programme for 13–15 year old girls in August 2008. Coverage overall was 85 %. Following the introduction of vaccination, the incidence of genital warts in females decreased by 3 % annually but no decline was observed in males (Baandrup et al. 2013). The most dramatic falls were in the youngest cohorts of 16–17 year old girls where genital warts were almost eliminated (Baandrup et al. 2013).

The rationale for immunising only one gender (females) against a sexually transmitted infection is that this generates herd protection by blocking transmission to effectively protect the non-immunised men (Garnett 2005). This hypothesis is supported by the Australian results but not, at the present, by the Danish data. The reasons for this are not clear currently, but geography may be relevant. Denmark is a small country easily accessible to countries with populations with low HPV vaccine coverage. Australia is a huge island with high vaccine coverage and major population centres thousands of kilometres distant from potential contact with non-immunised young women.

Disease Impact: Cervical Abnormalities

Reductions in cervical cancer will only be seen in the long term – decades after vaccination – but reductions in precancerous lesions caused by vaccine HPV types should be detectable in the medium term. Reductions in cervical abnormalities have been observed following the Australian National Vaccination Programme. In a retrospective cohort analysis between April 2007 and December 2011, the effectiveness of the HPV vaccine against CIN1, CIN2, CIN3 and AIS (histologically diagnosed) was assessed in vaccinated and unvaccinated women in the state of Victoria (Gertig et al. 2013). Vaccine effectiveness was highest in the cohort vaccinated at the youngest age (less than 14 years) with 75 % reduction in any

high grade histology (CIN2/3 or AIS) compared to 32 % in those vaccinated at 17 years. Overall the data from this study and from other Australian states (Crowe et al. 2014) indicates that in the vaccinated cohorts (age 12–26 years) high grade cervical abnormalities (CIN2/3, AIS) have decreased by about 48 %, a situation predicted by data from the earlier randomised controlled trials (Munoz et al. 2010).

Vaccine Impact: Reduction in Infection

A key outcome of vaccination should be a reduction in virus load in the population overall. In a study of women attending Family Planning Clinics in two centres in Australia the prevalence of HPV 6,11,16,18 DNA in cervical swabs fell from 28.7 % before vaccination to 6.7 % post vaccination (Tabrizi et al. 2012). In the USA, vaccine cervical HPV type prevalence in females 14–19 years old in the pre vaccine era (2003–2007) was 11.5 %, but post vaccine (2007–2010) this fell to 5.1 % (Markowitz et al. 2013). The UK used the bivalent HPV vaccine from 2008 to 2012. In Scotland women are called for cervical cancer screening from age 20 years and in a study determining cervical HPV prevalence in cervical smears from this cohort 3 years post vaccination, a significant reduction in HPV 16 prevalence was observed (Kavanagh et al. 2014). In England women are not called for screening until age 25 years, but HPV16/18 prevalence pre and post vaccination was assessed in a study using vulval/vaginal swabs collected for Chlamydia screening in sexually active 16–24 year old women (Mesher et al. 2013). In the 16–18 year age group who had an estimated vaccine coverage of 65 %, HPV16/18 prevalence fell from 19.1 % to 6.5 % after vaccination compared to no change in the 22–24 year old cohort who were not immunised (Mesher et al. 2013).

Overall, studies assessing the impact of routine use of both commercially available vaccines in several countries have shown a significant reduction in prevalence of vaccine HPV types in young women. Studies using the qHPV vaccine have shown a consistent decrease in genital warts and early evidence of a reduction in high grade cervical abnormalities. It can be concluded that so far the vaccines are doing their job reducing disease and infection.

Mechanism of Protection

The current assumption is that the protection afforded via these vaccines is antibody mediated since passive immunisation is protective in animal models (Suzich et al. 1995; Breitburd et al. 1995) but how can antibody in the serum protect against infection with a virus that is exclusively intra-epithelial? HPV infects cells in the basal layer of squamous epithelium at multiple sites in the anogenital tract – the cervical squamo-columnar junction, the ectocervix, the upper and lower epithelium of the vagina, multiple sites on the vulva, perianal and intra-anal epithelium, penile

shaft and the scrotal skin (Doorbar et al. 2012). The cervical squamo-columnar junction is bathed in cervical mucus and it could be argued that passive transport of serum antibody into these secretions would be the mechanism of protection. However, this could not explain protection at the well keratinised surfaces of the vulva, penis and scrotal skin. Virus neutralising antibody prevents virus entry into cells and the questions therefore are: how does HPV infect the basal cell of stratified squamous epithelium and how do neutralising antibodies prevent this?

These questions have been addressed in a series of elegant experiments with a cervico vaginal model of infection using a surrogate virus or pseudovirion (Roberts et al. 2007). Pseudovirions are L1/L2 VLPs that have packaged DNA encoding a reporter protein such as an enzyme or a fluorescent protein, the expression of which allows the pseudovirion to be tracked in cells or tissues. These studies showed that epithelial micro-abrasion and wound healing were necessary for HPV infection of basal cells. Only micro-abrasion that resulted in the removal of the full thickness of the epithelium but retention of the epithelial basement membrane permitted infection of basal cells, since pseudovirions attached first to the basement membrane (BM) before finally entering a basal cell. This sequence of events provides a mechanistic explanation for antibody protection and potentially for the recall or anamnestic memory response. The micro wound from the epithelial denudation would result in an immediate serous exudate into the wound bed. This exudate would be rich in large plasma proteins including serum immunoglobulins together with phagocytes and immunocytes including B memory cells. Virus neutralisation and potentially a modest recall response would then ensue.

Duration of Protection

Immune Memory

Immune memory is the basis of successful vaccination and the evidence from the vaccine RCTs and post-vaccine immunosurveillance suggests that HPV vaccines induce robust memory. The antibody response after the three dose immunisation schedule follows the expected pattern (Villa et al. 2006; Harper et al. 2006). After each vaccine dose antibody levels increase until a peak antibody concentration 50–1,000 times greater than natural infection is achieved 1 month after the 3rd and final dose in the primary schedule. Antibody concentrations wane over the subsequent 12–18 months but then stabilise at a plateau level with geometric mean titres (GMTs) on average 10 times greater than in the placebo groups. This pattern is consistent with the notion of the generation of a large population of antibody secreting plasma cells after dose 3, with varying life spans but some with the ability to migrate to the bone marrow surviving as long lived plasma cells maintaining a low but constant antibody production. Serum neutralising antibody persists with GMTs about 10 times greater than natural infection for the 7–9 year duration of the

published studies (Roteli-Martins et al. 2012a; Rowhani-Rahbar et al. 2012). Mathematical modelling predicts slow decay of antibody over a 30–50 year period and potentially, therefore, protection over that time. Both type specific and cross neutralising antibodies are generated by VLP vaccines although concentrations of cross neutralising species are on average 100 times lower than type specific (Einstein et al. 2011).

Antigen challenge at 60 months after the first dose with both vaccines results in a rapid and robust anamnestic or recall response with antibody levels rising within 3–5 days to levels greater than that achieved at peak in the initial immunisation schedule, demonstrating the presence of reactive memory B cells (Olsson et al. 2007; Moscicki et al. 2012). Collectively these data strongly imply that HPV VLP immunisation generates both components of the antibody memory response i.e. serological memory and reactive memory, a prerequisite for long term vaccine induced protection. However at the present there is no immune correlate, and no antibody concentration (or other immune measurement) has been defined that correlates with protection.

Safety

The safety profile of both vaccines was assessed extensively in the RCTs and by robust pharmacovigilance in the post licensure setting using both passive and active vaccine surveillance. Passive surveillance is voluntary reporting in daily practice by vaccinated persons (or others) and medical professionals to manufacturers, national surveillance systems such as the USA VAERS and Australian TGA databases or multinational databases, for example the WHO VIGIbase and EUVAX of the EU commission (Labadie 2011) Active surveillance is the implementation of systematic procedures to actively seek and identify clinically significant events that occur within a defined period and/or population and include large post-licensure studies sponsored by the manufacturer or national regulatory authorities (Gee et al. 2011; Bonanni et al. 2010).

The most commonly reported vaccine related adverse events (AE's) are injection site reactions including pain, swelling, erythema, these are usually of short duration and resolve spontaneously (Slade et al. 2009;Angelo et al. 2014). Systemic AE's, such as myalgia, fatigue, have been mild and self-limited (Harris et al. 2014). Post vaccination syncope has occurred and is considered to be a psychogenic reaction (Buttery et al. 2008) and it is recommended that after vaccination there is a 15 min observation period. Serious vaccine related AE's such as anaphylaxis are very rare. In Ontario between 2007 and 2011 691,994 doses of the qHPV vaccine were distributed in a school based programme, two cases of anaphylaxis were reported but on review the reports of anaphylaxis did not meet the Brighton anaphylaxis definition (Harris et al. 2014). No associations with new onset chronic conditions such as auto-immune disease have been identified in large well

conducted population based studies (Gold and McIntyre 2010; Chao and Jacobsen 2012)

The key challenge faced in pharmacovigilance is to distinguish real AE's from background conditions that would occur regardless of vaccination. Studies providing population based data on incidence of potential adverse events prior to vaccination allow analysis of observed/expected rates in vaccinated populations (Siegrist et al. 2007; Callreus et al. 2009). In the UK the MHRA (Medicines Health and Regulatory Agency) has the responsibility for monitoring HPV vaccine safety by analysis of passive surveillance data communicated via the yellow card report scheme (http://yellowcard.mhra.gov.uk/). A central element to this is the use of statistical tools to identify safety signals. As an example, to 2012 about 30 % of reports AE's after immunisation with Cervarix were related to nervous system disorders most of which, such a syncope, were psychogenic – the fear or anticipation of a needle injection. There were six reports of encephalitis and one of encephalitis lethargica but, given the expected background incidence of these conditions, this is consistent with chance not causality. No safety signals were identified in any analyses for neurologic, auto-immune or other disease states.

HPV vaccines are not recommended for administration during pregnancy but surveillance of pregnancy outcomes following inadvertent vaccination has revealed no adverse outcomes such as miscarriage, congenital abnormalities or premature labour beyond background rates. Both manufacturers have pregnancy registries monitoring outcomes in those inadvertently vaccinated (Dana et al. 2009).

HPV vaccines are now given to boys in the Australian National Immunisation programme and the safety profile parallels that observed in girls. The Global Advisory Committee on Vaccine Safety (GACVS) of WHO recently published a safety update on HPV vaccines and commented: *In summary, 4 years after the last review of HPV vaccine safety and with more than 170 million doses distributed worldwide and more countries offering the vaccine through national immunization programs, the Committee continues to be reassured by the safety profile of the available products.*

Alternative Dosage Schedules

In view of the overwhelming data on efficacy from the RCTs and the emerging data on population effectiveness, the focus of discussions about the current vaccines is no longer about efficacy but rather about implementation, access and affordability. In this context changing the dosage schedules has been a topic of discussion. HPV vaccines are delivered in three doses at 0, 1–2 and 6 months. In immunological terms this is a 'prime, prime boost' schedule with the extended period between dose 2 and 3 required for the generation after dose 3 of high concentrations of high affinity antibody and robust immune memory. Several studies have shown that the interval between doses 2 and 3 can be extended (but not reduced) to 12 and even 24 months (Lamontagne et al. 2013; Brown et al. 2012; Esposito et al. 2011). In

many settings this flexibility is important for implementation and high uptake of the vaccines.

Antibody responses in young adolescents before or at the time of puberty are optimal with antibody titres twice those achieved in the 16–26 year old women in whom efficacy has been demonstrated in the RCTs (Giuliano et al. 2007). Studies have investigated the feasibility in the young adolescent cohort of changing from the three dose 'prime, prime, boost' to a two dose 'prime, boost' at 0 and 6 months (Dobson et al. 2013; Romanowski et al. 2011). The evidence for both vaccines from these studies is that in 9–14 year old girls two doses at 0 and 6 months, antibody responses (titres and avidity) are non-inferior over a 3 or 4 year period to those achieved after three doses in 16–26 year old women (Boxus et al. 2014; Dobson et al. 2013).

At their meeting in April 2014 the Strategic Advisory Group of Experts on Immunization (SAGE) of WHO considered HPV vaccine schedules and made the following recommendations:

> SAGE reiterated the importance of providing human papillomavirus immunization to girls as early as necessary, i.e. in girls aged 9 to 13 years prior to sexual debut, based on local data and patterns of sexual activity. Upon review of the evidence, SAGE recommended a 2-dose schedule for girls, if vaccination is initiated prior to 15 years of age. A 3-dose schedule remains necessary if immunization is initiated after the girls' 15th birthday. The recommended minimal interval between the 2 doses is 6 months. This interval may be extended to 12 months if this facilitates administration. A 3-dose schedule (i.e. at 0, 1–2, and 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected.

Changing dosage schedules in the absence of robust data on duration of protection is a risk and when public health and regulatory authorities adopt or recommend alternatives to the licensed three dose regimens they need to address this question, make risk assessments based on the evidence and devise risk management strategies for worst case scenarios to minimise any impact on cancer prevention strategies and other immunisation programmes – there should always be a plan B.

Conclusions

Benign and malignant disease caused by HPV constitutes a global public health problem. Genital warts are the commonest viral sexually transmitted infection and 5 % of all cancers are HPV associated. The unfolding of the HPV story started in the 1970s with the recognition that HPVs are a large family of viruses that include types that cause cancer particularly cancer of the cervix, a disease that kills 250,000 women each year. It has resulted in the development of two prophylactic virus like particle (VLP) vaccines using sophisticated recombinant molecular techniques and protein expression. Both vaccines target infection by the oncogenic HPVs 16 and 18 and one also targets the low risk HPVs 6 and 11 that cause genital and laryngeal warts. These vaccines are now included in the national immunisation programmes in many countries, with young adolescent peri-pubertal girls the usual cohort for

immunisation. Population effectiveness in women is now being demonstrated in those countries with high vaccine coverage. Since HPV associated cancers in men are increasing in incidence, an issue of contemporary debate is extending HPV vaccination to adolescent boys.

HPV VLP vaccines are highly immunogenic, generating serum neutralising antibody that persists for at least 9 years and a robust recall response at 60 months post vaccination. Protection against vaccine type associated disease and infection lasts for at least a decade and models predict more than 30 years protection. At present the assumption is that the protection achieved by these vaccines against HPV induced disease is mediated via serum neutralising IgG and this is consistent with what is known of the mechanism of HPV infection in the genital tract. Emerging evidence shows that very low antibody concentrations are protective but at the present there is no immune correlate of protection, disease prevention remains the only measure of the effectiveness of HPV vaccines.

Safety is of paramount importance for vaccines and all findings for HPV vaccines from randomised control trials, passive and active vaccine surveillance reporting systems are highly consistent in showing that the HPV vaccines have a good safety profile. Vaccine adverse events are local injection associated and of short duration. Systemic events are mild and self-limiting, but safety monitoring continues in long term follow up studies.

The HPV vaccine story is a remarkable story of scientific achievement, entrepreneurial drive and commercial and scientific interaction. HPV 16 and HPV 18 DNAs were cloned from cervical carcinoma biopsies in Harald zur Hausen's laboratory in 1983 and 1984, starting the explosion in HPV molecular biology and epidemiology that showed unequivocally that oncogenic HPVs were the cause of cervical cancer. HPV VLPs were first made in 1991 and 1992 and prophylactic HPV VLP vaccines were first licensed in 2006–15 years later. By 2014 more than 160 million doses of these vaccines had been distributed and millions of girls and women (and now men) are and will be protected against HPV induced disease, a major public health achievement.

Frequently Asked Questions

- **Will being vaccinated prevent all cases of cervical cancer?**
  No, the two vaccines protect against HPV 16 and 18, the types that cause at least 70 % of cancers worldwide. Vaccinated women are at much lower risk but should still go for routine screening if it is available.
- **How effective are these vaccines?**
  Both vaccines in women and girls who are not already infected prevent more than 98 % of the HPV16/18 caused pre-cancers (e.g. CIN), the obligate precursors to HPV 16/18 caused cancers. The quadrivalent vaccine prevents >90 % of genital warts.

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- **Should women who are sexually active be vaccinated?**
  Both vaccines are most effective when delivered to girls before the onset of sexual activity. The vaccines prevent infection, they do not treat infection or disease. Sexually active women receive benefit from vaccination since they are protected from re-infection or new infections by the vaccine HPV types. There is evidence that vaccinated women adequately treated (complete lesion excision) for HPV associated cervical disease (CIN2/3) are at lower risk for disease recurrence or new disease in the genital tract (Joura et al. 2012).
- **What should I do if my patient becomes pregnant after the start of the immunisation schedule?**
  Immunisation should be stopped until the patient has delivered her baby. Immunisation can then be resumed following the original schedule. Thus, if the patient received one dose, then resume with two doses 6 months apart, if she received two doses give a third dose in the postnatal period. Extending the interval between doses does not reduce immunogenicity. It is not recommended that pregnant women receive the vaccines. However, the evidence is that pregnant women who have received the vaccine have no more or less risk of pregnancy related adverse events such as miscarriage, congenital malformation, stillbirth, than non-vaccinated women. Vaccines can be given to lactating women.
- **How safe are these vaccines, what about reports of deaths?**
  The main side effect of receiving the HPV vaccine is pain at the injection site, this usually resolves within 24 h. Some people experience local swelling and redness but again this is short lived. About 10 % feel dizzy or nauseous and about 18 % will faint. This is needle fear and the recommendation is that immunised subjects are observed and sit in the office or waiting room for about 15 min after immunisation before returning home.

  Deaths have been reported but none of these has been shown to be related to the vaccine – they are coincidental to vaccination. It is important to remember that there is a background incidence of death from unknown causes in girls and young women irrespective of vaccination and therefore in view of the large numbers of girls being vaccinated deaths will occur because of this background rate. Each tragedy has to be investigated thoroughly and swiftly and the bereaved families kept at the centre of events and informed at every stage of the investigations. It must be remembered that the main side effect of the HPV vaccine is a sore arm, the main side effect of cervix cancer is death.
- **Do I need to give a booster?**
  At the present the evidence is that protection in immuno-competent subjects remains for at least a decade, the longest follow up time of

(continued)

vaccinated women to date. Mathematical models plotting antibody decay suggest that protection will be maintained for at least 30 years without boosting. No boost is needed.

- **What about HIV infected and other immunosuppressed subjects – are the vaccines effective?**

  Safety and immunogenicity of the vaccines has been evaluated in small studies in HIV infected children and adults. The vaccines have an acceptable safety profile and are immunogenic with comparable antibody titres to immunocompetent patients but the studies so far only have a short follow up and the persistence of antibody and duration of protection is not known for these patients.

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Chapter 10
Medical Treatment of Chronic Pelvic Pain

Wayne R. Gillett and David Jones

Introduction

Chronic pelvic pain (CPP) is a common disorder with a significant health burden, yet is poorly understood with regard to its aetiology and management. This difficulty has arisen out of a poor evidence base resulting in "historical causes of disagreement among specialists that lead to confused clinical care" (Baranowski et al. 2014). The scope of this chapter is to appraise the reader of the medicines used in CPP and aims to correlate knowledge about persistent pain mechanisms in general and apply that to pain conditions in gynaecology, the most common being CPP. To address this it is essential that the multidimensional management of CPP is emphasised since no medicine can work in isolation; indeed medicines are just one small part of management of these conditions. We believe contemporary variation in care is attributed to a poor understanding of the aetiology and mechanisms of CPP. This chapter will advise on a pragmatic pathway of care including the medicines prescribed to women for this condition. It is pragmatic since there is still a dearth of evidence-based practice in CPP (Yunker et al. 2012; Cheong et al. 2014b).

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Definition and Epidemiology of CPP

The current and predominant definition of CPP is non-menstrual pain of at least 6 months duration (Howard 2003; Cheong and William Stones 2006). Although 3–6 months is a common qualifying duration for chronic diseases (Aggarwal et al. 2006), the altered neurophysiology and behavioral changes characteristic of persistent pain may occur within days of an acute painful injury (Carr and Goudas 1999). Persistent pain conditions do not need to be continuous and may present with recurrent episodes interspersed with pain-free periods over months or years.

A useful definition would include any condition where pain continues longer than is usual for that particular situation.

CPP is a very common condition in gynaecological practice. Howard cites his own study that estimated CPP accounts for 10 % of referrals to a gynecologist, 12 % hysterectomies and 40 % diagnostic laparoscopies (Howard 2003). In the community it is even more common. A United Kingdom (UK) prevalence study defined CPP as lower abdominal pain unrelated to pregnancy that lasted for at least 6 months (Zondervan et al. 2001). The prevalence of CPP was 24 % in this British study, which was similar to the prevalence found in a New Zealand survey (25.4 %) (Grace and Zondervan 2004). Both of these studies included mid cycle pain in their definition and both demonstrated the frequent association with dysmenorrhoea and/or dyspareunia (>80 %). Both studies used a postal questionnaire of 2,304 and 1,160 women (aged 18–50) respectively, which was a 74 % and 66 % response to a random sample. In the UK study the sample were selected from a local Health Authority register, and that from New Zealand was generated from the New Zealand Electoral Roll (Grace and Zondervan 2004). In the New Zealand study another 40.3 % of the women surveyed had dysmenorrhoea and/or dyspareunia, emphasising the high rates of any form of chronic gynaecological pain in the community (Grace and Zondervan 2004). The association of dysmenorrhoea and dyspareunia with CPP is a consistent finding in prevalence studies (Latthe et al. 2006a).

The clinical course of CPP can be for a number of years. In the British prevalence study, described above, one-third of women reported pain that started more than 5 years before (Zondervan et al. 2001). In a follow-up study of 72 women with CPP the cumulative proportion of women who had not reached full recovery after 6 years was 70 % (Weijenborg et al. 2007).

Pain Generation and Persistence (Chronicity): A Brief Review

The Biopsychosocial Model of Pain

This model is now accepted as the most appropriate construct for persistent pain. It embraces a complex interaction of biological, psychological and social factors

involving both disease and illness (Gatchel et al. 2007). Disease is defined as an objective biological event involving the disruption of specific body structures, and illness refers to a subjective experience or self-attribution that a disease is present (Gatchel et al. 2007). The neurobiological events are described in following sections. However the degree of suffering depends on an individual's perceived meaning for their (very real) pain (Grace 2001) and how they cope with suffering and associated losses (e.g. loss of a sexual relationship, guilt about letting people down or having time off work etc.). Cognitions alter reaction to pain with enormously variable observed pain behaviour. The belief that pain indicates serious damage frequently leads to avoidance of many activities. This fear avoidance behaviour adds to disability and increases in importance as the pain condition persists (Boersma and Linton 2005). Catastrophising, stoicism, coping style, analgesia use and extent of seeking help from others are also modifiers (Gatchel et al. 2007).

Mechanisms of Pain Generation and Persistence

Pain mechanisms can broadly be divided into (a) physiological (b) tissue damage and inflammatory mechanisms, or (c) those consequent upon neural damage and/or dysfunction (Loeser and Melzack 1999; Woolf and Salter 2000; Woolf 2011; Cohen and Mao 2014). It is useful to summarise these mechanisms to enable their application to clinical conditions involving pelvic pain. The interested reader can find more detailed descriptions and reviews of the neurobiology of pain mechanisms, including definitions, in a number of recent sources (Carr and Goudas 1999; Loeser and Melzack 1999; Woolf and Mannion 1999; Woolf and Salter 2000; Boersma and Linton 2005; Gatchel et al. 2007; Treede et al. 2008; Latremoliere and Woolf 2009; Woolf 2011; Cohen and Mao 2014).

Brief noxious stimuli such as heat and pressure lead to transient pain of no clinical significance (physiological pain). When the stimuli are sufficient to injure tissues, local inflammatory responses occur, as they also do in diseases like infections. Surrounding nerve receptors in peripheral tissues become sensitised (peripheral sensitisation). This includes both high threshold noxious sensory receptors (nociceptors) and low threshold touch, movement and warmth receptors. Sensitisation leads to pain often described by patients as aching and burning (spontaneous pain), enhanced responses to innocuous stimuli such as warmth, movement or light touch tenderness (allodynia) and enhanced responses to high level noxious stimuli such as heavy pressure and heat (hyperalgesia) (Carr and Goudas 1999; Loeser and Melzack 1999; Gatchel et al. 2007).

Fortunately, following injury sensitivity usually returns to normal as inflammation subsides during healing and/or when pain inhibitory mechanisms activate (see below). But when there has been damage to or sensitisation in the nervous system then pain can persist for long after healing is complete (i.e. persistent, or chronic).

When peripheral nerves are injured (e.g. transection during skin incision, stretching with retraction) damage responses include sprouting and

microneuromata formation (Woolf and Mannion 1999; Chen et al. 2002; Perry 2003). Such microneuromata can discharge spontaneously and repetitively (like ectopic beats in cardiac dysrhythmias), and over-respond to low threshold stimuli such as movement or touch (allodynia). Central and distant changes follow, which for transected nerves include new "basket-like" spider-webs of sympathetic nerve fibers growing around dorsal root ganglion cell bodies and sensitising them, new dendritic growths ("rewiring") and new synaptic functional connections in the dorsal horn (McLachlan et al. 1993). Recent evidence of microneuromata formation in postpartum myometrium and endometriosis add a further dimension to this mechanism, which we refer to later (Quinn and Kirk 2002; Quinn 2004; Atwal et al. 2005).

Peripheral sensitisation frequently triggers central sensitisation especially at the spinal cord level, as first described by Woolf in 1983 (Woolf 2011). Central sensitisation accounts for spread of tenderness or enhanced pain sensitivity (often called "wind-up") away from a primary injury site (secondary hyperalgesia) (Latremoliere and Woolf 2009; Woolf 2011; Cohen and Mao 2014). Inflammatory chemicals at the periphery, and central proinflammatory cytokines from immune competent glial cells in the spinal cord and brain, widen sensitisation to include immune system effects contributing to increased pain (Latremoliere and Woolf 2009; Cohen and Mao 2014). This interplay between peripheral tissue inflammatory processes and central sensitisation begs the question whether factors responsible for perpetuation of pain are mostly at initial peripheral injury or disease sites, or mostly at distant central nervous system sites? Central elements also provoke secretions by peripheral nerves which add to peripheral inflammation (neurogenic inflammation). The role of the nervous system in interstitial cystitis and irritable bowel syndrome are now well recognised examples of neurogenic inflammation.

The range of processes described above reflect some of what is known as neural plasticity i.e. the capacity of neurons to change their function, chemical profile or structure (Woolf and Salter 2000). In the clinical context they present as neuropathic pain. The current definition of neuropathic pain (sometimes known as neurogenic) is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Treede et al. 2008).

Convergence, Referred and Spreading Pain

The dorsal horn of the spinal cord is an important relay station along pathways carrying messages from periphery to brain, and a major locus of central sensitisation. At any one dorsal horn site messages from several nearby peripheral locations converge and synapse on the same projection neurons. These can be from both surface sites (somatic) and internal sites (visceral) (Wesselmann 2001; Malykhina 2007; Sengupta 2009). When messages from any particular dorsal horn relay station reach the brain, it may not be able to discriminate whether the message originated from nerves converging there from an external site, an internal visceral site, or even

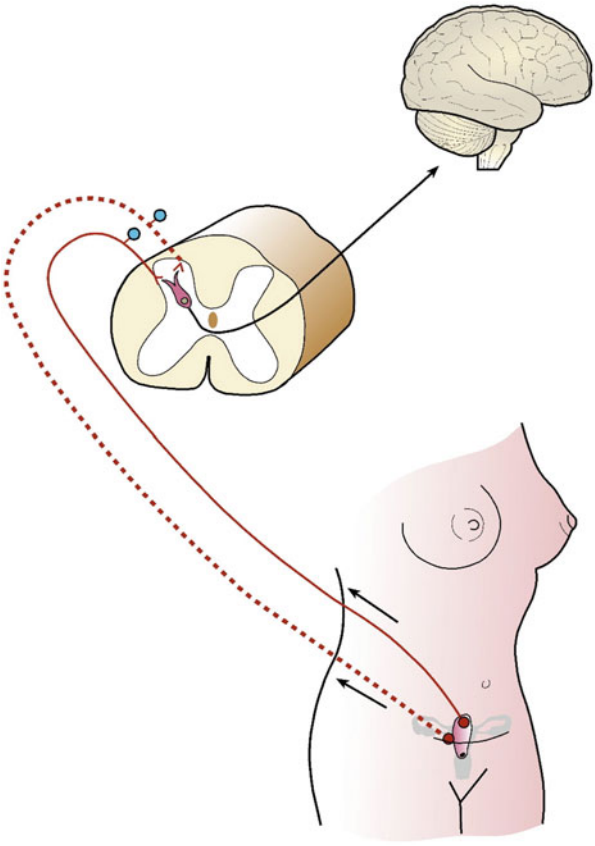

Fig. 10.1 When visceral fibers share the same pain projection neurons as the somatic components the brain has no way of knowing the actual source and mistakenly projects the sensation to the somatic or visceral structure
In this example, pain arising from a neuroma in a Pfannenstiel incision converge on the afferents from the visceral structures – in this case the uterus. The patient may experience dyspareunia. This may occur in reverse when microneuromata involving the uterus will give pain in the $T_{11}/T_{12}/L_1$ somatic distribution

adjacent otherwise normal visceral structures. Pain resulting from one source can spread to another site with converging inputs at the dorsal horn (i.e. is referred), and can even spread to contra-lateral sites (i.e. mirror image pain) (Milligan et al. 2003).

Sensitisation of neural connections from one pelvic organ may also lead to pain felt (perceived) in an adjacent normal organ or structure (cross-sensitisation or viscero-visceral sensitisation (Wesselmann 2001; Berkley 2005; Pezzone et al. 2005; Malykhina 2007).

Patient descriptions of pain locations are often unhelpful to locate their true source due to this convergence and referred pain phenomena. For example T_{10}–T_{12} and L_1 nerve branches supply the lower abdomen/iliac fossae. Their central receptor neurons also receive afferent inputs from the ovary ($T_{10–11}$), uterus and cervix (T_{12}–L_2) and parietal peritoneum. Therefore an injury to one of the nerve branches in the abdominal wall may trigger central sensitisation and pain referred to another site, e.g. the woman may experience dyspareunia (Fig. 10.1). For many CPP situations it is reasonable to consider both sensitisation and convergence processes co-existing, whereby between them they alter the pain dimensions of severity and location.

Pain Modulating Systems

Pain transmission can be either facilitated or inhibited by complex pain modulating systems especially those located in the brain stem (e.g. rostroventral medulla, or RVM) that send descending pathways to the spinal cord (Gebhart 2004; Cohen and Mao 2014). The balance of effect of these systems can shift between pain facilitation and inhibition. Concentrated collections of opioid receptive neurons and specialized nuclei in the brain stem initiate signals in these descending pathways. Signals from these pathways result in release into the spinal cord dorsal horn of enkephalins (natural opioids), noradrenaline and serotonin (inhibitory neurotransmitters) and dynorphin (facilitatory neurotransmitter). Added to this are the effects of segmental "gate closing" pain inhibitory mechanisms initiated by sensory stimuli from movement, warmth, light touch and gentle rubbing which generate 'stimulation produced analgesia' (SPA). Central inhibition mechanisms can diminish as a result of sleep disturbance/deprivation (Lautenbacher et al. 2006) and physical deactivation (Pilowsky et al. 1985). Disturbed sleep continuity (fragmentation), rather than sleep restriction, is the probable type of sleep dysfunction responsible (Smith et al. 2007; Finan et al. 2013).

Pain Amplification and Persistence in the Gynaecological Context

Even though CPP is frequently defined as persistent non-menstrual pain there is a common association with the events of the ovarian and menstrual cycles. Ovulation, menstruation and retrograde menstruation, as physiological cyclical events, produce inflammatory nociceptive stimuli in their own right (Brannstrom and Enskog 2002; D'Hooghe and Debrock 2002; Kelly et al. 2002). Experimental data suggests dysmenorrhoea is associated with increased muscle and visceral sensitivity and viscero-visceral sensitisation, even at times other than menstruation (Brinkert et al. 2007; Berkley and McAllister 2011; Vincent et al. 2011; Iacovides et al. 2013). This suggests dysmenorrhoea has many features of chronic pain especially with alteration in the central processing of noxious stimuli. These alterations persist when there is no background pain (Vincent et al. 2011).

When a normal cyclical painful event occurs, superimposed on central sensitisation from a neuropathic condition elsewhere (e.g. neuroma in the abdominal wall) it is not surprising that either or both the dysmenorrhoea and the neuroma pain is worse.

Childbirth may predispose some women to CPP. In a group of parous women who had hysterectomy for CPP, proliferation of small-diameter nerve fibers was found throughout the myometrium (Quinn and Kirk 2002). The authors postulated that childbirth induces neural plasticity, with initial denervation followed by reinnervation (collateral sprouting). Given the same physical state, not all

individuals experience pain. There is increasing recognition of the genetic influences of individuals who have different experiences to pain and response to analgesics (briefly reviewed by Kehlet et. al. 2006). Current knowledge does not allow us to define who is vulnerable.

Causes of Chronic Pelvic Pain

CPP is frequently described from a disease perspective (Howard 2003; Cheong and William Stones 2006; Farquhar and Latthe 2006). There is, however, increasing recognition that mechanisms in the nervous system common to other persistent pain conditions and inflammation of neurogenic origin play a major role (Wesselmann 2001; Berkley 2005; Berkley et al. 2005; Malykhina 2007). Because the abdomino–pelvic region is a nerve rich area for both somatic and visceral nerves (Fig. 10.2) (Wesselmann et al. 1997; Shoja et al. 2013) it should be expected that many

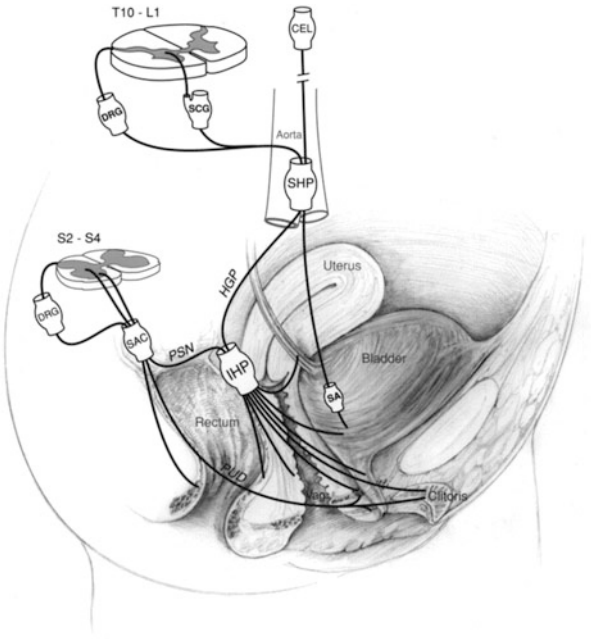

Fig. 10.2 Schematic drawing showing the innervation of the urogenital and rectal area in females (Reproduced with permission (Wesselmann et al. 1997))
CEL celiac plexus, *DRG* dorsal root ganglion, *HGP* hypogastric plexus, *IHP* inferior hypogastric plexus, *PSN* pelvic splanchnic nerve, *PUD* pudendal nerve, *SA* short adrenergic projections, *SAC* sacral plexus, *SCG* sympathetic chain ganglion, *SHP* superior hypogastric plexus, *Vag* vagina
Other nerves involved in CPP are the low abdominal wall nerves: ilioinguinal, iliohypogastric, genitofemoral and anterior divisions of 11th and 12th thoracic

persistent painful conditions seen in gynecological practice will also be influenced by these abnormal changes in the nervous system.

Causes of CPP have been summarized in a number of publications in the last 5 years but the majority only give brief reference to neuropathic pathology (Howard 2003; Cheong and William Stones 2006; Farquhar and Latthe 2006; Lamvu et al. 2006; Leserman et al. 2006). These causes perpetuate disease models of pain rather than mechanism based models. With the increasing knowledge of these mechanisms it seems that many of the traditional causes of CPP could ultimately be classified as having neuropathic or sensitisation components – some authors already promote this view (Wesselmann 2001; Berkley 2005; Berkley et al. 2005; Vercellini et al. 2009). The next section describes the main causes.

Endometriosis

Endometriosis is frequently described as a specific cause for CPP although its frequency is variable. The American Society for Reproductive Medicine suggests 70–90 % of patients with pelvic pain symptoms have endometriosis (The Practice Committee of the American Society for Reproductive Medicine 2014). In contemporary reviews, 35–60 % of women suffering from pelvic pain have a diagnosis of endometriosis (Giudice and Kao 2004; Giudice 2010). In contrast, a specialty pain clinic did not classify endometriosis as a cause of CPP, rather they noted its presence as a co-morbidity in approximately 20 % of cases, including 38 % with cyclical pain (Leserman et al. 2006).

Even though inflammatory and pressure influences from ectopic growths contribute to pain (Evans et al. 2007), a major contributing factor for endometriosis pain is how sensory and autonomic nerve activity from nerves that have sprouted from nearby tissues affect activity of neurons in the spinal cord and brain (Stratton and Berkley 2011). Uterine sensitisation from nerve fiber proliferation in the isthmic region and the myometrium and endometrium of women with endometriosis will contribute to this neural plasticity and the clinical presentation (Atwal et al. 2005; Tokushige et al. 2007).

In effect, several mechanisms probably account for the pain of endometriosis – inflammatory nociception and neuropathic pathology both of which may result in peripheral and central sensitisation. Despite this, an intriguing enigma in the clinical presentation of endometriosis is the poor relationship between the severity of the pain and the site and stage of the disease (Vercellini et al. 2007). Dysmenorrhoea is the predominant symptom affecting 57 % of individuals to a moderate or severe degree, whereas deep dyspareunia and non-menstrual pain affect 21 % and 30 % respectively (Vercellini et al. 2007). It seems that this variability could reflect a combination of factors such as extent of nociception, peripheral and central sensitisation, current efficacy of natural modulating mechanisms, and a variety of psychological and social modulating factors. Surgical nerve injury may add new mechanisms that contribute to pain which persists following treatment, this

frequently mimicking previous pain experiences and often wrongly attributed to endometriosis. All of these may result in variable pain experiences between individuals with comparable pathology, and within the same individual at different times.

Surgical Nerve Injury

Transection of nerves is inevitable in most surgery, including laparoscopy. This triggers a cascade of events, some immediate, some delayed. Immediate effects include a massive injury signal barrage followed by a shock like state of quiescence in the peripheral nerve. Neurochemical release in the spinal cord triggered by the injury barrage causes many biochemical and morphological changes in the central nervous system (plasticity) (Jensen and Baron 2003; Kehlet et al. 2006). These include lasting reduced thresholds, sensitisation and spontaneous signal generation, i.e. without the need for input stimuli. Various nerve growth factors stimulate new dendrite growths and connections (promoting spread of pain). These and other changes triggered by nerve damage have been described in the previous section on "Mechanisms of Pain Generation and Persistence." Other mechanisms of surgical nerve injury include compression and traction. Partial nerve damage affects some fiber types, more than others, resulting in a variety of sensory alterations (Jensen and Baron 2003).

Therefore surgery is prone to set off long-term painful processes. Persistent post surgical pain occurs in 10–50 % after common operations such as thoracotomy, breast surgery, inguinal hernia repair and leg amputation (Kehlet et al. 2006). For caesarean section incidences of 12–18 % have been reported (Nikolajsen et al. 2004; Kainu et al. 2010) and 32 % for hysterectomy (Brandsborg et al. 2007). In a systematic review of factors predisposing to CPP caesarean section significantly increased the risk of CPP (OR 3.18 1.91–5.30) (Latthe et al. 2006a). Caesarean delivery and longer time since birth are significant risk factors for CPP (Li et al. 2014).

Post surgical pain is largely an unrecognized clinical problem (Kehlet et al. 2006). We frequently see women who have been managed for years with treatments for pain deemed to have other causes who present many years after an original surgical nerve disturbance. Less easy to assess is the pain that may be generated from visceral nerve injury. It is illogical to consider nerve injuries as confined to somatic nerves, yet the phenomenon of visceral nerve injury is almost impossible to demonstrate clinically externally other than by the effects of viscero-somatic convergence.

Pelvic Floor Hypertonic Disorders

Pelvic floor dysfunction is a well-established entity with consequent weakness of the pelvic floor muscles causing urinary and fecal incontinence and pelvic organ prolapse. Developmental abnormal behaviors also lead to hypertonic muscle dysfunction (e.g. bladder or bowel elimination disorders), or to neuromuscular injury such as that occurs with traumatic vaginal delivery (Butrick 2009a). Pelvic floor muscle tenderness is very common in women with CPP (De Souza Montenegro et al. 2010). It is hypothesised that this tenderness is a form of viscero-muscle hyperalgesia, in essence a neuropathic condition secondary to all other sensitising conditions that make up CPP (Wesselmann 2001; Butrick 2009a). These women will present predominantly with dyspareunia but also with symptoms relevant to the other contributing CPP conditions.

Other CPP Conditions with Probable Neuro-sensitivity Mechanisms

Vulvodynia, irritable bowel syndrome (IBS), and interstitial cystitis (IC) as frequent causes of CPP share in common allodynia, a feature of neural hypersensitivity (Wesselmann et al. 1997; Price et al. 2006b; Gunter 2007; Parsons 2011). They also coexist, suggesting common etiology. Patients attending a vulvar disease clinic had double the prevalence of concurrent bladder and bowel pain syndromes compared to control subjects in a gynecology clinic (Kennedy et al. 2005).

Vulvodynia is the accepted term for a variety of vulvar pain syndromes, previously termed vulvodynia and vestibulitis. It is sub-grouped as generalized or localized depending on the distribution of the pain, and further subtyped into provoked (either sexual or non sexual) and unprovoked (Gunter 2007; Nunns and Murphy 2012). Chronic vulvar pain affects 3–16 % of women (Gunter 2007; Nunns and Murphy 2012) presenting frequently as dyspareunia that is the commonest cause of female sexual pain disorders (Schultz et al. 2005). Entry dyspareunia is commonly called vaginismus that is subtyped into primary (a woman has never been able to have completed intercourse) or secondary (pelvic floor hypertonic disorders) (Butrick 2009a).

Irritable bowel syndrome occurs in about 35–80 % of women with CPP (Howard 2003; Williams et al. 2005; Vercellini et al. 2009). The Rome III criteria (Drossman 2006) are the current accepted ones to define IBS. This classification identifies six subtypes for adults, one of these, relevant to CPP, is functional abdominal pain (FAPS) which is further subdivided into IBS (C1), functional bloating (C2), functional constipation (C3), and functional diarrhea (C4). IBS (C1) is more specifically defined as pain associated with change in bowel habit, and this is distinct from functional diarrhea (C4) characterized by loose stools and no pain, or functional bloating (C2) when there is no change in bowel habit (Drossman

2006). Recently there has been much interest in the role of the short-chain fermentable carbohydrates (termed FODMAPs) that induce gastrointestinal symptoms through their effects on luminal water handling and colonic gas production (Staudacher et al. 2014). Luminal distension will be pain inducing in those with visceral hypersensitivity (Staudacher et al. 2014).

Interstitial cystitis (IC) is also emerging as a common cause of CPP (Stanford et al. 2007; Parsons 2011). Using the Pelvic Pain and Urgency/Frequency (PUF) questionnaire 17.5 % of all women ≥18 years in a primary care setting were identified with potential IC (Rosenberg et al. 2007). In this study administration of intravesical potassium chloride (Potassium Sensitivity Test or PST) to selected cases yielded 4.3 % of all patients who were diagnosed with IC. The majority of these cases (95 %) were women. The PST induces discomfort or urinary urgency and is essentially a test for abnormal bladder permeability and neural sensitivity. The normal bladder epithelium acts a protective barrier of underlying nerves and muscles from toxic urinary solutes. Epithelial abnormalities may increase permeability of urinary metabolites provoking the symptoms of IC (Parsons 2011). For IC the most common symptoms at diagnosis are urinary urgency, daytime frequency, dysuria, nocturia and pain (Teichman and Parsons 2007). Pain with IC includes intermittent lower abdominal, urethral and low back pain with common descriptors for each of pressure, burning, and dull/aching (FitzGerald et al. 2006). Less commonly, vaginal or rectal pain occurs and may be triggered or exacerbated by vaginal intercourse (FitzGerald et al. 2006). These patients have often had a career of "bladder infection" labels, antibiotic treatments and sterile urine samples.

Pelvic congestion syndrome typically presents in multigravidae with post coital ache, occurring due to pregnancy related venous changes, an absence of valves in ovarian veins leading to reflux into the internal iliac veins (Phillips et al. 2014). These patients may have coexisting conditions of bladder irritability, gastrointestinal symptoms and backache (Nicholson and Basile 2006), all of which may be explained by viscero-visceral cross sensitisation.

There is an array of causes linked to the pelvis or close to the pelvis that most likely lead to neural sensitisation – they include pudendal neuralgia, proctalgia fugax, piriformis syndrome and levator ani syndrome, all presenting with functional anorectal pain (Bharucha et al. 2006). Practitioners who treat pudendal neuralgia believe it is more common than that the 1 % reported in the literature (Hibner et al. 2010). Pudendal neuralgia is caused mainly by mechanical injury to the pudendal nerve, either at surgery or with pelvic trauma including childbirth. Some commentators suggest the diagnosis of pudendal neuralgia by pudendal nerve entrapment may be made by using the "Nantes criteria" – with all five of the 'inclusion" criteria needing to be present: pain in the area innervated by the pudendal nerve, pain more severe when sitting, ability to sleep without pain, the absence of objective sensory signs and pain relieved by a pudendal (Labat et al. 2008). In our experience pudendal sensory alterations are found in some types of pudendal nerve pain (e.g. from episiotomy injuries or perineal tears).

Assessment

The evaluation of the patient with persistent pelvic pain has two main functions – to make a diagnosis and to identify factors that will aid in managing its effects. Assessment aims to identify the contributions of pelvic pathology, other biological perpetuating mechanisms usually arising from the nervous system and psychosocial modifiers of pain.

Difficulties in classifying patients have already been discussed, since both inflammatory and neuropathic causes of persistent pain will produce peripheral and central sensitisation. That many of the causes of CPP involve visceral sensitivity adds to these difficulties since the viscera are much less easy to assess.

When neuropathic and sensitising mechanisms are recognised, treatment options appropriate to them can be applied. Commentators even suggest that mechanism-based management obviates the need for a diagnosis (Jensen and Baron 2003; Woolf 2011). In our view much of the difficulty in the assessment and management of CPP is because of the lack of appreciation of these mechanisms. It is not surprising that failure to recognize a mechanism for pain leaves many women incorrectly labeled or dismissed under the guise of psychological problems.

In a UK study of women's attitudes about their consultation four key themes emerged from the participants (Price et al. 2006a): They sought:

- their wish for personal care that addressed them as individuals
- their pain to be taken seriously (most felt that their pain had not been believed by at least one doctor consulted)
- an explanation as much as cure
- reassurance (particularly that the pain was not serious, and not cancer). Reassurance included explanation that helped understand the pain was not 'all in the mind'.

The main implication from this study was that women with CPP want better communication (Price et al. 2006a). In another UK specialist CPP clinic individual patient needs are identified in order to meet their expectations as much as possible (Cheong and Stones 2005). Better patient satisfaction and improved pain control are achieved if the initial assessment meets these expectations (Stones et al. 2006).

History

A comprehensive history is the most valuable tool in assessing CPP (Gunter 2003; Vercellini et al. 2009). History should achieve three main goals:

- learn who is the individual with this pain
- evaluate the pain and its impact on physical and social function
- identify what aggravates and alleviates the pain

Cognitive factors like fear-avoidance beliefs and coping styles (Turk and Okifuji 2002), sleep disturbance (Lautenbacher et al. 2006), marital and family issues, mood and anxiety states, eating and behavioral disorders are all relevant in assessing the individual patient (Howard 2003; Cheong and Stones 2005; Latthe et al. 2006b) Tactful enquiry about domestic violence and abuse is appropriate (Gunter 2003; Howard 2003; As-Sanie et al. 2014). Of particular relevance is sleep disturbance since not only will pain disrupt sleep, but sleep deprivation increases muscle pain and pain sensitivity, thus generating a vicious circle (Lautenbacher et al. 2006).

In our own experience, referring practitioners frequently overlook a precipitating neural injury as a cause of neuropathic pain, which subsequently present as CPP. Examples include neural injuries following surgery or childbirth. A precipitating neural injury or event can occur many months or years before the patient presents with pain. Reasons for delayed neuropathic pain are not well understood. Gradual decline of endogenous inhibitory mechanisms (e.g. with aging), or dysfunction generated by deactivation, stressors or sleep disturbance are all possibilities.

Screening tools that seek information about common symptoms may distinguish neuropathic from non-neuropathic causes of pain (Bouhassira et al. 2005; Bennett et al. 2007). At best they correctly identify 80–90 % patients with neuropathy (Bennett et al. 2007). They use pain descriptors such as electric shocks, shooting, hot burning, all being common in neuropathic pathology, but these are often not evaluated in the gynaecological context. Pain evoked by many normal body movements and muscular actions like stretching, bending, walking, surface contact, and straining to empty bowel or bladder are common in neuropathic pain. Frequently sensory illusions like "swelling" are described at sites of deafferentation (lost sensation or 'numbing'). The reader may identify with this as being similar to the 'fat and heavy' lip felt after inferior dental nerve block at the dentist which looks normal in the mirror. A third neuropathic mechanism, hyperpathia, in which the pain persists as after sensations beyond the stimulus may also be sought in history taking and/or examination. In gynaecological practice a common example is pain that persists after sexual intercourse.

Physical Examination of Women with Persistent Pelvic Pain

Aspects of the physical examination are detailed in a number of reviews (Gunter 2003; Howard 2003; Cheong and Stones 2005). Critical to all of these accounts is the assessment of the anatomical sites that are tender or to demonstrate abnormal sensory changes.

The physical examination is the least understood from an evidence based perspective so the approach described here is the one used by our practice. It seeks to find evidence for neuropathic change. Frequently there are difficulties in

interpreting the examination findings most likely due to viscero-somatic convergence (Perry 2003).

When preparing the patient for examination an explanation is given that the aim is to establish likely sites of pain generation which could include a somatic nerve injury or sensitive pelvic organ, and warning them that their usual pain may well be reproduced. The abdomen is inspected for surgical scars and their relationship to pain sites indicated by the patient. A careful sensory examination is performed to ascertain both positive and negative sensory changes to the four modalities of light touch, sharp pricking, hot and cold (Jensen and Baron 2003). We use a soft bristled brush (a soft cotton bud will suffice), pointed wooden toothpick, hot water in a glass test tube and ice or acetone, respectively. Painful responses to light touch reflect allodynia. Increased responses to the other three modalities reflect hyperalgesia. Absent responses indicate deafferentation.

Next the abdominal wall is carefully examined using single digit palpation seeking painful foci that may indicate trigger points or neuroma sites. This is to avoid excessive manual pressure as is used for assessment of abdomino-pelvic organs. Other authors have emphasised the importance of the single digit examination of the abdominal wall (Gunter 2003; Howard 2003; Perry 2003). For somatic sites pain foci are easy to examine but much less accessible in visceral structures.

Peripheral and central sensitisation are also expected consequences of ongoing intra-pelvic pathology. However, sensory alterations are not easy to assess because the organs are less accessible but also the type of innervation (predominantly c-fibers) gives diffuse and poorly localized sensations. Although the cervix is accessible, if it is sensitive (from light touching or brushing with a swab) this could indicate either direct pathology or referred pain through spinal cord convergence from some other similarly innervated abnormal site (Perry 2003).

In interpreting examination findings the reader is reminded that the cervix and inner two thirds of the vaginal wall is innervated by sensory fibers from the inferior hypogastric plexus (T_{12}–L_2) while the outer few centimeters of the vagina are innervated by somatic pudendal nerve distributions (S_2–S_4). Other interpretation difficulties arise if there is a painful focus in the abdominal wall (e.g. neuroma). Bimanual examination of the uterus and the adnexae is expected to provoke pain via the external examining hand, and may be erroneously interpreted as uterine or adnexal sensitivity.

Some writers describe “trigger points” in the abdominal wall muscles and elsewhere (Gunter 2003; Howard 2003). These may reflect local sensory changes, or neuroma formation following surgery. We believe this type of sensitivity is actually another example of allodynia, which reflect central sensitisation. Multiple trigger points throughout the whole body suggest widespread central sensitisation (Pukall et al. 2006). Prolonged sleep disturbance can lead to myofascial tender points in normal volunteers without any prior pathology, similar to patients with chronic musculoskeletal pain (Lautenbacher et al. 2006).

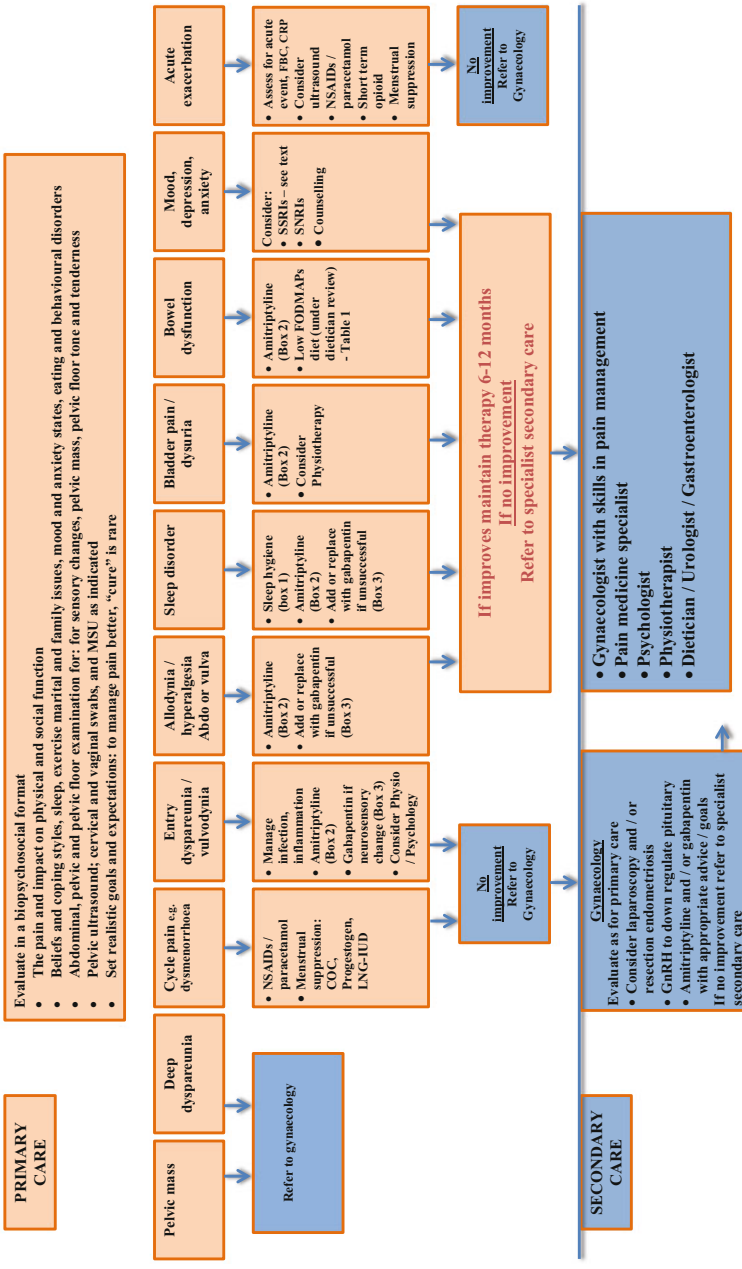

Fig. 10.3 Pathways of care for CPP

Investigations

A careful history and physical examination as outlined above will identify the majority of CPP conditions, particularly if neuropathic mechanisms are present. The standard and accepted base line investigations include ultrasound imaging of the pelvis (Cicchiello et al. 2011) and laparoscopy that will detect pelvic pathology (Howard 2003; Vercellini et al. 2009). Ultrasound is an essential investigation for all, to assess for any pelvic mass (e.g. endometrioma), chronic pelvic inflammatory disease or uterine abnormality (e.g. adenomyosis or leiomyomata). It is also an important step in assessing acute exacerbations of CPP that may have an underlying acute reason (e.g. haemorrhagic cysts) (Cicchiello et al. 2011). Laparoscopy has long been regarded as the gold standard for diagnosis of CPP but many causes are not identified at laparoscopy (Gunter 2003). The most common findings are endometriosis and adhesions although their presence may not necessarily be related to the patient's pain (Gunter 2003). A common view is that a negative laparoscopy may provide reassurance for the patient. Figure 10.3 gives our suggested approach to deciding when laparoscopy is indicated.

Treatment

Traditional treatments for CPP are directed at disease-based pathology and are covered extensively in a number of reviews (Gunter 2003; Howard 2003; Farquhar and Latthe 2006; Vercellini et al. 2009; Yunker et al. 2012; Cheong et al. 2014b). However, the evidence for effectiveness is weak at best. A systematic review of CPP treatment emphasised the lack of suitable studies with single studies representing much of the evidence we have (Cheong et al. 2014b). In one systematic review that evaluated over 2,000 citations for CPP, only 21 were controlled trials or prospective cohort designs with 50 or more women, or were cross sectional studies or case series with 100 women (Yunker et al. 2012). Of these only two were regarded as good quality. The lack of an evidence base is understandable given that CPP mechanisms (such as sensitisation and neuropathic conditions), as described earlier in the chapter, have been largely unrecognized.

Given the multidimensional nature of pelvic pain it follows that the best management should also be multidimensional. In many cases this could be at primary care level, moving to secondary care if needed and ideally by coordinated involvement of multiple teams (Baranowski et al. 2014). It is understandable that the multidisciplinary team environment is beyond the scope of many cases seen in primary care and gynaecological practice, but this does not mean that a multidimensional approach should not be aimed for.

Expert commentators on persistent pain emphasise the importance of general non-pharmacological measures such as stress reduction, improving sleep quality, maintaining physical activity (Dworkin et al. 2007). They also advocate a stepwise approach with pharmacological agents, including pharmacological combinations

(Dworkin et al. 2007; Gilron et al. 2013), however these combinations have not been adequately evaluated (Gilron et al. 2013).

It is logical that management of CPP should follow the same principles as for other types of persistent pain, modified by the events of menstruation, the ovarian cycle, reproduction and intimate relationships. In this chapter an attempt has been made to bring to the fore important contributions from sensitisation and neuropathic mechanisms, to assist the practitioner with the management of CPP. We offer pragmatic suggestions in a field with little evidence. Our aim is to identify management strategies that combine traditional therapeutic options for CPP with treatments directed towards sensitisation and neuropathic mechanisms and enhancing coping strategies. This approach has been used in our own practice for the last decade. Our premise is that no matter what the source/reason for the biological component of pain, alterations to central processing of nerve signals are probably common to all.

It should be emphasised that established persistent pain is rarely curable or able to be completely eliminated, therefore realistic goal setting is vital. CPP in women who seek medical advice is a long lasting condition (Weijenborg et al. 2009). A major goal is to provide realistic expectations and pain relief that is clinically meaningful where the accepted target is a 30 % pain reduction (Gilron et al. 2013). Typical pharmacologic treatments for neuropathic pain achieve only partial relief in 40–60 % of individuals (Dworkin et al. 2007). Management is not only directed at the sensation of pain, but pain related suffering. Increasing the intervals between exacerbations of pain gives a sense of gaining control that can improve life quality (Turk and Okifuji 2002). Because several co-existing visceral pain conditions in the same patient can compound the symptom level of each (i.e. viscero-visceral hyperalgesia), it is a principle of management that effective treatment of one condition can improve the symptoms of the other (Giamberardino et al. 2010).

Since we have used these measures our impression is that early intervention pays dividends. Helpful measures may be achievable by a single practitioner well versed in the multidimensional nature of CPP. In the more complex cases, including when diagnosis has been delayed, a multidisciplinary approach is recommended.

General Measures

An early comprehensive evaluation in primary or secondary care should fully assess biological and psychosocial factors to find pointers towards referral to a multidisciplinary team environment. This assessment should include altered mood and anxiety states, marital and family counselling, eating and behavioral disorders and sleep disturbances. A multidisciplinary team approach aiming to strengthen coping and cognitive strategies is of proven value (Turk and Okifuji 2002). Sudden spontaneous pain events often produce much fear, avoidance and disability. Reassurance that hurt does not equate with harm nor life threatening pathologies is often relieving in its own right.

General measures of treatment should include attention to aspects of health and wellbeing likely to enhance natural pain inhibitory mechanisms, e.g. sleep (Lautenbacher et al. 2006) and exercise (Turunen et al. 2004; Landmark et al. 2011). There are powerful inhibitory and pain gating mechanisms which are activated by inputs through nervous system stimulation. Not withstanding this, fear-avoidance beliefs will often cause patients to avoid exercise (kinesiophobia) in case it causes them harm, with loss of these beneficial effects.

Optimising sleep quality by both environmental measures (see Box 10.1: sleep hygiene) (Stepanski and Wyatt 2003) and appropriate pharmacological measures (see below) is frequently necessary in a persistent pain population. Caffeine excess may contribute to sleep disruption. Stimulus produced analgesia (SPA) can be invoked by natural stimuli such as warmth (but not noxious heat), light touch-massage and movement, or artificial inputs such as transcutaneous electrical nerve stimulation (TENS) (Nnoaham and Kumbang 2008) and acupuncture (Vickers and Linde 2014). In a systematic review of 29 trials involving 20,000 participants, acupuncture was associated with improved pain outcomes (pain reduction of 50 %) in 50 % compared to 30 % in patients with no acupuncture and 42.5 % for sham acupuncture (Vickers and Linde 2014). For TENS, however there is no evidence of efficacy (Nnoaham and Kumbang 2008). Self care strategies of movement (Tai Chi and yoga), mind-body therapies (meditation, relaxation) have, at best, weak recommendations based on mainly poor quality studies (Lee et al. 2014a, b). Although sensory art therapies (e.g. music) may be appealing coping tool distractions, there are no research data to show improvements in pain (Crawford et al. 2014).

None of these general measures have been evaluated for CPP, although they are widely used in managing other pain conditions.

Box 10.1 Sleep Hygiene Recommendations (Modified on Stepanski and Wyatt 2003)

1. Treat problems that disturb sleep e.g. anxiety and stress
2. Check medications that might disrupt sleep, and if necessary change time of day of administration
3. Exercise regularly
4. Do not avoid daylight during the day
5. Avoid day time naps
6. Avoid caffeine late in evening, alcohol and nicotine
7. Establish pre sleep rituals – reading, relaxing music, hot bath
8. If hungry at bedtime have a light snack e.g. ½ cup of milk
9. Avoid TV and computer screens close to bed time
10. Limit use of hypnotics
11. Avoid excessive fluids before bed time
12. Maintain consistent times for going to bed and getting up
13. Block out distracting noise and lights
14. Curtail time in bed
15. Eliminate the bedroom clock

Cognitive Factors and Psychological Treatments for CPP

While the title of this chapter states "medical treatment" of CPP we cannot avoid reference to the hugely important cognitive issues connected with such problems and treatment. We prefer the term "pain management" on the grounds that, for many, "cure" as a desired outcome from medical treatment is an unachievable goal. Cognitive factors can be considered on two broad levels:

1. Those relating directly to delivery of medical treatments
2. Cognitions affecting patients' day-to-day thoughts, beliefs, emotions, actions and interactions.

Internationally pain is recognised as a biopsychosocial experience, rather than just due to disease pathology. Disease based models fail to help many patients. Even when undisputed disease is identified, cognitions (e.g. thoughts and beliefs about its meaning and its perceived threat value) play a large role in the patient's quality of life. CPP's connection with reproductive function and intimate relationships adds further scope for impacting quality of life. Completely successful 'biologic' treatments often leave side effects, and therefore non-perfect outcomes. Repetitive re-presentations usually imply a problem remains, opening the way to seek further medical solutions. Detailed frank explanation of possible side effects and realistic limits to medical solutions outweigh over optimistic suggestions of cure.

A non-psychologist faced with patients seemingly obsessed with their disabling chronic pain could regard them as abnormal people. But it is normal behaviour to attempt to escape or avoid threats. As a current practitioner you will have to contend with the beliefs and promises of your predecessors. By definition "chronic" means the problem has gone on for a long time (>3 months). Patient beliefs and expectations about what was supposed to be an acute temporary condition will now be modified by likely conflicting opinions and explanations for it. This is a powerful reason for early *accurate* assessment and explanation.

All types of chronic pain challenge patients and practitioners alike. Outcomes sought are broadly analgesic and/or rehabilitative gains. Meta-analysis of results of psychological treatments (cognitive or behavioural) share equally small effect sizes on average with pharmacologic and surgical interventions (Morley et al. 2013). As a multidimensional problem, distress from chronic pain is compounded by resultant anxiety, sleep disruption, relationship distress, overuse of unhelpful medicines, disability, social role loss, depression and isolation (Eccleston et al. 2013). Therefore multimodal management of these problems must include psychological treatments alongside pharmacologic and surgical interventions. Interdisciplinary collaboration helps prevent confusing conflicting messages being transmitted, and usually is to the practitioner's benefit through sharing the load. Because the problem is not going away, acceptance of that is required along with reducing the threat value of the condition. This comes through explanation and learning. Cognitive Behavioural Therapy (CBT) helps patients learn specific pain-relevant coping and self-management skills.

At present meta-analyses show on average a beneficial effect from CBT, principally for disability, depression, and pain experience (Morley et al. 2013). These studies are of mixed chronic pain types, with a dearth of research specific to CPP (Cheong et al. 2014b), so extrapolation from experience with other chronic pain is the best for the present. Although CBT average benefits are with small effect sizes, but no worse than physical based treatments, they miss some substantial benefits at individual patient level. Ongoing research seeks more resolution of which psychological treatment strategies will best suit various subgroups of patients and conditions.

Suppression of the Ovary and/or Uterus

If CPP is aggravated by menstruation or other cyclical influences (such as ovulation), a variety of pharmacological treatments may be used to suppress ovarian and uterine function to assist with pain control. The added burden of menstrual pain may further amplify CPP experience via all components of the biopsychosocial model of pain. Suppression of cyclical activity has the potential to assist in pain management even when it is short term. The continuous use of the combined oral contraceptive, progestogens, danazol, gonadotropin releasing hormone (GnRH) agonists and antiprogestogens have all been used to manage pain in endometriosis and other CPP conditions (Stones et al. 2005; Farquhar and Latthe 2006; Cheong et al. 2014b; The Practice Committee of the American Society for Reproductive Medicine 2014). However evidence to support their use is limited, and frequently involve only single studies. Evidence of moderate quality supports the use of progestogens for CPP and for GnRH agonists the quality of evidence is low (Cheong et al. 2014b).

Despite the lack of evidence there are pragmatic reasons to suppress menstruation in some patients, since this may help pain control by at least four separate mechanisms:

- Atrophy of the endometrium and (if present) endometriosis
- Reduction in uterine activity, which may be contribute to cross-sensitisation of other pelvic organs or structures
- Menstruation is a negative psychosocial experience in women with coexisting pain conditions
- Ovarian suppression reduces the influence of estrogen on central sensitisation (Berkley et al. 2005).

Progestogens

Progestogens are synthetic drugs that interact with progesterone receptors to down regulate cell proliferation and increase apoptotic activity (Vercellini et al. 2003; Kuhl 2005). They also have anti-inflammatory and anti-angiogenetic effects, which together with the inhibition of estrogen-induced proliferation are effective for abnormal uterine bleeding and endometriosis. Other clinical indications include hormonal

contraception (see Chaps. 5 and 8) and hormone replacement therapy (see Chap. 11). Progesterone itself is not a useful therapeutic agent because of its rapid metabolism.

The two commonest oral progestogens are medroxyprogesterone acetate (MPA) and 19-nortestosterone derivatives, e.g. norethisterone (NET). The optimal dose of these medications has not been determined for CPP. Doses to achieve endometrial atrophy and suppress menstruation are higher than used for other clinical indications. For MPA doses of 30–50 mg have been used in RCTs for CPP (Cheong et al. 2014b). For norethisterone, doses of 10–20 mg per day are common. MPA does not undergo a first pass inactivation and its bioavailability is 100 % compared to that of NET of 40–80 % (Kuhl 2005). Norethisterone acetate offers advantages for longer term treatments with protective effects on bones (Vercellini et al. 2003). Doses of 10 and 20 mg, if taken chronically, may equate with estrogen levels of the oral contraceptive formulations in the 20–30 g range (Chu et al. 2007).

Progestogens appear to be effective for CPP but their efficacy beyond 12 months has not been studied. A systematic review identified only two studies of suitable, but low, quality involving MPA for CPP (Cheong et al. 2014b). In both trials, with of a total of 119 women using MPA for 4 months only, improvement in VAS pains scores was significant (Odds Ratio 3.0, 95 % CI 1.7–5.3). This benefit was maintained up to 9 months. Weight gain and bloating were the main side effects in this review (Cheong et al. 2014b). In studies of MPA in treating endometriosis, minimal side effects were reported in 10 % of patients compared to 2 % of those receiving placebo (Vercellini et al. 2003).

Gonadotropin Releasing Hormone Agonists

GnRH agonists achieve their effect by down regulation of the pituitary-ovarian axis resulting in hypoestrogenism. They are administered either by twice daily nasal spray or by injection of short acting or depot formulations. Our preference for CPP is for the long acting goserelin acetate every 1–3 months. Evidence for effectiveness is limited in CPP with only one small study suggesting they are at least as good as progestogens in reducing pain (Cheong et al. 2014b). In studies in endometriosis they were as effective as the levonorgestrel-releasing intrauterine device (LNG-IUD) and Danazol (Brown and Farquhar 2014). Side effects of hot flushes and vaginal dryness may be minimised by giving low dose estrogen replacement in combination with a progestogen ("add back" therapy) (Pickersgill 1998). Using add-back allows for longer treatment periods (The Practice Committee of the American Society for Reproductive Medicine 2014) and in our practice we monitor the patient for bone loss if treatment extends past 6 months.

Levonorgestrel-Releasing Intrauterine Device

The LNG-IUD (see also Chap. 8) induces endometrial atrophy and like the other menstrual suppressants may help those women whose pain is aggravated by

menstruation. Most of the small and limited studies on the use of the LNG-IUD for CPP have been in women with endometriosis. A systematic review identified 2 studies involving 95 women comparing the LNG-IUD with expectant management (Abou-Setta et al. 2013). There was a statistically significant reduction in the recurrence of painful periods in the LNG-IUD group (RR 0.22, 95 % CI 0.08–0.60). An advantage of the LNG-IUS is the potential for long-term use (5 years). A disadvantage is that persistent abnormal bleeding may occur for many months after insertion, diminishing the likelihood of good pain control during this time. We have managed women whose pain increases after insertion that, in our view, reflects abnormal neural sensitivity.

Other Pharmacological Treatment Options for CPP

Persistent pain that follows cyclical patterns may be helped by treatments directed at suppression of ovarian and/or uterine activity as discussed in the previous section. Menstrual pain is often helped by paracetamol and/or codeine, and non-steroidal anti-inflammatory drugs (NSAIDS), either as single agents or in combination. There are no randomised studies of these either alone or in combination for conditions that present as CPP.

There is a vast emerging literature on the pharmacological treatments of neuropathic pain. Apart from a brief overview, a detailed assessment is beyond the scope of this review. Sensitisation as a process will respond to the same medications no matter which anatomical location. The reader is directed to recent appraisals of the range of medications and their mechanisms of action (Dworkin et al. 2007, 2010; Finnerup et al. 2010). Treatments for neuropathic pain are limited by side-effects giving a narrow window between them and useful efficacy. Individual variation is huge, therefore a need for stepwise evaluation is expected. For example, amitriptyline as a pain and sleep improving measure has patients ranging in tolerance to it and its side effects between 5 and 75 mg. The degree of tolerance can vary according to whether treatment initiation starts low (e.g. 10 mg) with the intention to gradually increase (allowing adaptation to side effects) or starts at a median effective dose (e.g. 50 mg).

Therapeutic effectiveness may be indicated by the number needed to treat (NNT) and number needed to harm (NNH) and these have become popular in therapeutic decision-making (Sedgwick 2013a, b). NNT is the number of subjects that must be treated to achieve one more desired outcome with intervention than with the control. A very small NNT (approaching 1) means a favorable outcome occurs in nearly every patient who receives the treatment. NNTs of 2–5 usually indicate effective treatments providing NNH is high. However, interpretation of NNT needs to be with caution since its importance will depend on base rates of effectiveness, the higher the base rate, the lower the NNT will need to be. Conversely a higher NNT may indicate value if base rates are low. The NNH reflects the likelihood of withdrawing from the treatment due the side effects. NNH

indicates how many patients need to be exposed to a risk factor to cause harm in one patient that would otherwise not have been harmed. The higher the number the safer the intervention, although its interpretation is also influenced by base rates and the seriousness of the harm, where "harm" often describes discomfort or inconvenience such as a dry mouth.

Given that many CPP cases may have sensitisation and neuropathic mechanisms, it can be expected that anti-neuropathic treatments will be helpful to many women with CPP. We frequently observe women improve by the addition of a tricyclic antidepressant (TCA) medicine or an anticonvulsant as discussed in the sections below. Treatment for individual patients is best achieved using a combination of approaches, and many have to be modified because of the undesirable medication effects (Dworkin et al. 2007; Gilron et al. 2013).

Tricyclic Anti-depressants (TCAs)

Tricyclic ("antidepressant") medicines, particularly amitriptyline, can be effective analgesics in persistent pain states, including neuropathic pain (Saarto and Wiffen 2014). The analgesic and antidepressant effects of the tricyclics are independent and we prefer the term "antidepressant" be dropped in the context of pain management.

This class of medications inhibits serotonin or noradrenaline reuptake in nerve terminals throughout the central nervous system. Important sites of this action include brain stem nuclei in the descending pain modulating system, and dorsal horn gating mechanisms (Sindrup et al. 2005). In addition they have sodium channel blocking properties (like local anaesthetics), which are also active at peripheral sites of action (Sindrup et al. 2005). More recently amitriptyline has been shown to inhibit the TLR4 receptor on glial cells, thereby reducing pro-inflammatory cytokine release (Hutchinson et al. 2010). This effect is most likely to be relevant when an opioid is in place (Watkins et al. 2009). Due to large inter-individual pharmacokinetic variation, doses required for efficacy vary widely (Sindrup et al. 2005). The variability is caused by a genetic polymorphism of the drug metabolising enzyme CYP2D6 (Sindrup et al. 2005). Dosing according to effect and side effect is not expected to be successful, since side effects are often present even at sub therapeutic concentrations and not all patients will obtain a pain-relieving effect at all (Sindrup et al. 2005).

Box 10.2 describes our approach with our preferred tricyclic, amitriptyline. Evidence for its efficacy is extrapolated from its use in other neuropathic conditions. In a systematic review of eight studies including 687 participants there was a statistically significant benefit (RR 2.3, 95 % CI 1.8–3.1), NNT of 4.6 (3.6–6.6) (Moore et al. 2014). The analysis showed that 38 % of participants benefited with amitriptyline and 16 % with placebo; most participants did not get adequate pain relief. More participants given amitriptyline experienced at least one adverse event; 64 % of participants taking amitriptyline versus 40 % taking placebo – RR was 1.5 (95 % CI 1.4–1.7) and the number NNH was 4.1 (95 % CI 3.2–5.7) (Moore et al. 2014).

Box 10.2 Tricyclics for Analgesia
Principle – "start low go slow"

- 5 mg (i.e. half of smallest tablet) at night 1 h before bedtime
- expect side effects in early days (dry mouth especially)
- Raise dose in small increments each 3–5 days towards 50–75 mg

Determinants of final dose are tolerance and efficacy

Common, and usually minor, side-effects include dry mouth, sweating, dizziness, orthostatic hypotension and constipation. Tricyclic antidepressants cannot be used in patients with cardiac conduction disturbances, cardiac decompensation and epilepsy (Sindrup et al. 2005).

Despite tricyclics being commonly used in the management of CPP they have not been adequately evaluated (Farquhar and Latthe 2006). There is only one RCT using amitriptyline in CPP (Sator-Katzenschlager et al. 2005). This study was small involving only 20 patients given amitriptyline alone (two other arms of the study used gabapentin or the two combined). Nevertheless, using VAS (visual analogue scales), pain intensity was halved in women using amitriptyline alone. The effect was sustained for the 2 years studied using drug doses between 10 and 100 mg. Two of the 20 patients (10 %) discontinued because of severe (not stated) side effects.

The serotonin reuptake inhibitor class of antidepressants (SSRIs) are much less effective for analgesia (Saarto and Wiffen 2014), and may even aggravate some pains (Rahman et al. 2009). The serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g. Venlafaxine) have also been used for neuropathic pain, but have not been evaluated in CPP. Similar evaluation is needed for noradrenaline reuptake inhibitors with weak mu-opioid agonist actions (e.g. Tapentadol).

Anticonvulsants

Anticonvulsant medicines have been used extensively for chronic pain management since the 1960s, and tend to be confined to neuropathic pain conditions rather than inflammatory pain (Wiffen et al. 2013). Gabapentin and pregabalin are the current two most widely used although licensed indications for neuropathic pain vary in different parts of the world. For instance in our country, New Zealand, pregabalin is not publicly funded and gabapentin is licensed for neuropathic pain, but only funded if tricyclics have not succeeded. In the UK gabapentin is licensed for treatment of peripheral and central sensitisation at doses up to 3.6 g daily (Moore et al. 2014).

Gabapentin and pregabalin act by modulating calcium influx and reducing the ability of abnormal neurons to fire at high frequency (Wiffen et al. 2013). This mode of action provides both analgesic and sedative effects.

Most of the evidence for efficacy comes from studies using gabapentin in people with post herpetic neuralgia and diabetic neuropathy. In a systematic review of 37 studies given gabapentin (5,633 participants) 30–40 % had at least 50 % reduction in pain (Moore et al. 2014). In studies on postherpetic neuralgia NNT with an outcome of 50 % pain intensity reduction was 8.0 (95 % CI 6.0–12.0). In diabetic neuropathy NNT was 5.9 (4.6–8.3). For other neuropathic conditions there is limited evidence from, usually, single and/or small studies. In a placebo-controlled cross-over study of 120 patients with neuropathic pain caused by traumatic or postsurgical nerve injury, gababentin gave significantly better pain relief than placebo (Gordh et al. 2008). The study included cases of injury to low abdominal nerves. The NNT for at least moderate pain relief was 6.1, although about half of these patients had no pain relief. These studies illustrate that chronic pain is difficult to treat with single modality pharmacotherapy.

Except in the very small RCT described above (Sator-Katzenschlager et al. 2005) anticonvulsants have not been evaluated in women with CPP. In this study of 56 participants, pain relief was greater in patients receiving gabapentin alone (N = 20) or in combination with amitriptyline (N = 16) than in patients with amitriptyline alone, and was sustained for 24 months of the study. VAS scores were approximately 30 % of the entry VAS score. Nevertheless it is clear there is an urgent need for larger studies, with an attention to multimodal approaches.

Gabapentin is a safe agent with low-level side effects. There are no clinically important drug interactions and the side effects better tolerated by gradual dosage titration (Dworkin et al. 2007). In a systematic review of 22 studies with 4,448 participants taking at least 1,200 mg per day there was a withdrawal rate of 11 % for adverse events, compared to 7.9 % on placebo (Moore et al. 2014). Somnolence, drowsiness, or sedation was reported in 14 % of participants and in 5 % on placebo NNH was 11 (9.4–14). Other side effects include dizziness (19 % versus 6 % on placebo), peripheral oedema (7 % versus 2.2 %) and ataxia or gait disturbance (8.8 % versus 1.1 %).

Box 10.3 describes our approach with our preferred anticonvulsant gabapentin. Since dizziness and sedation are early side effects these can be reduced by starting with lower dosages and titrating cautiously (Dworkin et al. 2010). However, gabapentin is an expensive drug our obligation in NZ is to use cheaper options initially. Most of our experience is with sodium valproate as a single evening dose, which is tolerated better if introduced and incremented slowly over several weeks. However there are no research data that adequately assesses this drug for CPP (Gill et al. 2014).

Clonazepam has been used for treatment of neuropathic pain. Since dependence and tolerance occur with prolonged use, and there are no adequate trials with this drug, it cannot be recommended for treating CPP (Corrigan et al. 2014).

Box 10.3 Gabapentin for Neuropathic Pain/Disturbed Sleep
Usually start older subjects on 100 mg caps, younger ones on 300 mg caps.

- Day 1: *One* capsule after evening meal
- Day 2: *One* capsule after breakfast and after evening meal
- Day 3: *One* capsule three times daily, usually after food
- After 1 week: *IF*: Pain remains a problem *And*: The medicine is not causing severe side effects, *Then*: Double the dose
- Notes on gabapentin:
  - Commonest side effects are dizziness and tiredness
  - Does not cause gastric irritation; it may absorb better after food
  - Is not metabolized, and does not react with other medications.
  - Renally excreted unchanged – curtail dose if renal failure.
  - Increases amount of phase IV (deep restorative) sleep
  - Consider an additional pre bed time dose
  - Dose >3,600 mg/day usually does not increase efficacy

Opioids

Opioid analgesics target opioid receptor functions in natural pain inhibition systems. There are subtypes of opioid receptors, where the mu receptor (MOR) is the predominant analgesic moiety. Not all opioids are equal – different opioids have different combinations of receptor and metabolite actions. Some also combine non-opioid actions (e.g. tramadol as a weak opioid agonist with tricyclic-like actions, methadone with N-methyl-D-aspartate (NMDA) antagonist actions).

Clinically used opioids for any pain include morphine, methadone, oxycodone, hydromorphone, fentanyl, pethidine, dihydrocodeine and buprenorphine. In some European countries ketobemidone is available. Codeine is a pro-drug for morphine and requires hepatic metabolism by cytochrome P450 enzyme CYP2D6 for this conversion. A proportion (about a third) of the population lack the enzymes to do this (Williams et al. 2002), and SSRIs inhibit this transformation. Tramadol can be effective treatment for neuropathic pain (Dworkin et al. 2010) but only in some people. Its efficacy is similar to that reported for tricyclics and anticonvulsants but adequate direct comparisons are not available. Its use is often limited by side effects of nausea, dizziness, drowsiness, tiredness, fatigue, constipation and sweating (Dworkin et al. 2007). Seizures are possible in dose excess (Dworkin et al. 2007, 2010).

The evidence for opioids in chronic pain – including CPP – is not clear (Chou et al. 2009). However, they are often used in a misguided way as a first and only response. Judicious and short-term (less than 90 days) use of opioids should be considered as a last resort for poorly controlled pain, and only as part of careful a

management plan preferably directed by a specialist pain service (Tan et al. 2010; Baranowski et al. 2014). This needs to be balanced against potential adverse effects and safety including misuse or abuse (Dworkin et al. 2010; Finnerup et al. 2010). Constipation is a particular adverse effect that may be unhelpful, especially if there is already a functional bowel disorder. Increasing fluid and fiber intake, stool softeners and laxatives may help the patient to avoid constipation (Chou et al. 2009).

Other Agents

Many other agents can be combined synergistically to improve analgesia. The rationale behind this is targeting the many different pain inhibiting mechanisms. Local anesthetic analogues (e.g., flecainide) stabilise excitable nerve membranes (Dworkin et al. 2007; Gilron et al. 2013). Clonidine acts as an agonist at α_2 receptors with analgesic actions in the spinal cord (and probably elsewhere) (de - Leon-Casasola 2007). Paracetamol frequently, and ketamine occasionally, are used for blocking effects at NMDA receptors, and are effective analgesics for central sensitisation (Björkman et al. 1994; Visser and Schug 2006). Ketamine is only relevant in severe hospital cases and remains controversial.

Combination Pharmacotherapy

Since single agent measures have limited usefulness, practitioners managing chronic pain states employ combinations of drugs that might influence concurrent neural mechanisms contributing to sensitization, which may potentiate the efficacy of one or the other or may influence related symptoms such as sleep disturbance, anxiety etc. (Gilron et al. 2013). More than half of patients with chronic pain receive two or more different analgesics concurrently (Gilron et al. 2013).

In gynaecological practice combination therapy is common, e.g. use of paracetamol and NSAIDs, but we are aware of only one small clinical trial that evaluates combination therapy. In the above mentioned trial from Sator-Katzenschlager et al. pain relief was significantly better in patients receiving gabapentin alone or in combination with amitriptyline compared to patients receiving monotherapy with amitriptyline (Sator-Katzenschlager et al. 2005). However, a significant weakness of this study was its size and power, the study comprising 56 patients in total.

A systematic review of combination pharmacotherapy for the treatment of neuropathic pain identified 21 eligible studies, but meta-analysis was possible for only one comparison of one combination (gabapentin + various opioids versus gabapentin alone) (Chaparro et al. 2012). This meta-analysis included 2 studies of 423 participants and revealed the combination to be superior, RR 1.3 (0.5 %CI 1.04–1.61), although this combination produced significantly more side effects (Chaparro et al. 2012).

Pharmacologic Sleep Modification

Since persistent pain is associated with sleep disturbance, either by pain disrupting sleep architecture or poor sleep interfering with pain processing, measures to improve sleep are important in the management of CPP. Unhelpful use of benzodiazepines for pain related insomnia is commonplace. Benzodiazepines are not generally 'pain friendly'; due to rebound hyperexcitability and increased muscle tension as their effects subside leading to a vicious cycle similar to addictive processes.

Both tricyclics and anticonvulsant drugs have been used to improve sleep, as well as for their analgesic properties. An additional value of gabanoid anticonvulsants is their effect of enhancing phase IV restorative sleep (Foldvary-Schaefer et al. 2002). Restorative sleep describes the normal condition in which individuals feel refreshed and rested after sleeping. Most anticonvulsants have unwanted effects on sleep architecture and fragment sleep adversely (Legros and Bazil 2003). Hence people with epilepsy taking these medicines may have sleep problems, and are also more vulnerable to chronic pain problems. The gabanoids are currently the only ones that do not have adverse effects on sleep.

Surgical Options for Management of CPP

Historically hysterectomy has been used as the principal surgical treatment for CPP aggravated by menstruation, with bilateral oophorectomy an accepted treatment for severe debilitating endometriosis (The Practice Committee of the American Society for Reproductive Medicine 2014). All pain characteristics are improved by hysterectomy including pain frequency, pain intensity, dyspareunia, sleep disturbance and analgesic consumption (Hartmann et al. 2004; Farquhar et al. 2006; Brandsborg et al. 2007).

Conservative surgical procedures for pain management in women with endometriosis, dysmenorrhoea and other causes of CPP have been very commonly practiced in the last two decades, particularly following the development of advanced laparoscopic techniques. Procedures include the surgical ablation or excision of endometriosis including endometriomata, ablation of the uterosacral nerve and presacral neurectomy. Surgery for endometriosis appears to have a benefit in at least 50 % of women and may be improved by the addition of medical therapy (The Practice Committee of the American Society for Reproductive Medicine 2014).

The evidence for nerve interruption by uterosacral nerve ablation and presacral neurectomy is much less clear with no evidence of benefit (Daniels et al. 2009; Yunker et al. 2012). We concur with the view promoted by Rogers that there is compelling evidence for the abandonment of these procedures rather than resorting to further clinical trials (Rogers 2003). Uterosacral nerve ablation transects afferent sensory fibers in the uterosacral ligaments and presacral neurectomy intends to

disrupt afferents at the level of the superior hypogastric plexus (Rogers 2003). These surgical procedures cannot ablate all of the visceral pain fibers (Rogers 2003) and almost certainly do not rectify existing central components associated with persistent pain, but to the contrary likely provoke more of them.

Similar problems pertain to the role of adhesions in causing CPP and their surgical treatment. Despite the common use of adhesiolysis there is mixed evidence that this surgery will achieve pain control (Swank et al. 2003; Cheong et al. 2014a). Our view is that if an adhesion to a sensitised visceral structure transmits movements to that structure then this ought to contribute to pain sensations (allodynia). This type of surgery is not easy to assess, however, because of the propensity for adhesion to reform.

Summary of the Medical Management of CPP

Figure 10.3 (p. 305) summarises our stepwise approach to the assessment and management of women presenting with CPP. Because CPP by definition requires a history of up to 6 months of non-cyclical pain, the primary care doctor is in a unique position to engage the woman presenting with pain, earlier than 6 months, and introduce early interventions to guide appropriate and patient-centred management.

Overview of Treatments for Specific CPP Conditions

Endometriosis

Despite the prevalence of endometriosis and the frequent association with pain (CPP and/or dysmenorrhoea and/or dyspareunia) there are surprisingly few randomised trials evaluating treatment, and these are not of good quality (Brown and Farquhar 2014). The need for more studies was emphasised in a best practice report recently published by the American Society of Reproductive Medicine (The Practice Committee of the American Society for Reproductive Medicine 2014). The first line of treatments include NSAIDs (despite the absence of good trials) and medicines that suppress ovarian or menstrual function, as described in a previous section of this chapter.

Surgery is the second line treatment for women who do not respond to medical therapy. Repeat surgery is commonplace, which we do not condone because of the increasing evidence of contributing neural mechanisms. We agree with Stratton and others that we can only advance our knowledge in alleviating pain if the focus changes from the endometriosis lesions to pain (Stratton and Berkley 2011). We concur with the use of second line medical measures of tricyclics and anticonvulsants (Stratton and Berkley 2011).

Pelvic Floor Dysfunction, Pudendal Neuralgia and Vulvodynia

Since pelvic floor dysfunction is commonly associated with all CPP conditions, physiotherapy using biofeedback techniques are the mainstay of its early management. The patient is taught how to contract and then relax her pelvic floor (Butrick 2009b). Detail of physiotherapy, pharmacological therapy and special techniques including neuromodulation are given in two recent reviews for pelvic floor dysfunction (Butrick 2009b; Nelson et al. 2011) and for pudendal neuralgia (Hibner et al. 2010).

Desensitisation techniques using graded vaginal dilators is a behavioural therapy technique to reduce anxiety and fear associated with vaginismus, however these techniques have not been adequately evaluated (Melnik et al. 2012). New studies of botulinum neuroxin type A (BoNTA) have had promising effects on improving muscle spasm in the hypercontracted pelvic floor (Bhide et al. 2013) and may be used more than once (Nesbitt-Hawes et al. 2013). The injection of the affected muscles – usually puborectalis and Pubococcygeus – is best performed under conscious sedation, using 10 IU BoNTA at each site up to 80–100 IU (Bhide et al. 2013; Nesbitt-Hawes et al. 2013).

For pudendal neuralgia, medical treatment options have included nerve blocks and medications directed at neuropathy, but evidence of effect is poor (Tu et al. 2011). If vulvodynia has an infective basis then this condition should be adequately managed in primary care (Nunns and Murphy 2012). Otherwise a multidisciplinary approach may be required in this field with a poor evidence base. Treatment follows three main directions: drug based treatments similar to other neuropathic conditions, application of local anaesthetics, and psychological and psychosexual therapy (Nunns and Murphy 2012).

We do not advocate surgery procedures of vestibulectomy for vulvodynia (Nunns and Murphy 2012) or pudendal nerve decompression (Hibner et al. 2010) unless in advanced specialist centres and where all else has failed.

Other Causes of CPP: Irritable Bowel Syndrome, Interstitial Cystitis

For IBS, diet intervention may improve symptoms, but if self directed increases risks of nutritional inadequacy (Staudacher et al. 2014). Dietary intervention (ideally managed by a dietician involves 4–8 week exclusions of foods high in fermentable carbohydrates (Table 10.1) (Gibson and Shepherd 2010; Fedewa and Rao 2014; Staudacher et al. 2014), however evidence of effectiveness is weak, with most from uncontrolled or retrospective studies (Staudacher et al. 2014). Although RCTs are needed, it should be noted that placebo-controlled trials are difficult to undertake in studies of dietary advice (Staudacher et al. 2014). Drug therapy in IBS

Table 10.1 FODMAPS details – sources – various and including: (Choi et al. 2008; Gibson and Shepherd 2010; Ong et al. 2010; Fedewa and Rao 2014; Staudacher et al. 2014)

Category	Low fructose alternatives allowed	High fructose foods to avoid
Fruits	Avocado, cranberries, lime, rhubarb, pineapple, strawberries, bananas, mandarin orange, lemon cantaloupe	All fruits not on adjacent list, especially juices, dried fruits (e.g. prunes, apricots, raisins or dates), watermelon, apples, plum, figs, cherries, boysenberries, mango, tamarillo, pears and fruits canned in juice or syrup
Vegetables	Bamboo shoots, beets, bok choy, kale, carrots, celery, chives, turnip greens, parsnip, green pepper, spinach, plum tomato, radish, sweet potato, white potato, winter squash	Artichoke, asparagus, broccoli, cauliflower, chutney, leeks, okra, mushrooms, onions, garlic, peas, red pepper, shallots, spring onion, beetroot, celery in large amount, tomato paste, tomato products (e.g. canned tomatoes, ketchup)
	Allowed vegetables more likely to produce gas: Brussels sprouts, cabbage, cauliflower, lettuce	
Grains and cereals	Buckwheat flour, corn chips, rice, cornmeal, corn tortillas, oatmeal, gluten-free breads, crackers and pastas without added high fructose corn syrup (HFCS), grits, popcorn without HFCS, quinoa, rye breads without added HFCS, soba noodles and all other flours made from allowed grains	Foods with wheat as a major ingredient (wheat bread, pasta, couscous), grains with added dried fruit, grains with added HFCS, barley, cashews, lentils, pistachios
Meats	Plain unprocessed meats of any type (beef, chicken, fish, eggs, etc). Legumes, tofu (note that these tend to be more gas forming and may need to be avoided), nut butters that do not contain HFCS	Marinated or processed meats containing restricted ingredients
Dairy products	Milk, hard cheese, yogurt, soya milk, rice milk, almond milk without added HFCS	Any product with HFCS. Be especially careful with yogurts, soft cheeses, and flavoured milks
	EXCEPT if lactase deficient: then use lactose free milk products	
Other	Drinks sweetened with sucrose	Drinks sweetened with HFCS, low-energy sweeteners as in diabetic drinks (sorbitol, mannitol , xylitol), sugar-free gums, honey

HFCS high fructose corn syrup

is directed to the predominant symptom – constipation initially with dietary fibre supplementation or loperamide (2–4 mg when necessary) to reduce diarrhoea (Longstreth et al. 2006).

For interstitial cystitis, general conservative measures including physiotherapy may be directed in the primary care setting, but urogynaecologists or urologists best direct management. Short term cure rates (less than 1 year) of 50–70 % seem possible in specialist centres using pharmacological, intravesical, interventional

and surgical measures (Davis et al. 2014). Evidence for the use of amitriptyline is limited with two small RCTs suggesting efficacy providing the drug dose reaches at least 50 mg daily (Foster et al. 2010).

Conclusions

Pain is a multidimensional phenomenon. It is axiomatic that no matter what the biological cause of the pain, the way the person responds and presents is modified by environmental, psychological, cognitive and social influences i.e. it is a biopsychosocial experience. There is a rapidly evolving scientific enquiry into the nature of persistent pain that recognizes the biopsychosocial influences on pain and pain management. Fundamental to the biological aspects of this model is the role of plastic changes in the nervous system over time leading to sensitivity and spontaneous pain generation.

It is logical that causes and mechanisms of CPP should follow the same principles as other types of persistent pain, modified by the events of menstruation, the ovarian cycle, reproduction and intimate relationships. In this chapter an attempt has been made to bring to the fore important contributions from sensitising and neuropathic mechanisms, to assist the practitioner with the management of CPP. We offer pragmatic suggestions in a field with little evidence. Our aim is to identify management strategies that combine traditional therapeutic options for CPP with treatments directed towards sensitization and neuropathic mechanisms and enhancing coping strategies. This approach has been used in our own practice for the last decade. Our premise is that no matter what the source/reason for the biological component of pain, alterations to central processing of nerve signals are probably common to all.

It should be emphasised that established persistent pain is rarely curable or able to be completely eliminated. Therefore realistic goal setting is vital. Typical pharmacologic treatments for neuropathic pain achieve only partial relief in 40–60 % of individuals. Management is not only directed to the sensation of pain, but pain related suffering.

Since we have used these measures our impression is that early intervention pays dividends. Helpful measures may be achievable by a single practitioner well versed in the multidimensional nature of CPP. In the more complex cases, including when diagnosis has been delayed, a multidisciplinary approach is recommended. It is understandable that the multidisciplinary team environment is beyond the scope of many cases seen in primary care and gynaecological practice, but this does not mean that a multidimensional approach should not be aimed for.

Take Home Messages

- The biopsychosocial model describes not only the biological contributions to pain but also the degree of suffering experienced by the affected individual, and the behavioural responses of patient and others in their social environment to the pain
- Pain is a multidimensional phenomenon. No matter what the biological cause of the pain the way the person responds and presents is modified by environmental, psychological, cognitive and social influences i.e. it is a biopsychosocial experience
- Mechanisms of pain generation and persistence include inflammatory nociception and neuropathic (a disorder of the somato-sensory system), both characterised by peripheral and central sensitisation
- Even though CPP is frequently defined as persistent non-menstrual pain there is a common association with the events of the ovarian and menstrual cycles.
- Many of the traditional causes of CPP could alternatively be identified as having neuropathic or sensitisation components
- Persistent post-surgical pain is a largely unrecognised clinical problem and contributes much to CPP.
- Evaluation of the patient with CPP should identify the contributions of pelvic pathology, biological perpetuating mechanisms within the nervous system and psychosocial modifiers of pain.
- A systematic review of CPP treatment emphasised the lack of suitable studies, with only single studies representing much of the evidence we have. The lack of an evidence base is understandable given that nervous system contributions to CPP have been largely unrecognised.
- General measures of treatment should include attention to aspects of health and wellbeing likely to enhance natural pain inhibitory mechanisms, e.g. quality sleep and exercise.
- Cyclical patterns or exacerbations of persistent pain may be helped by treatments directed towards ovarian suppression and/or uterine activity.
- Tricyclics and anticonvulsants are effective analgesics in many persistent pain states, including neuropathic pain. However, these medicines have had limited evaluation in women with CPP.
- In the more complex cases, including when diagnosis has been delayed, a multidisciplinary approach is recommended.

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Chapter 11
Menopausal Hormone Therapy: A Safety Perspective

Emily Banks

Introduction

Menopausal hormone therapy (MHT) comprises the use of oestrogen(s), with or without progestagens (progestins), or related compounds, predominantly for the treatment of the symptoms of the menopause (International Agency for Research on Cancer 1999). It is often referred to as hormone replacement therapy or HRT; the term MHT is used here because it avoids the implicit assumption that postmenopausal women have a hormone deficiency that requires "replacement".

MHT has been commercially available since around the 1930s, with use of oestrogen-only products becoming common in the United States by the late 1960s (Beral et al. 1999). Findings of an elevated risk of endometrial cancer with use of oestrogen-only MHT led to a drop in use in the mid-1970s, along with the increasing addition of progestagens to oestrogen (known as 'combined oestrogen-progestagen MHT'), which had been shown to reduce the excess endometrial cancer risk. Use of MHT increased relatively rapidly in many industrialised countries during the 1980s and 1990s, largely due to the impression that MHT could improve quality of life and reduce the risk of disease in older women. Despite the uncertainties about its risks and benefits, in the late 1990s around half of women aged 50–64 in the UK had ever used MHT and one-third of women in this age group were current users (Million Women Study Collaborators 2002).

In 2002 the oestrogen-progestagen arm of the Women's Health Initiative Randomised Controlled Trial of MHT was stopped 3 years early, due to evidence of global harm in terms of the risks of serious disease, particularly breast cancer

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(Writing Group for the Women's Health Initiative Investigators 2002). In 2003, the UK Million Women Study results on breast cancer were published, providing large-scale evidence on the increased risk of breast cancer in women currently using MHT, compared to women who had never used it, with substantially greater risks in users of oestrogen-progestagen compared to oestrogen-only MHT (Million Women Study Collaborators 2003).

These results led to changes in prescribing policy and practice, with rapid and substantial declines in the use of MHT in many countries. The fall in MHT use has been shown in several settings to be followed by a decline in breast cancer incidence, consistent with evidence from observational studies that MHT-associated risks are rapidly reversible after MHT use ceases (Million Women Study Collaborators 2003; Collaborative Group on Hormonal Factors in Breast Cancer 1997). In the US, a 66 % reduction in use of MHT was followed by a significant 11 % reduction in breast cancer incidence from 2001 to 2004 among women aged 50 or more years, but not in younger women (Ravdin et al. 2007). Similarly, in Australia, a 40 % reduction in MHT use was followed by a significant 7 % reduction in breast cancer incidence from 2001 to 2003 in women aged 50 and over, but no significant change in breast cancer incidence in younger women (Canfell et al. 2008).

These reductions in breast cancer incidence demonstrate that more judicious, evidence-based prescribing of MHT can reduce the harms related to it, for both individuals and the population. However, use of MHT is still common, and strategies to minimise harm, while maintaining selective access to MHT for those in whom it is likely to have the best balance of safety and efficacy, remain important.

World-Wide Evidence to Date on Menopausal Hormone Therapy

A key principle of evidence-based medicine is that clinical practice is guided by the quantitative sum total of the appropriate evidence to date, not the results of single studies or subgroups of single studies. It is particularly important that reviews of the evidence are independently conducted. For cancer outcomes, where the disease event is unpredictable and other risk factors can be reasonably accounted for, data from observational studies are often reliable (Vandenbroucke 2004) and need to be combined with data from randomised controlled trials to summarise the current relevant evidence. Since MHT tends to be preferentially prescribed to healthier women, with fewer risk factors for cardiovascular disease (Million Women Study Collaborators 2002), in a way that cannot necessarily be fully accounted for by adjustment, observational data cannot be assumed to be reliable for assessing the effects of MHT on coronary heart disease and stroke. Randomised data are therefore emphasised for these outcomes.

This chapter predominantly uses data from the UK Public Assessment Report (Medicines and Healthcare products Regulatory Agency 2007), the most recent independent quantitative review of the effect of MHT on serious disease, supplemented by data from other large scale studies.

Efficacy

MHT is an effective treatment for vasomotor symptoms (hot flushes/flashes, night sweats) and vaginal dryness/atrophy associated with the menopause (MacLennan et al. 2004). These benefits occur rapidly after commencing therapy, but cease with cessation of therapy, if the underlying symptoms persist.

For less specific symptoms that are often attributed to the menopause (e.g. irritability, mood swings), the efficacy of MHT is less established. Women included in the Women's Health Initiative trials had an average age of 63 years; 12–17 % had moderate to severe menopausal symptoms at baseline. Health-related quality of life did not differ meaningfully between those randomised to MHT (oestrogen-only or oestrogen-progestagen) and placebo in the trials (Hays et al. 2003; Brunner et al. 2005). Bone mineral density is increased and the risk of fracture, including waist, hip and vertebral fractures, is reduced substantially among women currently using MHT (Banks et al. 2004a; Cauley et al. 2003). However, this protection wears off rapidly following cessation of use, and returns to that of a woman who has never used MHT within 5 years after stopping (Banks et al. 2004a). Hence, to reduce the risk of hip fracture at the age when it becomes a common health issue (i.e. when women are in their 70s and older), women must be currently using MHT.

Risks

The evidence to date shows that the risk of breast cancer is increased in current users of MHT, and that relative risks increase with increasing duration of use. Risks are also greater with use of oestrogen-progestagen versus oestrogen-only MHT. Current users of oestrogen-only MHT with around 5 years of use have a 20 % increase in the risk of developing breast cancer; use for around 10 years leads to a 30 % increase in risk (Medicines and Healthcare products Regulatory Agency 2007). The corresponding 5 and 10 year risks for current users of oestrogen-progestagen MHT are 60 % and 120 % (Medicines and Healthcare products Regulatory Agency 2007; Million Women Study Collaborators 2003; Collaborative Group on Hormonal Factors in Breast Cancer 1997). The risk does not appear to vary meaningfully according to the type of oestrogen or progestagen and whether the MHT is administered orally or transdermally (Medicines and Healthcare products Regulatory Agency 2007). The risk of death from breast cancer is elevated in

women who are currently using MHT (Million Women Study Collaborators 2003; Banks et al. 2004b) and use of MHT by women with a previous diagnosis of breast cancer increases the risk of recurrence (Holmberg and Anderson 2004).

The evidence indicates that an elevated risk of breast cancer is present relatively soon after commencing use, and increases with increasing duration of use. For example, in the Million Women Study, the relative risk of breast cancer was 1 · 45 (1 · 19–1 · 78) among women reporting <1 year of use of oestrogen-progestagen MHT at baseline (Million Women Study Collaborators 2003), compared to women who had never used MHT. The equivalent relative risk for <1 year of oestrogen-only MHT was 0 · 81 (0 · 55–1 · 20). It is not possible to estimate the likely effect of breast cancer for use of a few months for treatment of menopausal symptoms however most biological effects are on a continuum so it seems reasonable to assume some increase in risk, which will be smaller the shorter the duration of use.

The only personal characteristic found to significantly modify the effect of MHT on breast cancer is body size; MHT results in a larger increase in the risk of breast cancer in women who have a lower compared to a higher Body Mass Index (BMI), i.e. in thinner women. Consistent with this is the finding that the effect of MHT on breast cancer is greater in Europe than in North America (where average BMI levels are higher) (Medicines and Healthcare products Regulatory Agency 2007).

In women with a uterus, the risk of endometrial cancer is increased around 3 times with 5 years of use of oestrogen-only MHT and 9 times with 10 years of use. Risks with oestrogen-progestagen MHT where progestagens are added for 10 or more days per 28 day cycle do not differ significantly from those of women who have never used MHT. The risk of ovarian cancer is increased by around 20 % among current users of oestrogen-only and oestrogen-progestagen MHT, and increases with increasing duration of use (Medicines and Healthcare products Regulatory Agency 2007; Million Women Study Collaborators 2007).

The risk of stroke is increased by around 30 % in current users of oestrogen-progestagen and oestrogen-only MHT. The risk of venous thromboembolism is increased in current users of oral MHT, with a 30 % increase in risk among women using oral oestrogen-only MHT and a 130 % increase in risk among those using oral oestrogen-progestagen MHT (Medicines and Healthcare products Regulatory Agency 2007). Risks are greater in the first 2 years after starting use than in subsequent years (Sweetland et al. 2012). The risk of venous thromboembolism does not appear to be significantly elevated in women using transdermal oestrogen-only MHT (Sweetland et al. 2012; Olie et al. 2010); there are insufficient data on transdermal oestrogen-progestagen MHT for firm conclusions to be reached (Sweetland et al. 2012). Venous thromboembolism risks are greater for women using medroxyprogesterone acetate than for those using norethisterone or norgestrel as progestagens (Sweetland et al. 2012).

The current evidence is that the MHT-associated risks identified here generally wear off within a few years of ceasing use; the Million Women Study found that no significant difference in breast cancer risks between women who had ceased use of MHT within the 5 years prior to baseline and women who had never used HRT (Million Women Study Collaborators 2003; Collaborative Group on Hormonal

Factors in Breast Cancer 1997; Medicines and Healthcare products Regulatory Agency 2007).

Coronary Heart Disease and Colorectal Cancer

The main rationale for the Women's Health Initiative Trials was the possibility that MHT might reduce the risk of coronary heart disease. This was because previous observational studies had found that women using MHT had a lower risk of coronary heart disease than non-users and other studies had indicated beneficial effects on intermediate markers of coronary heart disease risk, including LDL and HDL cholesterol levels (Barrett-Connor and Stuenkel 2001; The writing group for the PEPI trial 1995). However, since MHT tends to be prescribed to healthier women, this lower risk is not necessarily because MHT *causes* a reduction in risk (Million Women Study Collaborators 2002). Meta-analyses of data from relevant randomised controlled trials, which are the most appropriate study design for examining coronary heart disease risks, including the Women's Health Initiative have not found any significant beneficial or adverse effect of MHT on coronary heart disease (Medicines and Healthcare products Regulatory Agency 2007).

The UK Public Assessment Report also found no significant effect of MHT on colorectal cancer (Medicines and Healthcare products Regulatory Agency 2007).

Balancing the Risks and Benefits

When quantitatively weighing up the risks and benefits of MHT it is important to compare like with like; hence robust analyses examine the absolute risk of potentially life threatening diseases significantly increased or reduced by MHT and estimate a quotient for its net effect. In these terms, MHT significantly increases the risk of breast cancer, stroke, ovarian cancer and venous thromboembolism and reduces the risk of fracture (Medicines and Healthcare products Regulatory Agency 2007; Banks et al. 2004a, c). Use of oestrogen-only MHT increases the risk of endometrial cancer in women with a uterus (Medicines and Healthcare products Regulatory Agency 2007).

When the major potentially life threatening conditions affected by MHT are considered together, the risk of overall harm is greater than the benefits, for both oestrogen-only and oestrogen-progestagen MHT (Medicines and Healthcare products Regulatory Agency 2007). However, the net adverse effects of oestrogen-progestagen MHT are greater than those for oestrogen-only MHT. The risks related to MHT increase with increasing duration of use; this relates not only to the fact that women are exposed to MHT-related risks for longer, but also because the relative risk of breast cancer increases with increasing duration of use (Medicines and

Healthcare products Regulatory Agency 2007). The risks of venous thromboembolism and stroke are elevated shortly after use commences.

The UK Public Assessment Report weighed up the absolute risks of breast cancer, ovarian cancer, endometrial cancer, colorectal cancer, stroke, coronary heart disease, venous thromboembolism and hip fracture and estimated the following:

5 years of use of oestrogen-only MHT results in:

- a net excess of potentially life threatening events affecting 5 per 1,000 users aged 50–59 [number-needed-to-harm = 200 (95 % CI 100–500)], or affecting 6 per 1,000 users aged 60–69 [number-needed-to-harm = 167 (67–∞)] among women **without** a uterus (Medicines and Healthcare products Regulatory Agency 2007).
- a net excess of potentially life threatening events affecting 9 per 1,000 users aged 50–59 [number-needed-to-harm = 111 (67–200)], or affecting 12 per 1,000 users aged 60–69 [number-needed-to-harm = 83 (34–200)] among women **with** a uterus (Medicines and Healthcare products Regulatory Agency 2007).

10 years of use of oestrogen-only MHT results in:

- a net excess of potentially life threatening events affecting 12 per 1,000 users aged 50–59 [number-needed-to-harm = 83 (45–200)], or affecting 17 per 1,000 users aged 60–69 [number-needed-to-harm = 59 (29–500)] among women **without** a uterus (Medicines and Healthcare products Regulatory Agency 2007).
- a net excess of potentially life threatening events affecting 44 per 1,000 users aged 50–59 [number-needed-to-harm = 23 (14–38)], or affecting 65 per 1,000 users aged 60–69 [number-needed-to-harm = 15 (9–29)] among women **with** a uterus (Medicines and Healthcare products Regulatory Agency 2007).

5 years of use of oestrogen-progestagen MHT results in:

- a net excess of potentially life threatening events affecting 14 per 1,000 users aged 50–59 [number-needed-to-harm = 71 (53–91)], or affecting 22 per 1,000 users aged 60–69 [number-needed-to-harm = 45 (32–63)] among women **with** a uterus (Medicines and Healthcare products Regulatory Agency 2007).

10 years of use of oestrogen-progestagen MHT results in:

- a net excess of potentially life threatening events affecting 40 per 1,000 users aged 50–59 [number-needed-to-harm = 25 (19–33)], or affecting 64 per 1,000 users aged 60–69 [number-needed-to-harm = 16 (12–22)] among women **with** a uterus (Medicines and Healthcare products Regulatory Agency 2007). The numbers above relate to European rates of disease and show that among women aged 50–59, one potentially life-threatening adverse

event is estimated to occur for every 200 women aged 50–59 using oestrogen-only MHT for 5 years and for every 110 women using oestrogen-progestagen MHT for 5 years, that is not outweighed by a beneficial effect (i.e. the number-needed-to-harm).

MHT is highly effective in the treatment of hot flushes, night sweats and vaginal dryness related to the menopause (MacLennan et al. 2004). As difficult as it may seem, it is the severity of these symptoms that women must balance against the risk of serious disease attributable to use of MHT.

The risk-benefit calculations have been done for 5 and 10 years duration of use. Use for shorter periods of time will be accompanied by lesser increases in risk, as outlined above. It is not possible to know exactly what risks accompany use for months or less than 1 year, except to say that risk exists on a continuum. Hence, it is likely to be elevated but to a lesser extent than long-duration use.

MHT effects on other non-life-threatening conditions such as increased risk of incontinence (Hendrix et al. 2005) and gallbladder disease (Simon et al. 2001; Liu et al. 2008) and reduced peripheral fractures (Cauley et al. 2003) should also be considered.

Does the Effect of MHT Differ According to a Woman's Age, How Long It Has Been Since Menopause, or the Dose?

A common misperception is that MHT has significantly different effects in younger compared to older women. Unfortunately, the available randomised controlled trials are too small to give reliable evidence about the effects of MHT in women of different ages or according to many attributes of MHT use, and a finding of "no significant effect" within specific groups is not meaningful evidence of safety. Examination of subgroups in trials is highly problematic and must include testing for "statistical interaction" or "effect modification", according to pre-defined stringent levels of significance. If no significant difference in the effect is detected, the effect of MHT in this subgroup must be considered to be same as the overall effect in the whole group. Moreover, even subgroup analyses which yield marginally significant findings must be viewed with caution if they were not specified prior to analysis, or make up one of many such comparisons.

According to the current evidence, the relative risks of the conditions examined here (i.e. the percentage increase in risk) associated with MHT use do not vary significantly according to a woman's age. However, as outlined above, the background absolute risk of all of these conditions does vary substantially with age. This difference in background rates means that the same duration of use of MHT at an older age will result in a greater number of excess cases of serious disease than use at a younger age, all other things being equal.

It has also been speculated that MHT initiated soon after menopause might prevent coronary heart disease, while therapy started later will have a null or

adverse effect (the "timing hypothesis") (Banks and Canfell 2009). This hypothesis arose because the null coronary heart disease findings of the Women's Health Initiative trials differed from the expectation of many researchers and clinicians, that hormone therapy would be cardio-protective; the timing hypothesis was one attempt to explain this difference.

Detailed analyses of Women's Health Initiative data designed specifically to address the timing hypothesis demonstrate:

- similar null or adverse effects of hormone therapy on coronary heart disease;
- similar adverse effects on stroke and venous thrombosis
- possibly greater adverse effects on breast cancer

with hormone therapy initiated soon after menopause compared to use starting later (Prentice et al. 2009)

Hence the overall findings regarding the risks and benefits of MHT should also apply to women initiating hormone therapy soon after menopause, with the caveat that relative risks of breast cancer may be greater.

Oestrogen-Only Versus Oestrogen-Progestagen MHT, Transdermal Versus Oral MHT, Use of Norethisterone/ Norgestrel MHT

For women who have had a hysterectomy and require treatment, as has been outlined above, oestrogen-only MHT is the most appropriate in terms of minimising risk. Although it is less widely recognised, use of oestrogen-only MHT is also likely to minimise excess potentially life-threatening adverse events in women with a uterus, compared to use of oestrogen-progestagen MHT.

Use of oestrogen-progestagen MHT leads to greater relative risks of breast cancer, ovarian cancer and venous thromboembolism than oestrogen-only MHT, but leads to lesser or no increases in the risk of endometrial cancer for women with a uterus (Fig. 11.1).

The background incidence of breast cancer (in European women) is around five times that of endometrial cancer (10 vs. 2 per 1,000 women aged 50–59 over a 5 year period, respectively); the incidence of venous thromboembolism is around 2.5 times that of endometrial cancer (5 per 1,000 women aged 50–59 over a 5-year period) (Medicines and Healthcare products Regulatory Agency 2007). Because of this difference in absolute rates, the excess breast cancers and venous thromboembolisms in users of oestrogen-progestagen MHT exceeds the increased risk of endometrial cancer. For example, in 1,000 women with a uterus aged 50–59 years, 5 years of oestrogen-progestagen MHT is estimated to result in six additional cases of breast cancer, seven additional cases of venous thromboembolism and no additional cases of endometrial cancer (Medicines and Healthcare products Regulatory Agency 2007). Five years of use of oestrogen-only MHT in an equivalent

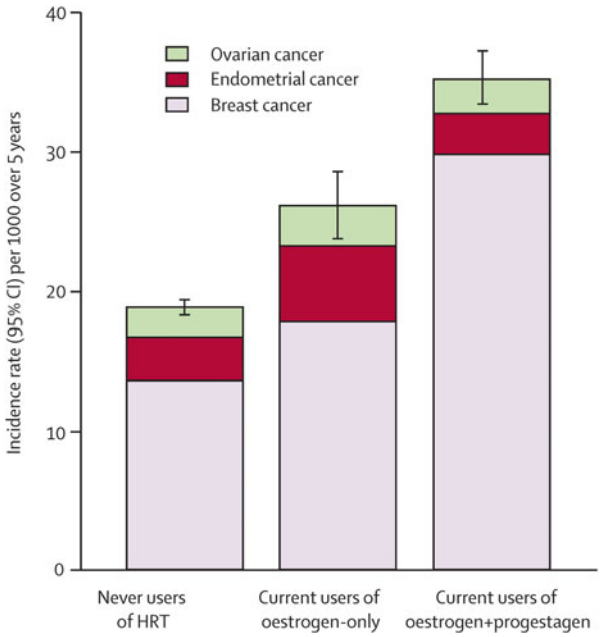

Fig. 11.1 Standardised incidence rates (95 % CI) for ovarian, endometrial and breast cancer per 1,000 women in the study cohort over a 5-year period, for current users of various types of MHT and for never users* (Reproduced from Million Women Study Collaborators 2007, with permission)

*Incidence rates are standardised by age, region of residence, socioeconomic status, time since menopause, parity, use of oral contraceptives, body-mass index, and alcohol consumption. Rates apply to women with a uterus and ovaries

population would lead to two additional cases of breast cancer, two additional venous thromboembolisms and four additional endometrial cancers (Medicines and Healthcare products Regulatory Agency 2007). Hence, the estimated net excess of potentially life-threatening events with 5 years use of oestrogen-progestagen MHT is greater than the net excess with use of oestrogen-only MHT, for women with and without a uterus (see above) (Medicines and Healthcare products Regulatory Agency 2007; Million Women Study Collaborators 2005, 2007).

If use is prolonged, which is not generally recommended but may be required if symptoms remain problematic, the high relative risk of endometrial cancer begins to have an impact on the overall safety profile, despite the low background risk. Ten years use of oestrogen-progestagen MHT for 100 women aged 50–59 is estimated to lead to 24 (20–28) excess breast cancers, 13 (8–20) additional VTEs and no additional cases of endometrial cancer. Ten years of oestrogen-only MHT in the same age group is estimated to lead to 6 (4–10) additional breast cancers, 3 (0–7) additional VTEs and 32 (21–48) additional endometrial cancers. Hence, the net

excess in risk is high and broadly comparable between oestrogen-progestagen and oestrogen-only (40 (30–53) excess potentially life-threatening events per 1,000 users of oestrogen-progestagen MHT versus 44 (26–70) per 1,000 users of oestrogen-progestagen MHT).

In summary, the current evidence indicates that, in terms of the overall risk of potentially life-threatening disease, use of oestrogen-only MHT carries fewer risks than use of oestrogen-progestagen MHT, for around 5 years for women with and without a uterus. In women with a uterus, more prolonged use carries substantially greater overall risks (due to the increased risk of endometrial cancer); the current estimates suggest that absolute excess risks with 10 years of use are similar for oestrogen-progestagen and oestrogen-only MHT.

It should be noted that in many countries, particularly parts of Europe and Australia, prescription of oestrogen-only MHT to women with a uterus is not accepted clinical practice, due to issues with uterine bleeding, endometrial hyperplasia and cancer. However, in other places, such as the US, such use, along with management of endometrial changes is more common.

The current evidence indicates that use of transdermal oestrogen-only MHT is likely to minimise the risk of venous thrombosis, compared to oral MHT (Sweetland et al. 2012; Olie et al. 2010). There is also initial evidence that oral preparations containing medroxyprogesterone acetate carry greater risks of venous thromboembolism than norethisterone and norgestrel containing preparations (Sweetland et al. 2012).

Strategies to Minimize Risk, Consistent with Guidance from Drug Regulatory Authorities

Increasing availability and consistency of data on the risks and benefits of MHT has been accompanied by agreement between key drug regulatory authorities that use should be targeted for moderate to severe menopausal symptoms only, and not for the prevention of disease. The US Food and Drug Administration (United States Department of Health and Human Services Food and Drug Administration 2005), the UK Medicines and Healthcare Products Regulatory Agency (2007), the Australian Therapeutic Goods Administration (Australian Drug Evaluation Committee 2004) and many other drug regulatory agencies world-wide are in agreement that:

- MHT should be used for the short term treatment of menopausal symptoms (e.g. hot flushes, night sweats, vaginal dryness) only;
- Women considering use of MHT should be informed of its risks and benefits;
- MHT should not be used for the prevention of disease, or (in Europe and Australia) as first line treatment for osteoporosis;
- MHT should be used for as short a period of time as possible and the need for continuing use should be reviewed six-monthly (Australian Drug Evaluation

Table 11.1 Evidence on certain risks related to menopausal hormone therapy (MHT) and related therapeutic approaches to minimise risk

Evidence on safety	Therapeutic approach to minimise risk
The older a woman is when she uses MHT, the greater the absolute risks related to use	Avoid MHT in older women, where possible The need for MHT should be reviewed regularly
Evidence of global harm and/or lack of overall benefit for prevention of disease Lack of long term benefits for fracture	MHT should be used for the treatment of moderate to severe menopausal symptoms and not for the long term prevention of disease
Evidence of global harm and/or lack of overall benefit for prevention of disease The relative risk of breast cancer increases with increasing duration of use	Use MHT for as short a period as possible The need for MHT should be reviewed regularly
The net average harms of combined oestrogen-progestagen MHT are greater than those of oestrogen alone, within the usual durations of use	Where possible, avoid combined oestrogen-progestagen MHT
There is an increased risk of venous thromboembolism with oral oestrogen-only and oestrogen-progestagen MHT but not transdermal oestrogen-only MHT	Use transdermal oestrogen-only MHT, where possible

Committee 2004) or annually (Medicines and Healthcare products Regulatory Agency 2007).

Unfortunately, there is no period of use of MHT that is not accompanied by risk and, since risks increase with increasing duration of use, minimising duration is important. As can be seen from the information above, 5 years of use carries considerable risk. As has been stated above, use for shorter periods of time, particularly use for less than 1 year will be accompanied by lesser increases in risk, although precise quantification of this risk is not possible with the current data.

The main strategies for minimising the risks relating to use of MHT, generally consistent with this guidance, are summarised in Table 11.1. There are additional strategies relating to preferential use of oestrogen-only MHT and transdermal oestrogen-only MHT that require consideration.

Conclusions

Menopausal hormone therapy (MHT) is an effective treatment for menopausal symptoms and reduces the risk of fracture. However, use results in a net increase in the risk of certain potentially life-threatening conditions including breast cancer, stroke, ovarian cancer and venous thromboembolism, and use of oestrogen-only MHT increases the risk of endometrial cancer in women with a uterus. Overall risks increase with increasing duration of use and with age and are greater for oestrogen-progestagen MHT than for oestrogen-only MHT.

Increasing availability and consistency of data on the risks and benefits of MHT has been accompanied by agreement between key drug regulatory authorities that use should be targeted for moderate to severe menopausal symptoms only, and not for the prevention of disease. Key strategies for minimising MHT-associated risks are consistent with advice from drug regulatory agencies and include the following: MHT should be used for the short term treatment of menopausal symptoms (e.g. hot flushes, night sweats, vaginal dryness) only; women considering use of MHT should be informed of its risks and benefits; MHT should not be used for the prevention of disease, or (e.g. in Europe and Australia) as first line treatment for osteoporosis; MHT should be used for as short a period of time as possible and the need for continuing use should be reviewed six-monthly or annually. Preferential use of oestrogen-only MHT and transdermal oestrogen-only MHT, including in women with a uterus, are also likely to reduce MHT-associated risks, compared to use of oestrogen-progestagen MHT and oral MHT.

Take Home Messages

- Large-scale data and guidance from drug regulatory authorities on MHT support targeted use of MHT;
- MHT should be used for the short term treatment of menopausal symptoms (e.g. hot flushes, night sweats, vaginal dryness) only;
- Women considering use of MHT should be informed of its risks and benefits;
- MHT should not generally be used for the prevention of disease, or as first line treatment for osteoporosis;
- The risks related to oestrogen-progestagen MHT are generally substantially greater than those related to use of oestrogen-only MHT;
- MHT should be used for as short a period of time as possible and the need for continuing use should be reviewed six-monthly or annually.

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Chapter 12
Bisphosphonates for Osteoporosis

Stuart Ralston

Introduction

Bisphosphonates are amongst the most widely used medicines in the pharmacopoeia and are indicated for the treatment of various bone diseases associated with osteoclast over-activity including osteoporosis, cancer-associated bone disease and Paget's disease of bone (Russell 2011). Prescription of bisphosphonates has increased over recent years, largely due to increased awareness of osteoporosis which us by far the most common indication for bisphosphonate therapy. Osteoporosis is a common disease but predominantly affects post-menopausal women. Reflecting this fact it has been estimated that about 30 % of women suffer an osteoporosis–related fracture at some point in life (Sambrook and Cooper 2006). This chapter reviews the beneficial effects and adverse effects of bisphosphonates used in the treatment of osteoporosis.

Historical Aspects

Bisphosphonates were first synthesised in the nineteenth century and initially used as chelating compounds in various industrial applications. An application which eventually led to studies of their use in bone disease was as water softening agents in detergents. The initial studies of bisphosphonates in bone focused on the hypothesis that they might be useful for the treatment of ectopic calcification based on the fact that that bisphosphonates are powerful inhibitors of mineralisation (Francis et al. 1969). However clinical studies have not shown beneficial effects of

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bisphosphonates on ectopic calcification and the clinical application of these drugs has focused on their inhibitory effects on bone resorption (Russell et al. 1970).

It was originally considered that bisphosphonates inhibit bone resorption by preventing dissolution of hydroxyapatite crystals (Fleisch et al. 1969) but it is now known that the inhibitory effects of bisphosphonates on bone resorption are not due to a physicochemical mechanism but rather, to a cellular mechanisms (Russell 2011). Nonetheless, the physiochemical interaction between bisphosphonates and hydroxyapatite plays a crucial role in targeting bisphosphonates to the bone surface and is an important determinant of potency (Nancollas et al. 2006). This activity continues to be exploited diagnostically through by the use of 99Tm-labelled bisphosphonates as reagents for radionuclide bone scanning. However, in this chapter I will focus on the clinical use of bisphosphonates as treatments for bone disease rather than as imaging agents.

Chemical Structure

Bisphosphonates share in common a core structure of phosphate-carbon-phosphate atoms (Fig. 12.1) which is responsible for the bisphosphonates' ability to bind calcium and hydroxyapatite crystals.

Bisphosphonates have a similar core structure to pyrophosphate which is a naturally occurring inhibitor of mineralisation. The central (or geminal) carbon atom of bisphosphonates render them chemically stable and resistant to hydrolysis,

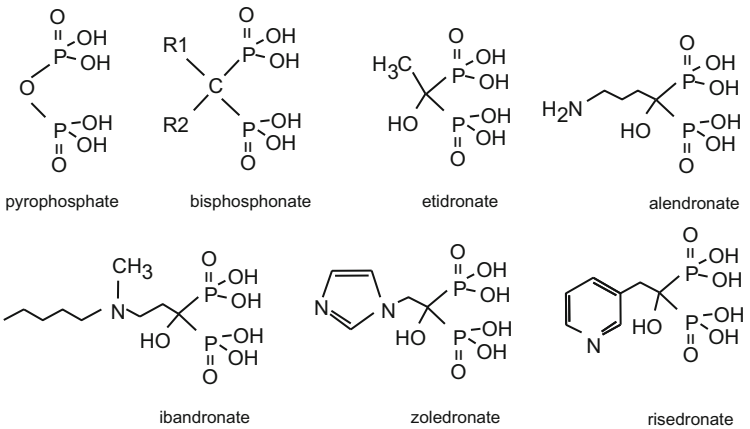

Fig. 12.1 Bisphosphonate structure
Bisphosphonates are chemically related to pyrophosphate and have a common core structure in which a central (geminal) carbon links two phosphonate groups. The phosphonate groups bind calcium and are responsible for the ability of bisphosphonates to bind hydroxyapatite crystals in bone. Different bisphosphonates have different side chains attached to the carbon atom at the R1 and R2 position and these influence both potency and affinity for mineral binding (see text for more details)

unlike pyrophosphate which is broken down rapidly by alkaline phosphatase. Chemical substitutions at the central (geminal) carbon atom of the bisphosphonates alter both the affinity for calcium binding and the mechanisms of action. For example the presence of a hydroxyl group at the R1 position tends to increase calcium binding affinity. Substitutions of nitrogen containing side chains at the R2 position not only alter the calcium binding properties of bisphosphonates but also increase potency considerably (Ebetino et al. 2011).

Pharmacology

Following administration, bisphosphonates are widely distributed in the extracellular fluid. About half of the administered dose is excreted by the kidney without further metabolism and the remainder is bound to the skeleton particularly at sites of high bone turnover (Russell 2011; Sato et al. 1991). When bone containing the bisphosphonate undergoes resorption, the drug is released within the osteoclast causing cell death and inhibition of bone resorption (Fig. 12.2).

It should be noted that the mechanisms of osteoclast inhibition differ for nitrogen-containing and simple bisphosphonates, as discussed in more detail below (Ebetino et al. 2011). Bisphosphonates also inhibit bone formation, but it is unclear to what extent this is due to the close coupling that exists between bone resorption and formation or a direct inhibitory effect on the osteoblast (Idris et al. 2008). Bisphosphonate that has become bound to bone which is not

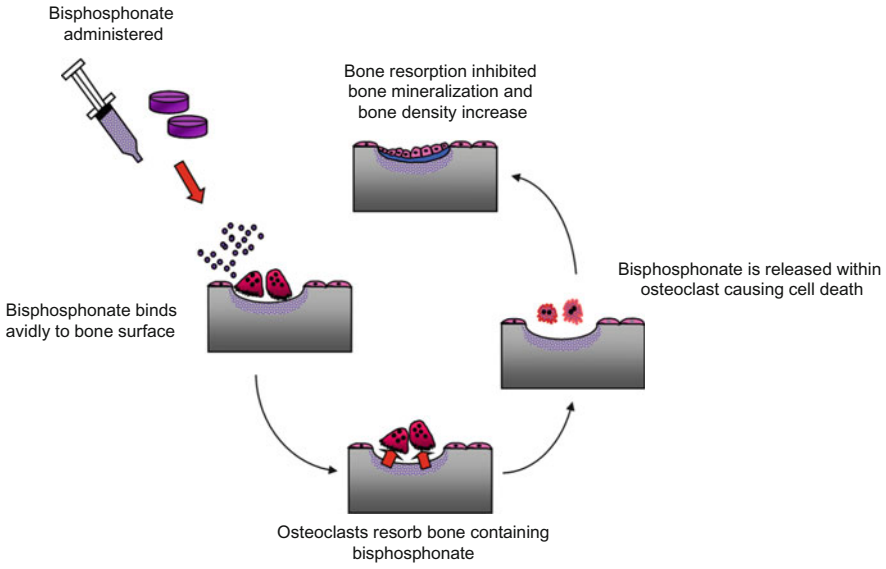

Fig. 12.2 Mechanism of action of bisphosphonates

immediately resorbed by osteoclasts can remain within the skeleton for prolonged periods. It is thought that slow release of bound bisphosphonate from the bone occurs subsequently over a period of months or years as the result of two processes; passive diffusion into the extracellular space and release during cycles of bone resorption (Russell 2011). The half-life of bisphosphonates in the skeleton is very long indeed such that inhibitory effects on biochemical markers of remodelling may be observed for one or more years after treatment has stopped. This is most relevant for bisphosphonates that have a high affinity for hydroxyapatite binding such as zoledronic acid and alendronic acid (Nancollas et al. 2006).

Bisphosphonates are poorly absorbed from the gastro-intestinal tract (<5 %) and absorption is further inhibited with food (Porras et al. 1999; Sansom et al. 1995), probably due to binding of the phosphonate moiety with dietary calcium (Janner et al. 1991). This, coupled with the tendency of some bisphosphonates to cause upper gastrointestinal (GI) upset, has led some pharmaceutical companies to develop intravenous formulations of bisphosphonates. All bisphosphonates have the potential to cause inhibition of bone mineralisation, but this is of most clinical relevance in the case of etidronate where the concentration required to inhibit bone resorption is close to that required to inhibit bone mineralisation (Flora et al. 1981).

Bisphosphonates inhibit osteoclastic bone resorption and this is accompanied by an increase in bone mineral density (BMD) (Ebetino et al. 2011). Although the increases in BMD observed during bisphosphonate therapy were originally thought to be due to infilling of the remodelling space (suppression of bone resorption with continued bone formation) it is now known that the increased BMD that occurs in response to bisphosphonate treatment mainly occurs through increased mineralisation of existing bone, rather than a gain in bone mass (Boivin et al. 2000).

Mechanism of Action

Bisphosphonates can be divided into two broad classes in terms of the mechanism by which they inhibit osteoclast activity (Rogers et al. 1999). Simple bisphosphonates such as etidronate, become incorporated into non-hydrolysable analogues of adenosine triphosphate (ATP) that result in cytotoxicity and cell death by depleting levels of ATP which plays an essential role in storing energy within osteoclasts and other cells (Frith et al. 1997, 2001). On the other hand, nitrogen containing bisphosphonates such as alendronic acid, risedronate, ibandronate and zoledronic acid inhibit the enzyme farnesyl pyrophosphonate synthase (FPPS) which is responsible for the addition of lipid chains (prenylation) to small GTPases such as Ras, Rac and Rho. This prevents the GTPases localising to cell membranes properly, resulting in osteoclast inhibition and loss of resorptive function (Coxon et al. 2000; Luckman et al. 1998).

Nitrogen-containing bisphosphonates (also known as aminobisphosphonates) are much more powerful inhibitors of osteoclast activity than simple bisphosphonates. There are also major differences between aminobisphosphonates in the potency with which they inhibit FPPS. The inhibitory effect of

aminobisphosphonates on bone resorption in man is correlated with the potency with which they inhibit FPPS, but also depends on factors such as their affinity for hydroxyapatite binding (Russell et al. 2008).

Bisphosphonates for the Prevention and Treatment of Osteoporosis

The bisphosphonates discussed below have been licensed in many countries for the prevention and treatment of osteoporosis although not all drugs are available in all countries. Whilst bisphosphonates share many properties in common, differences also exist in terms of chemical structure, mechanism of action and pharmacological profile which makes each bisphosphonate subtly different (Russell 2011). Because of this, the therapeutic and adverse effects of different bisphosphonates will be considered separately in the sections that follow.

Etidronate

Etidronate is licensed for the treatment of osteoporosis but is now seldom used due to the availability of more potent bisphosphonates. Indeed in the UK etidronate is no longer marketed for the treatment of osteoporosis even though the drug still has marketing approval for this indication.

Etidronate is administered orally and should be taken on an empty stomach and the patient advised to fast for at least 1 h after administration to ensure adequate intestinal absorption. Like other bisphosphonates, etidronate should be used with caution in renal impairment and is contraindicated in patients with a glomerular filtration rate (GFR) below 30. In osteoporosis, etidronate is given cyclically in a dose of 400 mg daily orally for a period of 10 days every 3 months, alternating with calcium supplements between the cycles of etidronate.

Efficacy

Cyclical etidronate was first marketed by Proctor and Gamble as Didronel PMO™ for the treatment of osteoporosis. The studies of etidronate in osteoporosis were small by today's standards. In one study 429 postmenopausal women were randomise to receive cyclical etidronate or placebo along with calcium supplementation or phosphate supplements over a 2 year period (Watts et al. 1990). Each treatment group consisted of about 100 patients. Bone density at the spine increased by about 5 % in the etidronate treated groups but did not change significantly in the placebo groups. Phosphate had no additional effect. Fewer patients in the etidronate treated groups suffered vertebral fractures (29.5/1,000 patient years vs. 62.9/1,000 patient years), a result which was just significant ($p = 0.043$) but there was no reduction in non-vertebral fractures.

Another smaller study with 33 patients per group showed similar effects on BMD over a 3 year period but, not surprisingly given the small numbers, there was no significant reduction in fractures (Storm et al. 1990). An observational study in the UK General Practice Research Database (GPRD) which compared fracture rates in etidronate treated patients with matched controls who had a diagnosis of osteoporosis but who were not treated with etidronate reported a reduced risk of fracture in the etidronate treated group (relative risk 0.80, 95 % CI 0.70–0.92). However it was not possible in this study to control for various confounding factors such as the severity of osteoporosis and selection bias so the results have to be treated with caution (van Staa et al. 1998).

Cyclical etidronate is also licensed for the treatment of glucocorticoid induced osteoporosis (GIOP). The largest randomised trial of etidronate in GIOP involved 67 etidronate and 74 placebo treated patients followed over a 12 month period. About 60 % of patients were women, the majority of whom were postmenopausal. Spine bone density increased by about 4 % in the etidronate group but fell in the placebo group – a result that was significant ($p = 0.02$). Vertebral fractures were less common in the etidronate group but the relative risk reduction was not significant (0.6, 95 % CI 0.2–1.6) (Adachi et al. 1997). A subsequent pooled analysis of etidronate from five randomised trials in GIOP confirmed that the drug increased BMD by about 5 % at the spine but reported no overall reduction in fracture risk (RR = 0.50, 95 % CI = 0.21–1.19).

Adverse Effects

The randomised trials placebo-controlled trials of etidronate, while limited in sample size, showed that the drug was well tolerated with an adverse effect profile that was not different from placebo. Adverse effects mentioned in the summary of product characteristics include diarrhoea, upper GI upset and leg cramps. Mineralisation defects and pathological fractures have been reported in patients with Paget's disease treated with etidronate (Boyce et al. 1984) but this does not seem to be a problem with the cyclical regimen used for osteoporosis (Storm et al. 1990). Renal impairment has rarely been reported in patients with hypercalcaemia given high doses of intravenous etidronate (Bounameaux et al. 1983), but this is not relevant in the osteoporosis setting.

Alendronic Acid

Alendronic acid is an aminobisphosphonates that is about 50 times more potent than etidronate at inhibiting bone resorption (Fleisch 1993). It also has a high affinity for binding hydroxyapatite (Nancollas et al. 2006) and this is thought to be responsible for its long duration of action. Alendronic acid, like other bisphosphonates, is poorly absorbed from the GI tract and must be taken on an empty stomach with a large glass of water and the patient should be advised to remain upright for 30 min

to minimise the risk of the tablet sticking in the oesophagus. This prompted Merck, the manufacturer of branded alendronate (Fosamax®) to introduce a film – coated tablet to ease passage through the oesophagus, although multiple generic brands of alendronic acid are now available that do not have any special coating. Following administration patients should be advised to wait for at least 30 min before taking other medication or food to ensure adequate absorption. This can prove inconvenient or impractical for some patients. Alendronic acid should be used with caution in renal impairment since it is primarily eliminated by renal excretion. Alendronic acid is contra-indicated in patients with a GFR below 35 ml/min.

Efficacy

Several large-scale randomised trials of alendronic acid have been performed in women with postmenopausal osteoporosis with the entry criteria of low BMD and/or pre-existing vertebral fractures (Liberman et al. 1995; Black et al. 1996; Pols et al. 1999). Meta-analyses have shown that alendronic acid reduces the risk of vertebral, non-vertebral and hip fractures in postmenopausal women as compared with calcium and vitamin D supplemented supplemented placebo. For vertebral fractures, data are available from six studies involving 7,361 postmenopausal women in which the relative risk was 0.55 (95 % CI 0.45–0.67) for alendronic acid as compared with placebo. For non-vertebral, non hip fractures, data from 9,625 women in six studies showed a relative risk of 0.84 (95 % CI 0.74–0.94) compared with placebo. For hip fractures data from 9,952 women showed a relative risk of 0.61 (95 % CI 0.40–0.92) compared with placebo (Wells et al. 2008a).

Alendronic acid is also effective at increasing BMD and reducing vertebral fracture risk in GIOP (Saag et al. 1998; Adachi et al. 2001). The studies in GIOP are much smaller than in postmenopausal osteoporosis and were designed with BMD as a primary endpoint rather than fracture. A key study was that of Saag and colleagues who compared the effects of two doses of alendronate (5 and 10 mg daily) with calcium supplemented placebo in 447 patients with GIOP over a 48 week period (Saag et al. 1998). About 70 % of the study group were women and two thirds were postmenopausal. Bone density in the alendronic acid treated patients increased by about 3 % but fell in the placebo group, a difference that was highly significant ($p < 0.01$). An extension of this study to 2 years in 66 men and 142 women (Adachi et al. 2001) showed that vertebral fractures were less frequent in the alendronic acid group versus the placebo group (0.7 % versus 6.8 %; $p = 0.026$). There was no significant difference in the frequency of non vertebral fractures. The only substantial experience of alendronic acid in premenopausal women is in the patients who were enrolled into GIOP studies. Subgroup analysis of these studies showed that the response of BMD in premenopausal women was similar to that in postmenopausal women.

Whilst the pivotal fracture trials of alendronic acid were performed with 10 mg alendronic acid daily, subsequent studies showed that 70 mg weekly was bioequivalent in terms of inhibiting bone turnover markers and increasing BMD (Schnitzer et al. 2000). Since the once weekly dosing is much more convenient, alendronic acid is now almost always given in a dose of 70 mg once weekly in the treatment of osteoporosis. In routine clinical practice it is also usual to prescribe alendronic acid in combination with calcium and vitamin D supplements since these supplements were used routinely in the randomised trials. A combination product containing alendronic acid 70 mg and cholecalciferol 5,600 units once a week is also available (Fosavance™).

Duration of Treatment

The optimal duration of alendronic acid for the treatment of osteoporosis remains a subject of debate. The effect of duration of therapy has been investigated in one randomised placebo controlled trial in women with postmenopausal osteoporosis who participated in the Fracture Intervention Trial (FIT) (Black et al. 1996). Patients who had already been treated for at least 3 years with alendronic acid in the FIT trial were invited to take part in an extension study in which they were randomised to receive therapy with placebo (n = 437) or to continue alendronic acid 5 mg daily (n = 329) or 10 mg daily (n = 333) for a further 5 years (Black et al. 2006). All patients received calcium and vitamin D supplements. The average duration of alendronic acid on entry to the study was 5 years. Patients with a total hip T-score of < -3.5 and those with a T-score below the baseline value in FIT were excluded. The proportion of patients who completed follow up according to protocol was close to 90 % and did not differ between the groups.

At the end of the study, patients who continued alendronic acid for 10 years maintained the increase in total hip BMD observed during the initial 5 years therapy, whereas those randomised to placebo experienced a fall in total hip BMD between years 5 and 10 of about 2 %. At the lumbar spine, BMD increased by about 4 % between years 5 and 10 in both alendronic acid groups but remained stable in the placebo group. The bone resorption marker N-telopeptide of type I collagen cross-links (NTX) remained suppressed in alendronic acid treated patients during the 10-years of study, but increased by about 60 % between years 5 and 10 in the patients assigned to placebo. At the end of the study, there were no differences in the rate of non-vertebral fractures or morphometric vertebral fractures between the groups, but clinical vertebral fractures were less common in the patents that had received 10 years therapy (5.3 % for placebo and 2.4 % for alendronate; relative risk, 0.45; 95 % CI, 0.24–0.85). Adverse effects were similar in the two treatment groups.

The long term effects of alendronic acid have also been documented in an observational study of postmenopausal women who were treated over a 10-year period with alendronic acid (Bone et al. 2004). This represented an extension study

of two randomised placebo controlled trials which together enrolled 994 women with postmenopausal osteoporosis. Of 804 women who entered the extension, 322 were randomised to receive continued alendronic acid 5 or 10 mg daily and 164 (50 %) completed 10 years therapy. The original trial included a cohort of 160 women who received 5 years of alendronic acid (20 mg daily for years 1–2 and 5 mg daily for years 3–5). These were reassigned to receive placebo for 5 years and 83 (51.9 %) completed 10 years follow up. The initial gains in BMD and reduction in bone turnover markers observed during the first 3 years of therapy of alendronic acid were maintained for 10 years in those allocated to 5 and 10 mg alendronic acid, with no difference between the groups. Those allocated to placebo following 5 years alendronic acid showed a ~20 % rise in NTX and a 2 % fall in femoral neck BMD but no change in lumbar spine BMD. The proportion of patients with fracture in women assigned to 10-years alendronic acid (5 and 10 mg combined) were similar to those who discontinued alendronic acid after 5 years. Adverse effect profile was also similar between the groups.

Taken together these studies suggest that increases in BMD and reductions in bone turnover are maintained in postmenopausal women who continued therapy with alendronic acid for up to 10 years. While the studies suggest that fracture risk reduction is also maintained with alendronic acid for up to 10 years without an obvious increase in adverse reactions, they had limited powered to detect differences in adverse events or fractures between the treatment groups.

Adverse Effects

The adverse event profile of alendronic acid was reported to be similar to that of placebo in randomised trials (Liberman et al. 1995; Black et al. 1996; Pols et al. 1999). However in routine clinical practice, upper gastrointestinal symptoms such as dyspepsia and epigastric pain have emerged as a common adverse effect occurring in about 5 % of patients (Mackay et al. 1998). Oesophageal ulceration and perforations have been reported in isolated patients but it is difficult to estimate the exact frequency with which they occur. They are thought to be due to the tablet sticking in the oesophagus (Mackay et al. 1998). Other rare adverse events which have emerged from post-marketing surveillance studies include uveitis, osteonecrosis of the jaw (Khosla et al. 2007), atypical subtrochanteric fractures (Schilcher et al. 2011) and bone, joint or muscle pain (Wysowski and Chang 2005; Bock et al. 2007).

Osteonecrosis of the jaw is a very rare adverse effect of oral alendronate. It is characterised by the occurrence of necrotic bone in the mandible or maxilla following tooth extraction although some cases occur spontaneously (Novince et al. 2009). In one series, based in the South East of Scotland, the incidence was estimated as less than 0.004 % per treated patient per year for alendronic acid prescribed for postmenopausal osteoporosis, but this increased to 0.1 % for patients treated for GIOP. The condition was first reported during the mid 1980s in patients

receiving high dose intravenous bisphosphonate therapy for metastatic bone cancer (Woo et al. 2006) and for this indication it remains a significant problem occurring in up to 2 % of patients (Stopeck et al. 2010). The pathogenesis is incompletely understood but it is thought to be related to over-suppression of bone turnover (Allen and Burr 2009) since it is rare in patients treated with the doses of bisphosphonates used in osteoporosis but is common in cancer associated bone disease where the dose of bisphosphonate is an order of magnitude greater (Woo et al. 2006). Emphasising this fact, osteonecrosis of the jaw has also been associated with denosumab treatment, another powerful antiresorptive drug (Stopeck et al. 2010).

Atypical subtrochanteric fractures are an uncommon adverse effect of alendronic acid with an estimated incidence of 5 cases per 10,000 patient years of treatment (Schilcher et al. 2011). Patients are at risk of developing these fractures within 1 year of starting alendronic acid but the risk increases progressively with duration of exposure (Schilcher et al. 2011). Following cessation of alendronic acid the risk falls rapidly. The clinical presentation is with a transverse fracture line in the lateral cortex with a medial spike (Fig. 12.3). Focal cortical thickening with a periosteal reaction may be seen in proximity to the transverse fracture line.

These fractures occur with minimal or no trauma and may be preceded by thigh pain localised to the affected side. Atypical subtrochanteric fractures are thought to be due to over-suppression of bone resorption with the development of stress fractures in the lateral cortex of the femoral shaft in susceptible individuals (Shane et al. 2014). It has been speculated that certain patients may be genetically predisposed to develop these fractures but the mechanisms that underlie

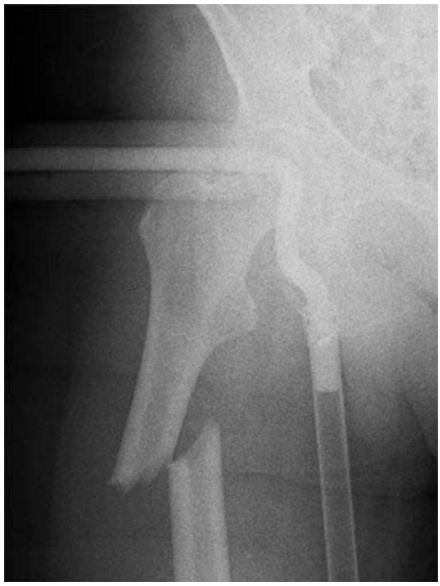

Fig. 12.3 Bisphosphonate associated atypical subtrochanteric fracture Radiograph from a 74 year old women who suffered a spontaneous fracture of the right femoral shaft showing the typical transverse fracture line through the lateral cortex and medial spike. She had been on oral alendronate for 8 years

susceptibility remain poorly understood (Shane et al. 2014). Risk factors that have been identified as being associated with atypical subtrochanteric fractures in one or more epidemiological studies include; duration of bisphosphonate treatment; being of Asian ethnicity; glucocorticoid use; active rheumatoid arthritis; prior fragility fracture and low serum 25(OH)D levels (as reviewed by Shane and colleagues (2014)).

Although the risk-benefit balance is overwhelmingly favourable in the vast majority of osteoporotic patients who receive treatment with alendronic acid and other bisphosphonates, the occurrence of this complication emphasises the importance of only giving bisphosphonates to patients with a substantially increased fracture risk (Shane et al. 2014; Abrahamsen 2010).

Risedronate

Risedronate is an aminobisphosphonate which is more potent than alendronate at inhibiting osteoclast activity in vitro but which has lower affinity than alendronate for binding hydroxyapatite (Nancollas et al. 2006). Despite its greater potency, risedronate inhibits bone turnover to a lesser extent than alendronic acid at the dose used clinically, resulting in less marked reductions in bone turnover and smaller increases in BMD (Rosen et al. 2005). Similarly the inhibitory effects of risedronate on bone turnover are of relatively short duration and are lost within about 12 months of stopping therapy (Mortensen et al. 1998). Risedronate is primarily used in the treatment of osteoporosis but is also licensed in several countries for the treatment of Paget's disease of bone. Risedronate is poorly absorbed from the GI tract and must be taken on an empty stomach as described for alendronic acid. Risedronate is mainly excreted by the kidney and should be used with caution in renal impairment. It is contra-indicated in patients with a GFR below 30 ml/min.

Efficacy

Large-scale randomised trials in women with postmenopausal osteoporosis have shown that oral risedronate 5 mg daily reduces the risk of vertebral, non-vertebral and hip fractures as compared with calcium and vitamin D supplemented placebo in postmenopausal osteoporosis. A meta-analysis of five randomised placebo controlled trials involving 2,620 postmenopausal women with pre-existing vertebral fractures or low BMD on dual energy X-ray absorptiometry (DEXA), showed that the relative risk of vertebral fractures in risedronate treated patients was 0.64 (95 % CI 0.52–0.78) as compared with placebo (Wells et al. 2008b). A further meta-analysis of six trials including 12,309 postmenopausal women showed a relative risk of 0.80 (95 % CI 0.72–0.90) for non-vertebral, non-hip fractures in risedronate-treated patients as compared with placebo. Four studies included in the above meta-

analysis had data on hip fractures and in these subjects, the relative risk of hip fracture was 0.74 (95 % CI 0.59–0.94) in risedronate treated patients (Wells et al. 2008b).

A further study was specifically designed to examine the effects of risedronate on hip fracture, in 9,331 elderly postmenopausal women. In this trial, 5,445 subjects were enrolled on the basis that they were aged 70–79 years and had low hip BMD on DXA (T-score <-3.0) whereas the remaining 3,886 subjects were enrolled on the basis that they were aged over 80 years with at least one clinical risk factor for hip fracture. This study showed a significant reduction in hip fracture risk overall (relative risk 0.70 95 % CI 0.60–0.90) but subgroup analysis showed that the risk of hip fracture was statistically significant in patients with low BMD (relative risk 0.60, 95 % CI 0.40–0.90) but not significant in those with clinical risk factors alone (relative risk 0.80, 95 % CI 0.60–1.20).

Risedronate has also been found to be effective at increasing BMD and preventing vertebral fractures in GIOP (Wallach et al. 2000). The effects of risedronate at doses of 2.5 or 5 mg daily in combination with calcium supplements versus placebo were investigated in two parallel trials of similar design involving 518 patients receiving glucocorticoid therapy. About 50 % of participants were female and of these, about 86 % were postmenopausal. One study sought to investigate the effects of risedronate in preventing GIOP (Cohen et al. 1999). In this trial participants had been on 7.5 mg prednisolone daily or more for less than 3 months.

Another study sought to investigate the effects of risedronate in the treatment of GIOP and here, prednisolone had been given in a dose of 7.5 mg daily or more for at least 6 months (Reid et al. 2000). Analysis of pooled data from both trials showed that risedronate was effective at increasing BMD as compared with calcium and vitamin D supplemented placebo in reducing vertebral fractures (relative risk 0.33, 95 % CI 0.13–0.81) but there was no significant reduction in the frequency of non-vertebral fractures (relative risk 1.08, 95 % CI 0.45–2.59) (Wallach et al. 2000). Trials of oral risedronate acid have also been conducted in children with osteogenesis imperfecta. These studies have shown increases in BMD as compared with placebo (Rauch et al. 2009; Bishop et al. 2013), and one study showed a reduction in fracture incidence compared with placebo (Bishop et al. 2013).

Adverse Effects

The adverse event profile of risedronate has been reported to be similar to that of placebo in randomised placebo-controlled trials (Reginster et al. 2000; McClung et al. 2001; Fogelman et al. 2000; Harris et al. 1999; Taggart et al. 2002). However in routine clinical practice, upper gastrointestinal symptoms such as dyspepsia and epigastric pain have emerged as a common adverse effects of risedronate. There are no published data on the frequency with which these adverse effects occur, but the

author's impression is that the incidence is similar to that in alendronic acid treated patients. Having said that, some patients who develop upper GI side effects with alendronate can tolerate risedronate perfectly well. Like other oral bisphosphonates, risedronate should be avoided in patients with dysphagia and other oesophageal disorders that might result in the tablet sticking in the oesophagus.

Other rare adverse events which are thought to be a class effect of bisphosphonates that have emerged from post-marketing surveillance studies include uveitis, osteonecrosis of the jaw (Khosla et al. 2007), atypical subtrochanteric fractures (Schilcher et al. 2011) and bone, joint or muscle pain (Wysowski and Chang 2005; Bock et al. 2007). There is much less information on the relative risk of these events with risedronate as compared with alendronic acid. However in the study of Schilcher, the relative risk of atypical subtrochanteric fractures with risedronate was similar to that of alendronate (Schilcher et al. 2011).

Observational studies have suggested that risedronate may be less likely to cause upper GI adverse effects than alendronate (Ralston et al. 2010) but randomised comparative studies of these two drugs showed no difference in GI side effects (Rosen et al. 2005). There have been fewer reports of ONJ and atypical subtrochanteric fractures in risedronate treated patients as opposed to alendronate treated patents. It has been speculated that this might be due to the fact that at the doses used clinically, risedronate is a less potent inhibitor of bone resorption than alendronate. However another possibility, given that these are rare adverse effects, is that this is simply because risedronate is much less widely used than alendronate.

Ibandronate

Ibandronate is a nitrogen containing bisphosphonate. It is a more potent inhibitor of osteoclast activity in vitro than alendronic acid, but is less potent than risedronate. Its binding affinity for hydroxyapatite is greater than risedronate but less than alendronate. Ibandronate is primarily used in the treatment of osteoporosis but is also licensed in the UK and Europe for the treatment of cancer-associated hypercalcaemia and for the prevention and treatment of metastatic bone disease. Administration instructions for oral ibandronate are similar to those described for alendronic acid. The medication must be taken on an empty stomach and 30 min should be allowed to elapse before taking other medication or food. Like other bisphosphonates ibandronate should be used in caution in patient with renal impairment and it is contraindicated if the GFR is less than 30.

Ibandronate is usually given in a dose of 150 mg once monthly in combination with calcium and vitamin D supplements in the treatment of osteoporosis (Reginster et al. 2005a) but can also be given intravenously in a dose of 3 mg every 3 months (Adami et al. 2004). The intravenous preparation is usually reserved for patients who have difficulty in swallowing tablets or those that experience GI upset with oral bisphosphonates. Most clinicians choose intravenous zoledronic

acid over intravenous ibandronate if a parenteral bisphosphonate is required in view of the similar adverse effect profile and more robust data on anti-fracture efficacy (Black et al. 2007).

Efficacy

The pivotal fracture trials with ibandronate were performed with a 2.5 mg daily dose and a rather complicated intermittent dose regimen in which 20 mg was given on alternate days for 12 days every 3 months (Delmas et al. 2004). The study involved 2,946 postmenopausal women with osteoporosis and was placebo controlled. All participants received calcium and vitamin D supplements. Both ibandronate regimens increased BMD, and reduced biochemical markers of bone turnover compared with placebo. The relative risk of vertebral fractures was 0.62 (0.41–0.75) with the 2.5 mg daily regimen and 0.50 (0.26–0.66) with the 20 mg intermittent regimen but there was no significant preventative effect of non-vertebral or hip fractures with either regimen.

A subsequent post hoc analysis of randomised trials of oral and intravenous ibandronate suggested that treated patients may experience a 24 % reduction in the rate of non-vertebral fractures in subjects treated with an annual cumulative ibandronate exposure of $\geq$10.8 mg (Harris et al. 2008). Although these data raise the possibility that ibandronate might have efficacy for non vertebral fractures, the results have to be treated with caution given the limitations of this type of analysis.

Adverse Effects

Randomised controlled trials of oral ibandronate showed no difference in adverse events compared with placebo (Delmas et al. 2004). The adverse events of oral ibandronate are much less well documented as compared with alendronic acid and risedronate probably because it is used relatively infrequently. However the author's personal experience with monthly ibandronate indicates that the adverse effects are very similar to those of alendronic acid and risedronate.

Like other amino bisphosphonates, intravenous ibandronate treatment can cause an acute phase response (APR) which presents as a transient flu-like illness, characterised by fever, arthralgia, bone pain and general malaise, lasting for 1–2 days after administration. Experience with other intravenous bisphosphonates such as pamidronate and zoledronic acid indicates that the APR does not recur or is much less prominent after second and subsequent infusions but there is little published data on ibandronate with regard to this issue. Similarly, hypocalcaemia is a potential adverse effect with intravenous ibandronate particularly in patients with vitamin D deficiency but there is little published data on the frequency with which this occurs. In clinical practice it is important to ensure that patients treated with

ibandronate have normal vitamin D levels or are on vitamin D supplements at the time of infusion.

There have been few reports of BRONJ and atypical subtrochanteric fractures in osteoporosis patients treated with ibandronate but this may simply be a reflection of the fact that ibandronate is less widely used than alendronic acid and is licensed in fewer countries.

Zoledronic Acid

Zoledronic acid is the most potent licensed bisphosphonate. It is a nitrogen-containing bisphosphonate with high binding affinity for hydroxyapatite. As a result of this it has very powerful inhibitory effects on bone resorption and a long duration of action. Zoledronic acid is licensed for the treatment of osteoporosis, cancer-associated hypercalcaemia, metastatic bone disease and Paget's disease of bone. It is administered intravenously for all indications. In osteoporosis the dose is 5 mg given intravenously over 15 min every 12 months. In most countries zoledronic acid is given in a day patient setting but it can be given by primary care physicians. Like other bisphosphonates zoledronic acid is excreted by the kidney and should be used in caution in patient with renal impairment. It is contraindicated if the GFR is less than 35.

Efficacy

The pivotal fracture trial (Black et al. 2007) showed that zoledronic acid 5 mg annually for 3 years combined with calcium and vitamin D supplements reduced the risk of vertebral, fractures non-vertebral fractures and hip fractures in patients with osteoporosis as compared with calcium and vitamin D supplemented placebo in women with postmenopausal osteoporosis. This study involved 7,765 postmenopausal women with DEXA proven osteoporosis who were randomised to receive intravenous zoledronic acid or placebo infusions 5 mg every 12 months for 3 years. Both groups received calcium and vitamin D supplements.

When compared with placebo, bone density increased at the spine by about 7 % and at the femoral neck by about 5 % in zoledronic acid treated patients over the 3 year treatment period ($p < 0.0001$). The relative risk of clinical vertebral fractures was 0.23 (95 % CI 0.14–0.37) in zoledronic acid treated patients when compared with placebo. Corresponding values for non vertebral, non hip fractures were 0.75 (0.64–0.87) and for hip fractures were 0.59 (0.42–0.83) (Black et al. 2007).

While there have been no comparative trials of zoledronic acid with oral bisphosphonates, it is of interest to note that the relative risk reduction of non-vertebral and hip fractures with zoledronic acid is very similar to that observed with alendronic acid and risedronate, whereas the relative risk reduction of

vertebral fractures is numerically greater with zoledronic acid. Zoledronic acid is unique in that it has been shown to exert a favourable effect on recurrent fracture and mortality following hip fracture (Lyles et al. 2007). In this study 1,065 patients who had suffered a low trauma hip fracture, who were unable or unwilling to take oral bisphosphonates, were randomised to receive zoledronic acid or placebo infusions. About 75 % of patients were postmenopausal women. Both groups were given vitamin D supplements prior to the first infusion and were subsequently supplemented with calcium and vitamin D during the study. The relative risk of recurrent fractures in the zoledronic acid treated group was 0.65 (0.50–0.84) and the relative risk of death was 0.72 (0.56–0.93) (Lyles et al. 2007).

Subsequent studies showed that the prevention of recurrent fractures explained only 8 % of the effect on mortality and also showed that adjusting for acute medical events eliminated the survival benefit (Colon-Emeric et al. 2010). Zoledronic acid-treated subjects were less likely to die from pneumonia and arrhythmias than placebo treated patients, although the mechanism by which these effects occurred remain unclear since at baseline the treatment groups were well matched for co-morbidities.

Duration of treatment

The duration of action of zoledronic acid on bone density and fractures was investigated in a 3 year extension to the pivotal fracture trial. In this study 1,223 postmenopausal women who had completed 3 years zoledronic acid treatment in the HORIZON study (Black et al. 2007) were randomised to receive a further three infusions resulting in a total duration of 6 years treatment (Z6) ($n = 616$) or to have placebo infusions ($n = 617$) for 3 years (Z3P3) (Black et al. 2012).

Bone mineral density values remained relatively stable between years 3 and 6 in the Z6 group but fell by about 1.3 % at the femoral neck and 2 % at the lumbar spine between year 3 and year 6 in the in the Z3P3 group, differences that were significant ($p < 0.001$). There was no difference in the occurrence of clinical fractures between the groups, but morphometric vertebral fractures were less common in the Z6 group (relative risk 0.51, 95 % CI 0.26–0.95). However, stroke was more common in the Z6 group (3.1 % vs. 1.5 %, $p = 0.06$). Because of this, and concerns about over suppression of bone turnover with long term zoledronic acid use, many clinicians favour a zoledronic acid regimen of 3 years on and 3 years off therapy.

There is evidence that single infusions of zoledronic acid can exert prolonged inhibitory effects on bone turnover (Grey et al. 2010) and favourably influence the risk of fracture in osteoporosis. Evidence of this comes from a post-hoc analysis of the pivotal fracture trials described previously (Black et al. 2007; Lyles et al. 2007) in which 746 patients who received a single infusion of zoledronic acid were found to have a 32 % reduction in fracture risk (95 % CI 2–53 %) compared with 610 patients who received a placebo infusion. The relative risk reduction with a single infusion was similar to the 34 % reduction (23–43 %) observed in the same

studies in patients who had three infusions (Reid et al. 2013). These interesting observations suggest that one zoledronic acid infusion might be enough to reduce the risk of fracture in many patients with osteoporosis in routine clinical practice.

Adverse Effects

The adverse effects of intravenous zoledronic acid are similar to those of other intravenous ibandronate but have been documented in much more detail. The incidence of an APR (transient flu like illness) with zoledronic acid in osteoporosis is about 42 % after the first infusion, falling to 11 % and 7 % after the second and third infusions (Reid et al. 2010). These reactions are more common in younger people, and NSAID users, but less common in smokers and those who have previously received oral bisphosphonates.

Osteonecrosis of the jaw has been extensively studied in relation to the high doses of zoledronic acid used in the treatment of metastatic bone disease. In this situation zoledronic acid is typically given in doses of 4 mg intravenously every 3–4 weeks, resulting in an annual exposure about 10 times higher than in patients with osteoporosis. In the AZURE study of women with breast cancer the incidence of ONJ was 2.7 % (Rathbone et al. 2013) whereas in the MRC XI myeloma study the incidence was somewhat higher at 3.7 % with zoledronic acid as compared with 0.5 % with clodronate (Jackson et al. 2014). In osteoporosis ONJ associated with zoledronic acid treatment is thought to be very rare and in one study the incidence was estimated as less than 1 in 14,200 patient years (Grbic et al. 2010).

There is little information on the risk of atypical subtrochanteric fractures with zoledronic acid but they appear to be rare in that there was no excess of these fractures in the randomised trials of zoledronic acid as compared with placebo (Adachi et al. 2011; Black et al. 2010). Intravenous zoledronic acid has been associated with an increased risk of atrial fibrillation in the pivotal fracture trial discussed previously (Black et al. 2007). In this study, which involved 7,765 postmenopausal women serious atrial fibrillation resulting in admission to hospital was observed in 1.3 % of the zoledronic acid group compared with 0.5 % of the placebo group ($p < 0.001$). However the overall incidence of atrial fibrillation was similar in both treatment groups (2.4 % vs. 1.9 %) (Black et al. 2007). This adverse effect was not seen in other studies and the mechanism remains unclear.

Role of Bisphosphonates in the Prevention and Treatment of Osteoporosis

Over the past 10 years bisphosphonates have become established as the principle treatment of osteoporosis, due to their relatively low cost, robust anti-fracture efficacy and generally good tolerability and adverse event profile. In contrast, and

as discussed elsewhere in this book, the use of hormone replacement therapy (HRT) as a treatment for osteoporosis has declined due to concerns about the increased risk of cardiovascular disease and breast cancer with long term therapy in postmenopausal women (Rossouw et al. 2002).

Comparative studies of bisphosphonates with other agents used in the treatment of osteoporosis are limited in number. Randomised controlled trials have shown that teriparatide (TPTD) is superior to alendronic acid at increasing BMD and reducing the risk of vertebral fractures in GIOP (Saag et al. 2009) and is superior to risedronate in reducing the risk of vertebral fractures in postmenopausal osteoporosis (Hadji et al. 2012). Whilst superiority of teriparatide over bisphosphonates in preventing vertebral fractures has also been observed in observational studies (Oswald et al. 2014), treatment with teriparatide is usually reserved for patients with severe spinal osteoporosis or those in whom the response to bisphosphonates has been inadequate, due to the much greater cost of TPTD and need for daily injections.

There have been no comparative studies of bisphosphonates with other anti-osteoporosis treatments in which fractures have been an endpoint. However, the relative risk reduction in non-vertebral fractures that has been observed with bisphosphonates in placebo controlled randomised trials (~20–25 %) is numerically superior to that observed with strontium ranelate (Reginster et al. 2005b) (~16 %) and is similar to that observed with HRT (~24 %) (Rossouw et al. 2002) and denosumab (~20 %) (Cummings et al. 2009).

Bisphosphonates in Pregnancy and Lactation

Bisphosphonates are contraindicated during pregnancy. Preclinical studies have shown that bisphosphonates cross the placenta and adversely effect development of the fetal skeleton. There are several case reports of patients receiving bisphosphonate therapy during pregnancy however and these have shown no obvious adverse effects on the foetus (Shenker et al. 2010; Levy et al. 2009; Djokanovic et al. 2008; Hellmeyer et al. 2007; O'Sullivan et al. 2006; Ornoy et al. 2006). In one case series, 51 patients were treated with various bisphosphonates before or during pregnancy and this did not seem to affect outcome of the pregnancy or the fetal skeleton (Djokanovic et al. 2008). Similar observations were reported in another case series of 21 patients (Levy et al. 2009).

There is very little information on the use of bisphosphonate therapy during lactation, but one case report of a patient with pregnancy-associated osteoporosis reported no adverse effects on mother or child (Shenker et al. 2010). These observations suggest that there is no major reason for concern if a woman is exposed to bisphosphonate therapy during pregnancy.

Bisphosphonates and Aromatase Inhibitor Induced Bone Loss

The aromatase enzyme is responsible for conversion of adrenal androgens to oestrogen in various tissues including bone (Morishima et al. 1995). Oestrogen produced by this pathway protects against bone loss particularly in postmenopausal women. With the increasing use of aromatase inhibitors such as anastrozole and letrozole as adjuvants treatment for breast cancer, aromatase inhibitor-induced osteoporosis has become an important issue in clinical practice (Reid et al. 2008).

Aromatase inhibitors are now widely used in preference to tamoxifen as an adjuvant treatment of breast cancer following large scale trials which showed advantages in progression free survival (Baum et al. 2002, 2003). Aromatase inhibitor therapy is associated with accelerated bone loss as compared with tamoxifen however, and an increased risk of fractures (Baum et al. 2002; Coleman et al. 2007; Eastell et al. 2006).

The bone loss associated with aromatase inhibitor therapy can be prevented by antiresorptive drugs and the bisphosphonates zoledronic acid and risedronate have both been found to be effective in this situation in randomised placebo controlled studies (Safra et al. 2011; Van Poznak et al. 2010).

On the basis of this, current guidance in the UK suggests that women who are to commence aromatase inhibitor therapy should undergo DEXA scanning and that bisphosphonates and calcium plus vitamin D supplements should be prescribed in those with T-score values of less than −2.0 (Reid et al. 2008). Although there is good evidence to suggest that this approach will prevent bone loss, there is no evidence as yet that it will prevent fractures.

Bisphosphonates and Corticosteroid-Induced Osteoporosis

Bisphosphonates are widely used for the prevention and treatment of corticosteroid induced osteoporosis as discussed previously in this chapter. Randomised controlled trials have shown that alendronic acid (Saag et al. 1998; Adachi et al. 2001), risedronate (Wallach et al. 2000) and etidronate (Adachi et al. 1997) increase BMD and reduce the risk of vertebral fractures when compared with placebo. Zoledronic acid has been shown to be superior to risedronate at increasing BMD in corticosteroid induced osteoporosis, although no difference was seen in fracture occurrence (Reid et al. 2009). The trials of bisphosphonates in corticosteroid-induced osteoporosis have been much smaller than those in postmenopausal osteoporosis and have been designed with changes in BMD as the primary endpoint rather than fracture. Perhaps reflecting this fact, there is no evidence as yet to show that bisphosphonates reduce the risk of non-vertebral fractures in corticosteroid induced osteoporosis.

The indications for treatment in GIOP differ somewhat from postmenopausal osteoporosis. In clinical practice, prophylactic bisphosphonate therapy is usually initiated in patients who are expected to be on corticosteroids in a dose of 7.5 mg daily or more for more than 3 months where BMD T-score values are less than −1.5 at either the spine or hip (Eastell et al. 1998). Although bisphosphonates have positive effects in this situation, comparative studies with alendronic have shown that the bone anabolic agent teriparatide gives a better outcome in terms of BMD and vertebral fractures (Saag et al. 2009). This probably reflects the fact that corticosteroids cause bone loss principally by inhibiting bone formation rather than increasing bone resorption (van Staa 2006). Despite this, bisphosphonates remain the mainstay of prevention and treatment, principally because of the fact that the mode of administration is simpler and they have a much lower acquisition cost.

Conclusions

Bisphosphonates are among the most widely used medicines for the treatment of bone diseases. They share a common core structure but are functionally divided into two groups, based on the presence or absence of nitrogen containing side chains. Nitrogen containing bisphosphonates are highly potent inhibitors of bone resorption and are of clinical value in the treatment of many bone diseases associated with osteoclast activation including osteoporosis, Paget's disease and cancer-associated bone disease.

Bisphosphonates are generally well tolerated and serious adverse events are rare. Accordingly the overall risk-benefit risk profile for bisphosphonates in the treatment of postmenopausal women with osteoporosis is overwhelmingly favourable. Numerous randomised placebo controlled studies have shown that in patients with low BMD and/or pre-existing vertebral fractures, bisphosphonates reduce the risk of new vertebral fractures by about 50 %; of non vertebral fractures by 20–25 % and of hip fractures by 40 %.

For some patients, the requirement to take oral bisphosphonates on an empty stomach is a limiting factor as are upper gastro-intestinal side effects, but these problems can be circumvented by the use of intravenous bisphosphonates. The emergence of atypical subtrochanteric fractures as an adverse effect of bisphosphonates, emphasises the fact that treatment should be reserved for patients with low BMD who are at increased fracture risk where the benefits are considerable (Shane et al. 2014). However initiation of bisphosphonate therapy as a preventative measure in younger women with osteopenia who are at low risk of fracture now seems inadvisable and in this situation, HRT may prove to be a more favourable option, at least in terms of bone health.

Take Home Messages

- Bisphosphonates are small molecule inhibitors of bone resorption which are of clinical value in the treatment of many diseases associated with increased osteoclast activity
- Bisphosphonates preferentially target to bone and have a prolonged skeletal half life, exerting inhibitory effects on bone resorption for months or years after therapy is stopped.
- Oral bisphosphonates are poorly absorbed from the gastrointestinal tract and they need to be taken on an empty stomach to ensure adequate absorption.
- When administered to patients with osteoporosis, bisphosphonates reduce the risk of non-vertebral and hip fractures by 20–40 % and of vertebral fractures by 50–70 %.
- Upper gastro-intestinal upset is the most common adverse effect with oral bisphosphonates
- With intravenous bisphosphonates the most common adverse event is a transient flu-like illness which is self limiting.
- Other less frequent, but more serious adverse effects include adverse skeletal effects related to over-suppression of bone remodelling, resulting in osteonecrosis of the jaw and atypical subtrochanteric fractures in some patients.
- The benefit risk ratio of bisphosphonates is positive in the vast majority of patients.

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Chapter 13
Herbal and Complementary Medicines Used for Women's Health

Sheila M. Wicks and Gail B. Mahady

Introduction

Reports from the World Health Organization's Traditional Medicine Programme indicate that a large percentage of the global population rely on traditional medicines as a part of their normal healthcare (WHO 2013). Traditional medicines are usually culturally acceptable within their country of origin and are also used by many populations worldwide. Herbal medicines, which are the primary focus of traditional medicine systems, are often more accessible and affordable than Western medicines in many countries (WHO 2013). It is this accessibility and affordability of most herbal medicines (HMs) that makes their use very practical in light of increasing healthcare costs.

There are several different terms used in the field of traditional and herbal medicines and the definitions for these are presented in Table 13.1 below.

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Table 13.1 Definitions of terms used in this chapter

The Dietary Supplement Health and Education Act was enacted by Congress in 1994, defined **dietary supplements** as products intended to supplement the diet but not intended to treat, prevent, or cure any disease
Traditional Medicines are the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness
The terms "**complementary medicine**" or "**alternative medicine**" are used inter-changeably with traditional medicine in some countries. They refer to a broad set of health care practices that are not part of that country's own tradition and are not integrated into the dominant health care system
Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations
Herbs: crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered
Herbal materials: in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials
Herbal preparations: the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials
Finished herbal products: herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal

According to WHO TRM (2013)

Global Sales of Traditional and Herbal Medicines

The interest in traditional and herbal medicines has continued to increase over the past 10 years, as billions of people worldwide are using herbal medicines and other traditional complementary and alternative treatments such as acupuncture, massage therapy and traditional practitioners (healers), as part of their daily healthcare services. Recently, the Nigeria Natural Medicine Development Agency (Nigeria) has suggested that the global market for herbal medicines may be as high as $160 billion USD (Anon 2013). While the exact number is difficult to determine, it is known that the output for the Chinese Materia Medica (encompassing Chinese herbal medicines) alone was approximately $83 billion for 2012 (WHO 2013), so an estimate of over a $100 billion USD for the entire herbal market does not appear to be inflated.

Dietary Supplement Use in the United States

In 2012 dietary supplement sales reached an estimated $11.5 billion in the United States, and are predicted to hit $15.5 billion by 2017 (Schultz 2013a, b). Consumers over the age of 50, aging Baby Boomers and adolescents make up a large percentage of dietary and herbal supplement users (NIH 2007; Schultz 2013a, b). The most popular dietary supplements are those related to maintaining youth, joint health, probiotics, multiple vitamins, vitamin D, omega 3s/fish oils, calcium and vitamin C (Daniels 2013; Schultz 2013a, b). A "Consumer Survey on Dietary Supplements" published by the Council of Responsible Nutrition in 2013 in the U.S. has found that an estimated 68 % of Americans are now consuming dietary supplements, with 53 % considering themselves regular users, 12 % occasional users and 4 % seasonal users (CRN 2013; Daniels 2013). In terms of gender differences, women have always used more dietary supplements than men, so it comes as no surprise that this is still the case with 72 % women claiming to take dietary supplements over 64 % of men in 2013 (CRN 2013; Daniels 2013). In terms of age groups, 64 % of the 18–34 year olds reported dietary supplement use, which was similar to the 35–54 year olds (66 %). In 2013, dietary supplement use in the 55 year old and over group was an astonishing 74 % in the U.S. (CRN 2013; Daniels 2013).

Herbal Medicine Use in the United States

In the year 2000, only about 17 % of U.S. women took at least one herbal supplement (Yu et al. 2004). Logistical regression analyses showed that these women were non-Hispanic white, aged 35–64 years, well educated, not poor, current alcohol users, residents of the South and West, and those with functional limitations or chronic conditions were significantly more likely to use herbal supplements (Yu et al. 2004). By 2007, the percentage of the U.S. population that were using herbal supplements had increased to approximately 20 % (NIH 2007).

Factors associated with the use of herbal medicines included: ages 45–64 years old, being uninsured, being female, having a higher education, living in the West, using prescription medications or over-the-counter (OTC) medications, and self-identified as "non-Hispanic other" (Gardnier et al. 2007). Factors associated with no herb use included being non-Hispanic black and living in the South or Midwest. Seventy-two percent of those who used herbal medicines, also used prescription medications, and 84 % of those who used herbal medicines also used an OTC medication in the past 12 months. Among adults who used herbal medicines, the most commonly mentioned were Echinacea (41 %), ginseng (25 %), gingko (22 %), and garlic (20 %). The most frequent conditions for herbal use were head or chest cold (30 %), musculoskeletal conditions (16 %), and stomach or intestinal illness (11 %) (Gardnier et al. 2007).

In 2013, it was reported that almost 30 % of U.S. adults were using herbal medicines, and of the $11.5 billion spent on dietary supplements in the U.S., over half a billion dollars are spent on herbal medicines alone (Lynch and Blumenthal 2013).

Worldwide Use of Herbal Medicines

Interestingly, the global herbal supplements market is estimated at $160 billion with some of the most widely used herbal supplements being cranberry (*Vaccinium macrocarpon*), garlic (*Allium sativum*), saw palmetto (*Serenoa repens*), soy (*Glycine max*), ginkgo (*Ginkgo biloba*), milk thistle (*Silybum marianum*), black cohosh (*Actaea racemosa*), Echinacea (Echinacea species), St. John's wort (*Hypericum perforatum*), ginseng (*Panax ginseng*), valerian (*Valeriana officinalis*), green tea (*Camelia sinensis*), Evening primrose (*Oenothera biennis*), and bilberry (*Vaccinium myrtillus*) (Anon 2013; Lynch and Blumenthal 2013; Schultz 2013a, b).

However, there are literally thousands of herbal medicines used worldwide, as all countries have their own system of traditional medicine that includes indigenous forms of healing and plant species that are native to these countries. These traditional medicines are firmly rooted in their own culture and history. Some of these systems of traditional medicine include more formal structures such as Ayurveda, traditional Chinese medicine (TCM) and Unani medicine, and other CAM systems such as anthroposophy, chiropractic, homeopathy, naturopathy and osteopathy are also recognized. However, is important to remember that in many developing countries, the traditional medicine system may not be formalized (written or organized) and thousands of plant species may be used as medicines in these countries even though there is little in the way of research or even written records for these plants.

It is currently estimated that over 100 million Europeans currently use complementary and alternative medicines, with one fifth regularly using TRM/CAM and there are millions of TRM and CAM users in Africa, Australia, China and Japan (WHO 2013). However, when it comes to accurate estimates on how many women are using herbal medicines in these different countries, much of this information is generally not available or only available for specific conditions and disease states. For example, in Western countries many patients with multiple sclerosis resort to CAM use with a prevalence ranging from 41 % in Spain to 70 % in Canada and 82 % in Australia (WHO 2013). This is often due to the fact that Western medicine has no specific cure or sufficient treatment for MS. While in Africa and countries in Central America, such as Guatemala, it is estimated that the overall use of traditional medicines may be as high as 80 % of the population due to the general lack of access and affordability of Western medicines (WHO 2013). Thus, in the countries where the use of herbal medicines is high, approximately 80 % of women would be using herbal medicines to treat ALL illnesses, not just conditions that have no sufficient modern treatment. The problem with this situation is that most of the

herbal medicines used by women in developing countries have not been tested for safety or efficacy. Thus, there are literally millions of women using herbal therapies that have not ever been tested for their therapeutic effects or safety.

However, in cases where there is acceptable data, in the form of clinical trials, such as China and India, there is a great deal of interest in these specific traditional medicines that have sufficient scientific information concerning safety and efficacy. In fact, recently there has been an increase in TCM use in the U.S., and an influx of Chinese medicinal herbs, with sales up 10 % in 2012, to approximately $98 M USD (Lynch and Blumenthal 2013). Many of the Chinese traditional medicines are officially monographed in the Chinese Pharmacopoeia, and also have clinical trials supporting safety and efficacy.

Use of Herbal Medicines by Women

Since women make up the majority of consumers for dietary supplements in the U. S., it is also not surprising that they are the largest user of herbal medicines as well. What is clear from the data obtained from previous surveys is that the use of herbal medicines in the U.S. is *increasing not decreasing*. In 2000, approximately 16 % of the U.S. population used herbal medicines, and this number has increased to approximately 30 % in 2013. Women continue to be the primary users of dietary and herbal supplements in the U.S., although exact numbers are not available.

However, data suggest that women worldwide are increasingly using herbal medicines to treat or prevent a wide array of ailments including anxiety, depression, dysmenorrhea, pain during pregnancy and delivery, menopause, the common cold, and other non-life threatening medical conditions (Gardiner et al. 2007; Kim Sooi's Lean Keng 2013; Low Dog 2009; Mahady et al. 2003; NIH 2007). In the U.S., the reason for the increased use of herbal medicines include a desire to have personal control over their health (Low Dog 2009), as well as a personal lifestyle choices. Other reasons included dissatisfaction with conventional treatment and its disregard for a holistic approach, as well as concerns about the side effects of medications (Gardiner et al. 2007; Low Dog 2009; Mahady et al. 2003; NIH 2007). These concerns may explain, in part, the fact that many women are also using herbal remedies during pregnancy.

Use of Herbal Medicines During Pregnancy and Labour

A 2009 survey of 578 pregnant women in the eastern United States reported that 45 % of respondents had used herbal medicines (Low Dog 2009). In a 2014 study in Australia involving 1,835 women, most used pharmacologic (81.9 %) or non-pharmacologic (74.4 %) pain management therapies for labor and delivery (Steel et al. 2014). Many women (60.7 %) also used some form of CAM during pregnancy and delivery. More than two thirds of women (66.7 %) who used

non-pharmacologic interventions, also used a CAM during pregnancy. There was an apparent inverse effect on use of epidural analgesia for women who consumed herbal teas during pregnancy (Steel et al. 2014), suggesting some therapeutic efficacy.

In developing countries the use of herbal medicines during pregnancy and delivery is a normal part of healthcare. For example, in Malaysia a cross-sectional, descriptive study was performed in 460 Malay women admitted in the antenatal and postnatal ward to determine their use of herbal medicines during pregnancy (Kim et al. 2013). Of the women surveyed, 34.3 % used herbal medicines during pregnancy, and 73 % used herbal medicines during labor. Herbal medicines use by these women was unsupervised (81 %), with most women getting information from their family (60.7 %) and 77 % agreed upon its efficacy and safety, although their knowledge of the medicines was low (Kim et al. 2013).

Another study published in 2007, Rahman et al. (2007) studied the relationship between the use of herbal medicines during pregnancy and perinatal mortality in Tumpat District, Kelantan, Malaysia (Rahman et al. 2007). Of a total of 316 mothers (106 cases and 210 controls), the use of unidentified herbs prepared by traditional midwives and other types of herbal medicines during the first trimester of pregnancy was positively associated with perinatal mortality. The use of a few unidentified herbs and coconut oil during the third trimester of pregnancy were negatively associated with perinatal mortality. This study demonstrates that the use of some herbs early in pregnancy may be dangerous and the lack of safety data for many of the herbs being used by women worldwide may negatively impact maternal and fetal mortality rates worldwide.

It is impossible to prevent the use of these herbal medicines without proper safety and efficacy testing. There should be a global initiative to catalogue and review or test herbal medicines used by women worldwide, particularly in countries with high maternal and fetal death rates.

Commonly Used Herbal Supplements by Women Worldwide

As mentioned previously, there are literally thousands of herbal medicines used worldwide by women for a wide range of conditions and ailments. However, the WHO has determined that specific herbal medicines are commonly used worldwide, and published monographs of the plants in the "Monographs of Selected Medicinal Plants", Volumes 1–4 (WHO 1999a, b, c; WHO 2009a, b). Some of the main herbal medicines used by women are summarized in Fig. 13.1. In this section, we have outlined the issues of safety and efficacy for some of these most commonly used herbal medicines by women.

Herbal/Botanical	Use	Dose and dosage form	Adverse events Reported	References
Chasteberry *Vitex agnus-castus* L. Lamiaceae	Premenstural syndrome Cyclic mastagia	20 mg daily capsules/tablets	Rash, headaches, Fatigue. May interact with L-dopa	Mahady et al., 2010; WHO 2009
Black Cohosh *Cimicifuga racemosa* (L.) Nutt. Ranunculaceae	Menopausal symptoms Clinical evidence is equivocal	40-80 mg daily tablets, capsules, liquid	Muscular weakness Hepatitis case reports	Mahady et al., 2008; WHO 2002
Chamomile *Chamomilla recutita* (L.) Rauschert Asteraceae	Dyspepsia, epigastric bloating, Restlessness, insomnia, skin irritations. Poor clinical trials.	Varied depending on the product. Teas, liquid, capsules	Allergic reactions. Do not use if allergic to daisies, ragweed, Echinacea.	WHO 1999
Cranberry *Vaccinium macrocarpon* Ait. Ericaceae	Urinary track infection prevention and treatment, Clinical data now equivocal	Varied depending on the product. Capsules, liquid, juice	No congenital malformations reported. Not associated with an increased risk for stillbirth or neonatal death, low birth weight, small gestational age, preterm birth, low Apgar score (<7), neonatal infections or maternal vaginal bleeding in early pregnancy. May increase INR of warfarin	WHO 2009
Dang gui *Angelica sinensis* (Oliv.) Diels Apiaceae	Dysmennorhea, Infertility, menopausal symptoms. Clinical trails for menopause are conflicted.	Varies depending on the product. Crude drug, 4.5-9 mg per day. Fluidextract, teas, capsules	Do not use with anticoagulants.	Upton 2010; WHO 2002
Evening Primrose oil *Oenothera biennis* L. Onagraceae	Atopic eczema, diabetic neuropathy, mastalgia, premenstrual syndrome. Clinical trials data poor.	240-480 mg capsules	May precipitate symptoms of undiagnosed temporal lobe epilepsy, may interact with anticoagulants. May cause haedaches, nausea, loose stools or diarrhea.	WHO 2002
Green tea *Camellia sinensis* L. Theaceae	Effect for weight loss is controversial	Varied depending on product used	Due to the number of cases of associated adverse liver events, the therapeutic to safety ratio suggests that products with high ECGC concentrations should not be recommended to women for weight loss.	Manzzati et al., 2009; Sarma et al., 2008; Tsai et al., 2013
Ginger *Zingiber officinale* Roscoe Zingiberaceae	Prophylaxis of nausea and vomiting associated with motion sickness, seasickness and pregnancy.	0.5 to 4 gm dried root daily. Crude drug, extracts, capsules or liquid.	No teratogenic effects. May cause bleeding if used in combination with anticoagulants.	WHO 1999

Fig. 13.1 (continued)

Ginseng *Panax ginseng* C.A. Meyer Araliaceae	TCM use is for the treatment of chronic illnesses, and it is especially given during periods of convalescence, to restore the person to a normal state of good health. According to the World Health Organization's Monographs of Selected Medicinal Plants, *Panax ginseng* is used clinically as a tonic or immune stimulant for enhancement of mental and physical capacity during fatigue, chronic illness, and convalescence. May improve quality of life in menopausal women	1-2 gm of root 100-200 mg of a standardized extract	Panax ginseng has no apparent estrogenic effects. Panax ginseng has a good safety profile, but may interact with specific drugs such as warfarin, and phenelzine	Mahady et al. 2001; WHO 1999
Red clover *Trifolium pretense* L. Fabaceae	Menopausal symptoms (Vasomotor, headaches, anxiety, depression). Clinical studies are conflicted.	Varied depending on product used.	Potential estrogenic effects, do not use with hormone-related disorders or estrogen-dependent cancers. Contraindicated in pregnancy, breast feeding and children	WHO 2009
Valerian *Valeriana officinalis* L. Valerianaceae	Nervous anxiety and insomnia. Clinical trials for insomnia are inconclusive.	Varied depending on product. Teas, capsules, tablets, liquid	Should not be used during pregnancy or breastfeeding. May cause headaches, or excitability. In large doses may cause arrhythmias in certain women.	WHO 1999

Fig. 13.1 Commonly used herbal supplements, uses, and adverse events, for women's reproductive health issues

Black Cohosh (*Actaea racemosa* L., Ranunculaceae)

The Efficacy of Black Cohosh for Menopausal Symptoms

Dietary supplements and herbal medicinal products containing Black cohosh are among the most commonly used products by women worldwide for the management of menopausal symptoms (Leach and Moore 2012; Low Dog 2005; Mahady et al. 2006). Data from numerous clinical trials suggest that black cohosh may be a useful alternative approach for the management of menopausal symptoms such as hot flashes, and night sweats, although the clinical trial data have been inconsistent to date (Leach and Moore 2012; Low Dog 2005; Mahady et al. 2006). The most recent Cochrane systematic review has suggested that currently there is insufficient clinical evidence to support the use of black cohosh for the treatment of menopausal vasomotor symptoms (Leach and Moore 2012).

Interestingly, a recently published re-analysis of all appropriate placebo-controlled clinical studies suggests that there is a standardized mean difference of 0.385 ($p < 0.0001$) in favor of black cohosh for the management of menopausal symptoms (Beer et al. 2013). This makes the point that there may be adequate justification for conducting further large-scale clinical studies to investigate the

efficacy of black cohosh for menopausal symptoms. However, any new clinical trial must have significantly improved methodologies, including larger numbers of participants, and detailed descriptions of the study products, placebos and protocols, particularly with regards to allocation concealment and the handling of incomplete outcome data (Leach and Moore 2012). The impact of black cohosh treatments on health-related quality of life, sexual health, bone health, night sweats and cost-effectiveness should also been included in any new study (Leach and Moore 2012).

Safety Issues Associated with Black Cohosh

In 2006–2008, the regulatory agencies in Australia, Canada, and the European Union released statements regarding the "potential association" between black cohosh containing products and hepatotoxicity (Mahady et al. 2008). Thirty-six cases of black cohosh associated hepatotoxicity were also reviewed by the United States Pharmacopoeia (USP) and based on this safety review, as well as the need to guard public safety, it was determined that all U.S. black cohosh products should be labeled to include a cautionary statement for potential hepatotoxicity (Mahady et al. 2008).

Proving direct causality for black cohosh products and hepatotoxicity is very difficult, as has been pointed out by various groups and the results of such reviews depend on the method and scale used to determine causality (ATGA 2006; Beer et al. 2012; EMEA 2009; HMPC 2007; Mahady et al. 2008; MHRA 2006; NHPD 2007; Teschke 2010, 2011). Using a more general scale such as the Naranjo scale the USP review indicated that causality is possible (Naranjo et al. 1981; Mahady et al. 2008). However, when using a more liver specific scale such as the Council for International Organizations of Medical Sciences (CIOMS, also known as the Roussel Uclaf Causality Assessment Method-RUCAM) scale with modifications to review the case reports, causality is unlikely or excluded (Teschke et al. 2009, 2011). However, the CIOMS scale used in this study was modified by Teschke et al. (2009), but they did not provide evidence of validation. The European Medicines Agency (EMEA) concluded that changes made by Teschke of the established CIOMS scale were not validated, and thus the procedures recommended by Teschke and coworkers for the assessment of black cohosh hepatotoxicity were not feasible because nearly all cases would be rated "not assessable" according the proposed modifications (EMEA 2009). Teschke's conclusions differed with those of the EMEA, that also analyzed reports of liver damage from black cohosh–containing products using a validated CIOMS scale. Similarly, the conclusions of "unlikely or excluded" causality were not supported by evaluations from several other organizations, although they used different causality analysis approaches (Mahady et al. 2012).

It should be noted that analyses of herbal medicines by regulatory bodies and government agencies have different objectives than private individuals or

companies. Regulatory agencies regularly review safety and efficacy for herbal medicines both in Europe and the U.S. in order to identify possible safety signals. Currently, in the U.S. black cohosh is regulated as a dietary supplement under the Dietary Supplements Health and Education Act 1994. In Europe, black cohosh is regulated as a herbal medicinal product and there are stricter guidelines for these products. Furthermore, while the USP provides quality monographs for dietary supplements such as black cohosh, these standards are voluntary only and unlike Europe, there is no mandatory monograph system for companies to follow to manufacture these products. As a consequence, many dietary supplements such as black cohosh, are consumed by women with little guidance from healthcare professionals and there is usually no patient information leaflet provided with such products. This is problematic considering that many women in the U.S. consume herbal medicines concomitantly with prescription drugs, over-the-counter medications, and also with alcohol and drugs of abuse (Mahady et al. 2003).

The global number of adverse drug reaction (ADR) reports concerning liver damage associated with black cohosh was 82 in 2009 (Mahady et al. 2009). However, this number has since increased from reports worldwide (Guzman et al. 2009; Lim et al. 2013; Pierard et al. 2009; Zimmerman et al. 2010). While a direct causal role for black cohosh has not been established, the U.S. Pharmacopeia (the standards-setting organization for foods and drugs) put this explanation in many body of text and advises that black cohosh products be labeled with the following cautionary statement: "Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice" (Mahady et al. 2008).

Since none of the clinical trials that performed liver tests when investigating the efficacy of black cohosh showed any signs of liver problems (Leach and Moore 2012; reviewed in Beer et al. 2013), it has been suggested that adulteration of black cohosh products may have occurred, and in fact this has been shown for some products (Jordan et al. 2010). Adulteration or substitution of black cohosh with ingredients of similar binomial name or similar common name (for example, blue cohosh, *Caulophyllum thalictroides*) may have occurred and is cause for concern. The recent introduction of cGMP in the U.S. will hopefully reduce the risk of adulterated products being on the market in the U.S.

The U.S. National Toxicology Program (NTP) assessed the toxicity of several commercially available black cohosh extracts (BCE) in rodents (Mercado-Feliciano et al. 2012). Female B6C3F1/N mice and Wistar Han rats were treated with increasing doses of black cohosh extracts up to 1,000 mg/kg/day BCE by gavage for 90 days starting at weaning. Administration of black cohosh extracts caused a dose-dependent non-regenerative macrocytic anemia and increased frequencies of peripheral micronucleated red blood cells (RBC) in both species. Mice showed decreased RBC counts at all doses and increased micronucleated RBC at doses above 125 mg/kg. Dose-dependent thymus and liver toxicity was observed only in rats. Uterotrophic assays conducted in mice found no estrogenic or anti-estrogenic effects after 3 days of treatment (Mercado-Feliciano et al. 2012). This was the first report of sub-chronic toxicity studies and liver toxicity in rodents due to the

ingestion of black cohosh. The lowest administered dose to have an effect was 62.5 mg/kg/day, which is 125 times the currently recommended amount for daily human consumption (~0.5 mg/kg/day for a 70 kg human) (Mercado-Feliciano et al. 2012). While it is difficult to extrapolate these results from rodent studies to humans, it none-the less points to a need for at least a cautionary label to protect and inform consumers.

Cranberry (*Vaccinium macrocarpon* L.)

Efficacy of Cranberry for Urinary Tract Infections

Cranberry, the fresh or dried ripe fruit of *Vaccinium macrocarpon* Ait., Ericaceae, is currently used as a herbal adjunct therapy for the prevention and symptomatic treatment of urinary tract infections (Mahady et al. 2001a). Data from clinical trials indicates that extracts of cranberry or cranberry juice may reduce the bacterial load of *E. coli* and also suppress the inflammatory symptoms caused by the bacteria (Huang et al. 2009). Cranberry is one of the most commonly used herbal medicines by women in the U.S., and approximately $65 M USD was spent on cranberry containing products in 2012 (Lynch and Blumenthal 2013). While cranberry juice and products are used in complementary and alternative medicine for the management of urinary tract infections and during pregnancy, clinical trials supporting its use are conflicted (Jepson and Craig 2008; Jepson et al. 2013).

In the most recently published systematic review of clinical trials, the study concluded that prior to 2012, there was some evidence that cranberry juice decreased the number of symptomatic UTIs over a 12-month period, particularly for women with recurrent UTIs (Jepson and Craig 2008; Jepson et al. 2012). However, with the addition of 14 new clinical trials published from 2008 to 2012, (total of 4,473 participants) the review now indicates that cranberry juice may not be as effective as previously shown (Jepson et al. 2013). The authors of the systematic review further suggest that the lack of efficacy of cranberry on UTIs in clinical trials may be due to lack of participant adherence, lack of sufficient active ingredient in the cranberry product, or lack of sufficient statistical power (Jepson et al. 2013).

Safety of Cranberry Supplementation During Pregnancy

In terms of safety during pregnancy, one recent study performed in Norway found that of 68,522 women in the study, 919 (1.3 %) women had used various cranberry products during pregnancy (Heitmann et al. 2013). Information on pregnancy outcomes was retrieved from the Medical Birth Registry of Norway. The results of the

study showed that of the women who used any cranberry when pregnancy, had no statistically significant increased risk to the fetus of congenital malformations. Cranberry was also not associated with increased risk for stillbirth/neonatal death, low birth weight, small gestational age, preterm birth, low Apgar score (<7), neonatal infections or maternal vaginal bleeding in early pregnancy (Heitmann et al. 2013). However, there was an association between cranberry use late in pregnancy and vaginal bleeding after week 17 of pregnancy (9.7 % vs. 5.8 %, $p < 0.001$). Sub-analyses of more severe bleeding outcomes did not support a significant risk (Heitmann et al. 2013).

Drug Interactions and Adverse Events Associated with Cranberry

In terms of drug interactions, since 2003 there have been published reports of an interaction of cranberry juice with warfarin resulting in increased International Normalized Ratios (INRs) and bleeding (Grant 2004; Isele 2004; Rindone and Murphy 2006; Suvarna et al. 2003). Since then there have been many published reports from different countries and speculation as to the potential interaction and its possible mechanism (Aston et al. 2006; Griffiths et al. 2008; Haber et al. 2012; Hamann et al. 2011; Niklasson and Andrén 2006; Rindone and Murphy 2006; Srinivas 2013). The adverse reactions caused by this interaction range from minor bleeding to fatal haemopericardium and gastrointestinal hemorrhage (Griffiths et al. 2008). Thus, it is prudent that women taking anti-coagulant drugs such as Coumadin should be very cautious when using cranberry products, and consult with their healthcare provider before they use cranberry to treat or prevent a UTI.

Dang Gui (Dong Quai)

Traditional Use of Dang Gui

Dang gui (*Angelica sinensis* [Oliv.] Diels Apiaceae), also known as Chinese angelica or female ginseng, has been used for thousands of years in traditional Chinese medicine (TCM) to treat a variety of women's reproductive disorders and is available in the U.S. as a dietary supplement (Upton 2010). While dang gui has traditionally been used primarily for gynecological conditions such as irregular menstruation, amenorrhoea and dysmenorrhoea, more recent research has focused on its cardiovascular, hematopoietic, hepatoprotective, antioxidant, antispasmodic, and immunomodulatory properties (Upton 2010). Results from a very limited number of clinical trials also suggest that dang gui may have cardioprotective and

hypotensive effects useful for the treatment of stroke and chronic obstructive pulmonary disease with pulmonary hypertension (Upton 2010; Wu et al. 2012).

In terms of traditional gynecological use, dang gui is used to treat uterine fibroids, endometriosis, amenorrhea, dysmenorrhea, and certain forms of infertility, as it has anti-inflammatory effects (Fu et al. 1998; Upton 2010). Results from a published survey from Taiwan showed that 53.4 % of 12,349 women with primary dysmenorrhea used TCM and 92.2 % of them sought TCM with the intention of treating their menstruation-related pain symptoms (Pan et al. 2014). In this Taiwanese study, of a total of 213,249 TCM visits for women with primary dysmenorrhea, more than 99 % were treated with Chinese herbal products. Dang-gui-shao-yao-san a combination Chinese herbal medicines containing dang gui was the most frequently prescribed formula for menstruation associated pain (Pan et al. 2014).

Clinical Efficacy of Dang Gui

Despite the extensive traditional use of dang gui, there are few randomized controlled clinical trials substantiating the efficacy. Two uncontrolled trials (no placebo control group) found that dang gui, both alone and in combination with other traditional Chinese medicinal herbs, was effective in the treatment of dysmenorrhea (Gao et al. 1988). In another uncontrolled study, infertility due to tubal occlusion was treated with a 9-month treatment using a uterine irrigation containing dang gui extract (Fu et al. 1998). The results of the study suggested that 79 % of the women regained tubal patency and 53 % became pregnant (Fu et al. 1998). However all of these clinical trials were uncontrolled and the methodology was poor based on current modern standards.

Three additional clinical trials have assessed the effects of dang gui on menopausal symptoms (Haines et al. 2008; Hirata et al. 1997; Wang et al. 2013). A randomized placebo-controlled trial involving 71 postmenopausal women concluded that 4.5 g of dang gui root daily in capsule form for 24 weeks had no effect on vasomotor menopausal symptoms such as hot flushes (Hirata et al. 1997). No differences were observed between groups in terms of serum hormone levels, vaginal cytology, hot flashes, or Kupperman Index scores (Hirata et al. 1997). As with most Chinese botanicals, dang gui is most often used in multi-ingredient formulas rather than as a single agent. However, a second 6-month randomized, double-blind, placebo-controlled study of the effect of Dang Gui Buxue Tang (DGBT); a 1:5 combination of Dang Gui (*Angelica sinensis*) and Huang Qi (*Astragalus membranaceus*) on acute menopausal symptoms in 103 women failed to show any effect of the combination product over placebo (Haines et al. 2008). However, the most recent study on the same combination reported more positive effects (Wang et al. 2013). These researchers performed a randomized, double-blind, multiple-dose escalation trial involving 60 postmenopausal women experiencing severe hot flushes and night sweats. Women were randomized to ingest 1.5, 3.0, or 6.0 g/day of dang gui root for 12 weeks. Both women receiving

3 and 6 g/day showed a dose-dependent reduction in hot flushes over time. The DGBT formula at a dose of 6.0 g/day (higher dose than used in previous studies) significantly improved physical and psychological scores and significantly reduced vasomotor symptoms from baseline as measured by the Greene Climacteric Scale (GCS) score. The treatment was well tolerated, with no serious adverse events noted during the 12-week intervention period. No effects on hormones and lipid profiles were observed (Wang et al. 2013).

Safety of Dang Gui

In terms of safety, few adverse events have been reported in the published clinical studies. One review article assessing 200 reports on dang gui pharmacology concluded that dang gui had no major side effects (Mei et al. 1991). In one published case report, a female patient developed occupational asthma and rhinitis (Lee et al. 2001). The patient had a positive response to skin prick tests using an extract of dang gui and had an early asthmatic response to dang gui in a broncho-provocation test. Dang gui caused a greater histamine release from basophils in the patient compared to a healthy control (Lee et al. 2001).

Anticoagulant Effects of Dang Gui

In a recent review of Chinese medicinal herbs, the primary the mechanism of interaction of dang gui with other medicines was found to be attributable to its pharmacodynamic interactions, particularly when used with anticoagulant or antiplatelet drugs, where it induces additive effects (Tsai et al. 2013). Dang gui is one of the most commonly used Chinese herbs and has blood-activating or stasis-resolving effects and is widely used for the treatment of cardiovascular or cerebro-vascular diseases (Tsai et al. 2013). Limited clinical evidence supports the effects of these Chinese herbs on stroke or coronary diseases and further large scale, rigorous clinical trials are needed to confirm the benefit and safety risks. Women interested in using Chinese herbs such as dang gui for reducing cardiovascular risk factors need to disclose their concurrent use of conventional medications, particularly those patients who are taking anticoagulant or antiplatelet drugs (Tsai et al. 2013). Dang gui contains several coumarin derivatives and should be used with caution in women on anti-coagulants because of the increased risk of bleeding.

Green Tea

Use of Green Tea by Menopausal Women

In 2003, we published a survey of women between the ages of 40 and 60 years at the University of Illinois at Chicago (UIC) clinics, to determine their use of botanical dietary supplements (Mahady et al. 2003). Of the 500 women interviewed, 79 % ($n = 395$) used herbal supplements, of which 36.5 % used herbal supplements daily. Commonly used botanicals included soy (42 %), green tea (34.68 %), chamomile (20.76 %), gingko (20.51 %), ginseng (17.97 %), Echinacea (15.44 %), and St. John's wort (7.34 %) in the form of teas, capsules, tablets, and liquids (Mahady et al. 2003). Interestingly, with the exception of chamomile, all of the herbal supplements in the top five products in our study in 2003, are still in the top-ten list of best selling herbal supplements in the U.S. in 2013, including green tea (Sarma et al. 2008; CRN 2013).

Tea (*Camellia sinensis* (L.) Kuntze; Theaceae) is one of the most widely consumed beverages worldwide, second only to water (Anon 2000). Fermented black, semi-fermented oolong, and green tea are all produced from its leaves. Green tea is made from steaming the fresh leaves at high temperatures, thus inactivating the oxidizing enzymes and leaving the polyphenol content intact, which make up 30–40 % of the extractable solids of dried green tea leaves (Anon 2000; Brown 1999). The primary catechins in green tea include epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCG), with EGCG being the most abundant. In the United States, green tea products rank in the top ten selling dietary supplements (Sarma et al. 2008).

Green Tea Research

Over the past 30 years, research has focused on the medicinal aspects of tea polyphenols, with demonstrated antioxidant, anticarcinogenic, anti-inflammatory, thermogenic, probiotic, and antimicrobial properties in numerous human, animal, and in vitro studies. Green tea extracts and supplements are commonly used by women worldwide to prevent breast cancer, reduce weight and improve digestion. Some clinical and epidemiological studies show an inverse relationship between green tea consumption and cancer risk, supporting a possible chemopreventive effect of green tea (Brown 1999). Thus, green tea is perceived by many women as having multiple health benefits, however when asked to articulate these benefits, most women in our survey were unable to do so (Mahady et al. 2003).

Green Tea as a Weight Loss Agent

Over the past 10 years there has been an increase in the number of studies investigating the usefulness of green tea as a natural weight loss supplement, a subject that is of great interest to many women (Thavanesan 2011). It is widely believed that the polyphenolic constituents of tea increase thermogenesis or reduce fat absorption, thereby having an anti-obesity effect. However, the published clinical data are inconsistent, with some studies showing no effect on weight loss and other studies showing minor to moderate effects (Thavanesan 2011). Evaluation of the available clinical data supporting the role of green tea in weight loss is conflicted, however considering that there are some positive results from a few studies, larger scale clinical trials using a well define product are warranted (Thavanesan 2011).

Hepatotoxicity Associated with the Ingestion of Green Tea

In a situation very reminiscent of the black cohosh story, six of the clinical trials conducted using various green tea preparations reported no difference in adverse reactions compared with placebo during these investigations (Sarma et al. 2008). However, in 2003 both the French and Spanish regulatory authorities suspended marketing authorization of Exolise, a weight-loss product containing a hydro-alcoholic extract of green tea (standardized to 25 % catechins) (reviewed in Sarma et al. 2008). In these countries, the product was associated with elevated liver enzymes in 13 female subjects, 9 cases reported in France, and 4 cases reported in Spain (Sarma et al. 2008). Of the 13 affected women, hepatoxicity appeared after approximately 50 days of use of Exolise, and the problem resolved in 12 of the subjects following discontinuation of the product. Unfortunately, one woman who had concomitant alcohol and other drug use finally progressed to complete liver failure (Sarma et al. 2008).

In 2008, the USP Expert Committee on Dietary Supplements analyzed case reports pertaining to green tea and liver damage using the Naranjo causality algorithm scale (Naranjo et al. 1981), along with historical use, regulatory status, and current extent of use of green tea products (Sarma et al. 2008). A total of 216 adverse event reports for green tea products were analyzed, including 34 reports concerning liver toxicity (Sarma et al. 2008). Of the 34 cases of potential liver toxicity, 27 were categorized as *possible* causality and 7 as *probable* causality (Sarma et al. 2008). Further analysis of clinical pharmacokinetic and animal toxicological data suggested that the ingestion of concentrated green tea extracts on an empty stomach may lead to more adverse effects than taking the products with food. Since Exolise was a weight-loss product, it seemed likely that the affected women were taking the product on an empty stomach in attempts to lose weight.

In 2009, another extensive review of the case reports was published, which included two new previously unpublished reports (Mazzanti et al. 2009). These authors reviewed a total of 34 cases of hepatotoxicity associated with green tea ingestion. For some cases, histological evaluation of the liver showed inflammatory reactions, cholestasis, occasional steatosis, and necrosis. Fortunately, in most cases ($n = 29$), de-challenge (withdrawal of the medicine/product) resulted in complete recovery, but one death was reported. Positive re-challenge (reoccurrence of hepatotoxicity on re-administration of the product) was reported in seven cases (20 %) which strongly supports a casual association. In the two new cases, the causality assessment was judged as "possible" according to the RUCAM score (Mazzanti et al. 2009).

After the withdrawal of Exolise (the product with the most reported cases of liver toxicity) from the market in Europe, other green tea-based herbal supplements were marketed, and as a consequence, the reports of hepatotoxicity from green tea are still increasing. Since most of the cases of green tea associated hepatotoxicity involve women (particularly since these products are used for weight control), host genetic factors and gender may play a role in these cases (Jimenez-Saenz and Martinez-Sanchez 2007). To this end, it has been reported that Epigallocatechin gallate (EGCG)-mediated liver toxicity is more predominant in female than male mice (Goodin et al. 2006). Mazzanti et al. (2009) concluded that the suspected liver toxicity due to the ingestion of green tea extracts was likely due to the presence of the catechins, particularly to EGCG. Although the bioavailability of the tea catechins is low after oral administration, under fasting conditions, and repeated administration, the catechin plasma levels can build up and may reach toxic levels (Mazzani et al. 2009).

Hepatotoxicity of green tea extract may be due to the ability of EGCG or its metabolites to induce oxidative stress in the liver. Since many of the cases involved women, the reaction may be gender specific, however an idiosyncratic or an immune-allergic mechanism cannot be excluded (Mazzanti et al. 2009). While green tea products have been used for their health benefits, their efficacy has not been conclusively established, and in the light of associated adverse liver events, the therapeutic to safety ratio suggests that products with high ECGC concentrations should not be recommended to women for weight loss.

Impact of Green Tea on Sex Hormone Levels

On an interesting note, there is limited evidence suggesting that green tea may reduce the levels of circulating sex-steroid hormones, whereas black tea may actually increase hormone levels (Wu et al. 2012). One investigation of the relationship between tea intake and plasma estrogen and androstenedione levels was performed in 130 healthy post-menopausal Chinese women in Singapore (Wu et al. 2012). Of the 130 women, 84 were non- or irregular (less than once a week) tea drinkers, 27 were regular (weekly/daily) green tea drinkers and 19 were

regular (weekly/daily) black tea drinkers. Analysis of plasma estrone levels in non- or irregular tea drinkers showed estrone at 29.5 pg/ml, which were 13 % lower in regular green tea drinkers (25.8 pg/ml) and 19 % higher in regular black tea drinkers (35.0 pg/ml). Although this was small study, these differences in estrone levels were statistically significant ($P < 0.03$) even after adjusting for age, body mass index, intake of soy, and other covariates. A similar pattern of differences between tea intake, and plasma levels of estradiol and androstenedione were found, but these were not statistically significant (Wu et al. 2012). These results preliminarily suggest that green tea may have chemopreventative effects for estrogen-dependent cancers by reducing circulating hormone levels over a lifetime.

Ginseng (*Panax ginseng*)

Ginseng History and Traditional Use

Some of the most popular and well-known herbal medicines used by menopausal women are known generically as "ginseng" (Mahady et al. 2001b; WHO 1999). The ginsengs are not similar taxonomically, and there are over 30 different species of plants commonly referred to as "ginseng" (Awang 2003; Mahady et al. 2001b). The common name "ginseng" is derived from the Chinese word "jen-shen", which translated means "man-root" as the shape of the roots can resemble the human body (Awang 2003; Hu 1976). *Panax ginseng* is a traditional Chinese medicine (TCM) and has been used for thousands of years in Southeast Asia as a tonic to promote longevity (Shibata et al. 1985). The oldest Chinese Pharmacopoeia, *Shen-Nung Pen Tsao Ching*, described the use of ginseng for the "repairing of the five viscera, quieting the spirit, curbing the emotion, stopping agitation, removing noxious influence, brightening the eyes, enlightening the mind and increasing wisdom" (Shibata et al. 1985). Ginseng is used in prescriptions as a drug to restore Yang or to recover balanced homeostasis.

The traditional Chinese medical use of *Panax ginseng* is for the treatment of older patients with chronic illnesses, and it is especially given during periods of convalescence, to restore the person to a normal state of good health (Hu 1976; Mahady et al. 2001b). In the World Health Organization's Monographs of Selected Medicinal Plants, *Panax ginseng* is used clinically as a tonic or immune stimulant for enhancement of mental and physical capacity during fatigue, chronic illness, and convalescence (WHO 1999; Mahady et al. 2001b).

Panax ginseng*'s Effect on Cancer-Specific Mortality in Women*

A 2009 study investigated the association between *Panax ginseng* intake and mortality among Korean elderly subjects, both male and female (Yi et al. 2009). The study involved a total of 6,282 subjects, over 55 years of age that were followed over 18.8 years in this progressive cohort study. The Cox proportional hazard regression model was used to evaluate effects of ginseng intake on overall mortality. After adjusting for age, education, occupation, drinking, smoking, self-reported chronic disease, body mass index, and blood pressure, the all-cause mortality for male ginseng users was significantly lower than that for male nonusers, but unfortunately a similar association was not observed in women (Yi et al. 2009). However, cancer-specific mortality was lower in female ginseng users than female nonusers after adjustment of relevant covariates. The cancer-specific mortality was not associated with ginseng intake in male subjects. Mortality caused by cardiovascular diseases was not related to ginseng intake in either men or women (Yi et al. 2009). To date no further studies have either confirmed or refuted this report.

Panax ginseng*'s Effect on Fatigue*

In a 2013 published study, the anti-fatigue effects of *P. ginseng* were investigated in a double-blind, randomized, placebo controlled study involving 90 subjects (21 men and 69 women) with idiopathic chronic fatigue (ICF; Kim et al. 2013). A 20 % ethanol extract of *P. ginseng* (oral dose of 1 g or 2 g day) or a placebo was administered to each group for 4 weeks, and then fatigue severity was monitored using a self-rating numeric scale (NRS) and a visual analogue scale (VAS) as the primary endpoints. After 4-weeks of treatment, *P. ginseng* decreased the total NRS score, but this was not statistically significant as compared with placebo ($p > 0.05$). Mental NRS score was significantly improved by *P. ginseng* administration for 1 g and 2 g, as compared with placebo ($p < 0.01$). However, only 2 g *P. ginseng* significantly ($p < 0.01$) reduced the VAS score as compared with placebo (Kim et al. 2013).

Panax ginseng*'s Effect on Quality of Life for Post-menopausal Women*

One randomized, multicenter, double-blind, parallel group study assessed the effects of a standardized ginseng extract compared with those of a placebo on quality of life (QoL) and on physiological parameters in 384 symptomatic post-menopausal women (Wiklund et al. 1999). Validated questionnaires [Psychological

General Well-Being (PGWB) index, Women's Health Questionnaire (WHQ)] and Visual Analogue (VA) scales were used as outcome measures. To assess the safety of the ginseng extract, physiological parameters such as follicle-stimulating hormone (FSH) and estradiol levels, endometrial thickness, maturity index and vaginal pH were measured at the same time points. The results on the PGWB index showed that the extract showed only a tendency for a slightly better overall symptomatic relief, but this was not statistically significant. Further analysis of PGWB subsets showed a statistically significant difference for depression, well-being and health subscales in favor of ginseng compared with placebo. The results of this study suggest that the effects of ginseng were not mediated through estrogenic like effects such as changes in FSH and estradiol levels, endometrial thickness, maturity index and vaginal pH (Wiklund et al. 1999).

Panax ginseng *is not Estrogenic*

In a double blind, placebo controlled clinical trial (60 females and 60 males), administration of 200 mg of a standardized ginseng extract per day for 12 weeks did not have any significant effect on sex hormone blood levels (luteinizing hormone, follicle stimulating hormone, testosterone, estradiol) in comparison with the placebo groups (Forgo et al. 1981). Furthermore, one clinical trial involving 49 menopausal women (33 of whom had a hysterectomy) regular speculum examinations and cytological smears from the cervix and the vaginal wall did not show any changes during 3 months of oral treatment with 20 standardized ginseng extract per day (Reinhold 1990).

The Safety of Panax ginseng

With few exceptions, *Panax ginseng* appears to be safe when administered within recommended therapeutic doses (WHO 1999a). However, according to WHO, *Panax ginseng* may reduce the blood concentrations of alcohol and warfarin (WHO 1999a). It has also been reported to induce mania when used concomitantly with phenelzine (WHO 1999a), and interestingly may increase the efficacy of the influenza vaccination (WHO 1999a). While co-administration of ginseng with warfarin did not appear to alter the International Normalized Ratio (INR) or platelet aggregation in one clinical trial, another study noted alterations (Yuan et al. 2004), therefore co-administration of warfarin with ginseng or any herbal medication is not recommended.

Information Resources for Herbal Medicines and Dietary Supplements

There are literally thousands of resources for finding information for herbal medicines and dietary supplements. In 1995 the WHO started a monograph series on commonly used medicinal plants worldwide. This work is published in a series of books entitled the "WHO Monographs on Selected Medicinal Plants" Volumes 1–4. These books cover global information on the most widely used herbal medicines from different countries. In addition to this global resource, the ESCOP has a continually updated series of monographs. ESCOP was founded in June 1989 as an umbrella organization representing national herbal medicine or phytotherapy associations across Europe. Their monographs are state-of-the – art reviews by leading herbal medicine experts and go through extensive scientific reviews. In the United States there are numerous websites for free information for herbs including the National Institutes of Health's websites:

1. http://nccam.nih.gov/health/atoz.htm Providing short summaries of a variety of CAM topics and herbal medicines.
2. http://www.nlm.nih.gov/medlineplus/druginformation.html, providing information via Medlineplus for Drugs & Supplements Information.

There are also subscription services such as:

1. http://www.naturalstandard.com
   This is the Natural Standard Database, providing information on herbal standards, safety and efficacy.
2. http://www.naturaldatabase.com, which is the Natural Medicines Comprehensive Database, a comprehensive resources for all information on natural medicines.

In addition, the United States Pharmacopoeia ANON (2009), the European Pharmacopoeia, the British Herbal Pharmacopoeia, the African Pharmacopoeia, the Chinese Pharmacopoeia and many other global pharmacopoeias, most having information on the official herbal medicines of each country. These are all adequate resources for finding information on the quality, safety and efficacy of commonly used herbal medicines.

Discussion

Globally, herbal products are regulated differently in almost every country in the world with perhaps the exception of the European Union which is trying to harmonize the regulatory aspects of herbal medicine products before they are approved for the EU market. The EU has an official monograph system for most

herbal medicines that is constantly in the process of review for quality, safety and efficacy to protect public health. Canada has a similar system.

In the United States herbal medicines are regulated as dietary supplements under the Dietary Supplements Health and Education Act of 1994 (Mahady et al. 2001; Jordan et al. 2010). While there are cGMP's in place in the U.S., dietary supplements are not monitored for safety or efficacy by the FDA. Under the U.S. system, herbal medicines are not to be used as drugs for the diagnosis, treatment or cure of any disease, only to supplement the diet. However, women in the U.S. continue to use these products exactly to treat common disorders such as PMS, menopause, common cold, fatigue, etc. For some of these herbal medicines there is sufficient clinical data for safety and efficacy, however for many herbal drugs being used by women worldwide there is little in the way of information on quality, safety or efficacy.

This is particularly a problem in developing countries where herbal medicines are used commonly by women to treat all disease conditions, due to a lack of access of other types of healthcare. WHO estimates that the use of herbal medicines as part of the primary healthcare in parts of Africa and Guatemala may be as high as 80 %. However as was pointed out earlier in this chapter, the use of herbal medicines by American women is currently 30 % and increasing.

There are many products on the market in the U.S. that have no associated safety and efficacy studies, particularly the combination products. These products are directly marketed to women as treatments for menopausal symptoms, sleep, bone health, enhancing memory and reducing fatigue, etc. In developing countries the situation is much worse for women due to a lack of adequate health care and a lack of scientific information on the herbal medicines that make up their everyday healthcare (Locklear et al. 2013). The WHO and other international groups are not sufficiently funded to facilitate the review of all herbal medicines, and thus this kind of initiative needs to come from the governments of these countries perhaps working in concert with WHO or other regulatory agencies.

Conclusions

Data suggests that the global herbal medicines market continues to increase, with estimates of sales as high as $160 B USD. In the United States, the most recent surveys suggest that almost 30 % of U.S. adults use herbal medicines, and of the $11.5 billion spent on dietary supplements in the U.S., over half a billion dollars are spent on herbal medicines alone. Women continue to be the primary users of herbal supplements in the U.S. (10–80 % depending on age) and are increasingly using these products to treat or prevent a wide array of ailments including symptoms of menopause, the common cold, depression, and other non-life threatening medical conditions.

In terms of herbal medicines used by women, black cohosh, cranberry, dang gui, green tea, and ginseng are the most common in the U.S. Women use these products

to treat a wide range of conditions including symptoms of menopause, premenstrual syndrome and urinary track infections. While the clinical data for efficacy are equivocal for most of these herbal medicines, there are contraindications, drug interactions and some serious adverse events associated with the use of these products. Where no clinical efficacy has been proven and serious adverse events have been reported, the safety risk in negative (no benefit and potential safety risk) and thus such products should not be recommended.

Take Home Messages

- The global use of herbal medicines and dietary supplements continues to increase with annual sales of herbs estimated at $160 B USD.
- The use of herbal supplements by the U.S. population has risen from ~15 % in 2000 to 30 % in 2013, and is expected to continue to increase over the next 5–10 years.
- Women are the largest users of herbal medicines in the U.S., and use them to treat or prevent a wide array of ailments including menopause, common cold, depression, pregnancy and other non-life threatening medical conditions.
- Women in developing countries are often dependent on herbal medicines for their primary healthcare.
- While some herbal products have quality, safety and efficacy data, many herbal medicines, many others particularly in developing countries have not been sufficiently scientifically investigated.
- Official pharmacopoeias, monographs and databases are good sources for scientific and medical information for herbal medicines.

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Part III
International Perspectives on Medicines for Women and Risk Communication

Chapter 14
A Primary Care Perspective on Prescribing for Women

Dee Mangin

Introduction

While evidence for the prescribing of medicines is largely generated in secondary care settings, the majority of prescribing actually occurs in the primary care setting. This raises uncertainties about generalizability of data on efficacy and safety for a population where a greater proportion have milder forms of illness. Prescribing for women in primary care is especially challenging for two reasons: firstly because of the uncertainties inherent in the evidence for safety and efficacy of prescription medicines in women, and secondly due to the complexity of the primary care patient context.

Generation of evidence for prescribing in secondary care settings, likely overstates the magnitude of any efficacy in the primary care population where the milder end of the spectrum of disease is more commonly seen than in clinical trials (Kendrick et al. 2008). Evidence for prescribing medicines for women in primary care is even less certain than for men. Women are less likely to have been included in research on medicines. Chapter 17 documents how recent this issue is – it wasn't until 1993 that the NIH Revitalisation Act mandated the inclusion of women in clinical research protocols –yet evidence is emerging that women may respond differently than men, as outlined in this chapter. In some cases, women are less likely to benefit and overall are more likely to suffer adverse effects of medicines than men.

Women are prescribed more medicines than men – on average 5 compared with 3.7 for men in a United States study (Medco Health Solutions & Society for Women's Health Research 2012). Data from primary care in the United States and Scandinavia also shows some drug groups are prescribed more often to women

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than to men – in particular psychotropic medication and pain medications (Hausken et al. 2007). Women are also likely to suffer more multiple comorbidities than men, and, as managing multiple comorbidities now represents the majority of primary care work, women are vulnerable to the inherent risks of being prescribed multiple medications simultaneously in this situation, compounding their increased vulnerability to adverse effects and dose inaccuracies.

Further, there are reproductive issues to take into consideration. Prescribing in primary care is longitudinal – over a woman's lifetime, and that of her family. Because of the possibility of transmission of most drugs across the placenta, women and primary care providers have to factor the future possibility of pregnancy in to their decisions to take and prescribe medicines. Prescribing of some specific drugs and devices for women that are commonly used in primary care (contraception, hormone replacement therapy, bisphosphonates) have been covered in previous chapters so will not be repeated. Rather, this chapter deals with broad principles and issues for prescribing in primary care, attending to some other common patterns and problems of prescribing for women in this setting. It covers both the background for prescribing for women in these circumstances and includes practical recommendations for dealing with the uncertainties.

Assessing Risk and Benefit in Women

Assessing the value of medicines in women requires balancing the evidence for effectiveness and safety along with a woman's preferences and priorities for care. As already noted, assessment of the evidence to support primary care prescribing for women is more complex than for men. Some research indicates that women may experience the benefits and risks of some medicines differently to men. However, such evidence to nuance prescribing is limited as most regulators including the FDA do not require analysis of sex differences in either efficacy or safety outcomes when licensing medicines. In fact, until relatively recently, the FDA had a ban on women being included in early stage clinical trials (Cotton 1993). Active efforts have been made to increase recruitment of women into clinical trials and disaggregate reporting by gender. This included the 1993 NIH Act which mandated participation, and guidelines from Health Canada in 1994 advocating for inclusion of women at all stages of research into drug development. However, a study published 20 years later indicates there is little change in published research (Geller et al. 2011).

Some examples of these differences in women's experiences of the benefits and risks of medicines include statin drugs, which are very commonly prescribed in primary care. An analysis across all major prevention trials showed the absolute risk of benefit was less for women than for men, with no demonstrated statistically significant advantage in all-cause mortality, no clinically significant benefit in primary prevention and less absolute benefit (and therefore a higher number needed to treat) than men in secondary prevention (Roberts and Redberg 2013). Women

also experienced some side effects such as myopathy and diabetes development at a greater rate than men (Roberts and Redberg 2013). Diuretics are more likely to be chosen for treatment of hypertension in women than in men (Klungel et al. 1997, 1998) however research indicates women are more susceptible to hyponatremia as a result, and this can be after treatment is well established (Sharabi et al. 2002). In some cases, drugs work less effectively; women are less responsive to anesthesia, for instance, than men are (Buchanan et al. 2011).

Acknowledging the uncertainties in the data for women on risks and benefits of medicines is an important part of the shared decision making process around decisions to take medicines. Women's preferences and priorities for care are equally important, and a key aspect of Evidence Based Medicine, which incorporates, in equal measure, research evidence, the patient's context and patients' preferences for care. These aspects are synthesized with clinical wisdom in the shared decision making process (Sackett et al. 1996).

Women and Adverse Reactions to Medicines

Women experience higher rates of adverse drug reactions than men, even when age and rate of exposure are taken into account (Figueras et al. 1994; Tran et al. 1998; Domecq et al. 1980; Pouyanne et al. 2000; Fattinger et al. 2000; Rademaker 2001; Martin et al. 1998; van der Klauw et al. 1998). For example, one study based in the UK that analysed ADR patterns by age and sex found nearly double the ADR rate per unit of exposure for women compared to men (20.6 per 10,000 patient months exposure compared with 12.9 for men. OR 1.5 (1.5–1.7)) (Martin et al. 1998).

While it is possible there are other reporting biases, there are pharmacokinetic differences between women and men as well as known differences in metabolism, both increased and decreased, related to specific drugs (Kando et al. 1995; Harris et al. 1995; Ochs et al. 1981).

Women are at greater risk of some particular drug side effects. A review conducted by the US General Accounting Office of 10 prescription drugs withdrawn from the market (January 1997 to December 2000) indicated that eight of these posed greater health risks for women than men (troglitazone, lotronex, fenfluramine, dexfenfluramine, mibefradil, terfenadine, cisapride, astemizole). The first four drugs were prescribed more often to women, which may have accounted for the increased reports of harms with these four, however, in the second group of four, where there was no differential, the likely reason was felt to be women's increased susceptibility to the adverse cardiovascular effects of the drugs. Mibefradil lowered or stopped the heart rate in healthy adults and in particular in elderly women. Cisapride, astemizole and terfenadine are all known to prolong the QT interval. (Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women, United States General Accounting Office Washington, DC, GAO 01286R) Six of these eight drugs caused heart problems in women (Heinrich 2001).

QT prolongation is one example, and is an important one as it can represent the additive effect of several medicines. Research has documented the greater sensitivity of women to the effects of medicines that affect the heart and prolong the QT interval, the influence of their menstrual cycle and the corresponding increase in life-threatening arrhythmias and deaths in women (Benton et al. 2000; Yap and Camm 2003; Ebert et al. 1998; Bednar et al. 2002).

Whenever data have been available for analysis, more women are reported to have developed heart arrhythmias with cardiovascular medicines despite the greater rate of prescription of anti-arrhythmic agents to men (Makkar et al. 1993). At least 90 prescription medicines have this effect on the heart and many may be co-prescribed in multimorbidity. Research indicates that when drug interaction warnings for QT interval based interactions are overridden, ECGs are only ordered by prescribers 33 % of the time and in those where ECGs are ordered, 31 % had clinical significant QTc interval prolongation (Van Der Sijs et al. 2009).

Additionally some particular risks pertain almost exclusively to women, either because the drugs are mostly prescribed to women or because the side effect is mostly experienced by women. For example, a recent paper reported a risk of atrial fibrillation with long term bisphosphonates (Sharma et al. 2013) which are prescribed to high numbers of women worldwide for osteoporosis (see Chap. 12), and suggestions of an increased risk of breast cancer with calcium channel blockers (Coogan 2013). While many of these prescriptions will be initiated by secondary care prescribers, primary care prescribers are best placed to assess potential cumulative adverse effects of drugs initiated by multiple prescribers – for example, the effects of additive QT prolongation or pro-haemorrhagic risk. There are multiple medications available that are commonly prescribed that increase the tendency to haemorrhage – from the obvious such as warfarin, aspirin, antiplatelet agents, to the less obvious which may be additive in their effect and, given the frequency of prescription, are likely to be co-prescribed e.g. SSRIs, cholesterol lowering agents, NSAIDs.

The Super Precautionary Principle

Women have hormonal cycles, smaller organs, generally smaller body mass index and higher body fat composition, all of which are thought to play a role in how drugs affect women's bodies (see Chap. 2 for more detail). There may also be basic differences in gene expression, which can make differences in the way we metabolize drugs. For example, men metabolize caffeine more quickly, while women metabolize certain antibiotics such as erythromycin and anxiety medications such as diazepam more quickly.

The entire prescribed medicine research pipeline is male dominated – from animal studies that are done in male animals to avoid any hormonal effects, to clinical trials, which have been also largely performed on men, yet the efficacy and safety results, datasheets and recommended doses take a 'one size fits all' approach.

The need for being alert to the potential for these differences between men and women is rarely accounted for in either research language or in primary care datasheets and guidelines recommending dosing.

The one drug where differential recommendations are made is zolpidem, a commonly prescribed sleeping tablet in the United States, where it was discovered that the same dose resulted in a doubling of blood levels in women compared with men (FDA 2013). In 1992 these data were included in the FDA review of the drug, however the recommendation for differential dosing was not made until January 2013 (News).

To account for the differences discussed here, I would advise use of a 'super precautionary principle'. This might mean, in prescribing medications for chronic conditions in women in primary care, that dosing could start at the lowest possible dose of a medication – lower than the standard dose recommendation – and be titrated upwards according to effect where possible.

The Complex Prescribing Landscape of Primary Care

Prescribing in primary care is more complex than in secondary care. Family physicians address a mean of 3.05 problems per visit and in 37 % of the encounters more than three problems are addressed (Katerndahl et al. 2011). The more comorbidities a patient has, the more drugs they are prescribed. The more drugs they are prescribed, the higher the risk of adverse events.

In an aging population, the majority of patients attending primary care now experience multiple chronic comorbidities (Mangin et al. 2012). Half of people over 65 years of age have at least three coexisting chronic conditions. One in five has five or more. Although the proportion of patients who have comorbidities increases in older age groups, the largest numbers of patients with multiple comorbidities are under 65 years of age and more than half of patients attending primary care in the UK have multiple chronic conditions and such patients take up an even greater proportion of consultations (Salisbury et al. 2011). In a US study of Medicare beneficiaries, the proportion of patients with more than five treated conditions increased from 31 % to 50 % from 1987 to 2002 (Thorpe and Howard (2006). Women live longer than men and are also more likely to suffer from chronic disease (Malmusi et al. 2012). In some conditions, for example heart disease, they experience these at an older age (Roberts and Redberg 2013). Age-related changes in hepatic and renal function lead to alterations in drug clearance, and this, combined with the uncertainties in the evidence overall and for women in particular, makes prescribing in this situation complex.

Seniors in developed countries take a median number of seven medications (Mangin et al. 2012; McCarthy et al. 2007). Drugs for cardiovascular risk such as high blood pressure and cholesterol are the most commonly prescribed in seniors over 65 as well as drugs for heart failure. In Canada, spending in public drug programs was greatest on statins for cholesterol lowering, proton pump inhibitors

for dyspepsia, gastro-oesophageal reflux and ulcer treatment, and calcium channel blockers use for hypertension and other cardiovascular conditions. The highest growing expenditure group is TNF alpha inhibitors used for conditions such as rheumatoid arthritis and Crohns disease (Canadian Institute for Health Information). In the United States in adults over 60 cholesterol drugs are the most commonly used (45 % of the population) followed by beta blockers and diuretics (Gu et al. 2010). Medication side effects and polypharmacy, and associated morbidity and mortality from drug side effects are major and costly problems for healthcare and for individual women. In a Canadian study people taking more than five medications were more likely to experience a medication related side effect that required health care than those taking less than 2 (13 % vs. 6 %) (CIHI 2011). Less than half of those taking more than five medications reported having a medication review (CIHI 2011).

Margaret (Case Study Box 14.1) is a very typical woman of her age – with two conditions that cause symptoms and three risk factors for conditions that may cause symptoms in the future. Margaret's doctors follow the condition based guidelines for each of her problems. An elegant study by Boyd et al. demonstrates that this results in 19 doses of 12 different medications (thiazide diuretic, ACE inhibitor, metformin, sulphonlyurea, statin, B2 agonist inhaler, aspirin, calcium, Vitamin D, alendronate, NSAIDs, a proton pump inhibitor) taken at five times during the day (Boyd et al. 2005). Merging data on interactions and recent data on emerging adverse events updates Boyd's estimate of potential interactions either between drugs or drugs and diseases to 16. These are outlined in Table 14.1

Applying single disease guidelines in multimorbidity to a woman (like Margaret) with five chronic comorbidities, no matter what they are, results in potentially harmful polypharmacy (Boyd et al. 2005). Measurably better care may be meaningfully worse for the patient. This is a more common situation among women and discriminatory and wise prescribing is required, prioritising medicines that are most important to the patient and being alert to side effects and interactions. While the initiation of some of these medicines might be in secondary care settings, it is the primary care clinician who is almost always responsible for ongoing prescriptions. With increasing specialisation and subspecialisation, and guidelines to match this, prescribing is increasingly done with a partial focus on the patient – on one system or disease of expertise.

Box 14.1: Case Study: Margaret

Margaret is 70 years old and has Chronic Obstructive Pulmonary Disease, arthritis, diabetes, hypertension and osteoporosis. Her arthritis stops her from playing with her grandchildren as she would like to, while her COPD makes her too breathless to go dancing with her husband any more. The other conditions she is only aware of because her primary care doctor did some measurements.

Table 14.1 Potential drug-drug and drug-disease interactions in case study "Margaret"

Drug	Interacting drug/condition	Interaction risk
Statin	Diabetes	Increased risk of diabetes
ACE inhibitor	Diuretic, aspirin	Increased risk renal failure
NSAID	Hypertension	Increased risk renal failure
NSAID	Hypertension	Increased risk hypertension
NSAID	Aspirin	Bleeding
Calcium	Hypertension, diabetes	Increased risk CV events
PPI	COPD	Increased risk pneumonia
Thiazide	Diabetes	Increased risk diabetes
Aspirin	Alendronate	GI upset
Calcium	Aspirin	Decreased efficacy
Thiazide	Sulphonylurea	Decreased efficacy
Calcium	Alendronate	Lowered serum level alendronate
NSAID	Diuretic	Decreased efficacy
Sulphonylurea	Aspirin	Hypoglycaemia
Aspirin	ACE inhibitor	Decreased efficacy
Alendronate	Hypertension	Both increase the risk of atrial fibrillation

Similarly, evidence of drug efficacy and safety is also generated largely in single disease, controlled trial settings – patients who are older or who have multiple comorbidities or other medications are frequently excluded from clinical trials of medicines. In contrast, the expertise of primary care clinicians is a view that encompasses the whole patient – their multiple comorbidities and medications – with a focus on the individual: patient centered care is a core value of primary care. Primary care prescribers are also experts in longitudinal care, making them best placed to assess the relative value of different medications over time. This is crucially informed by the direct observation of the actual effects and side effects of medicines over time in the individual sitting in front of them. It is often forgotten that the 'n = 1 trial' is the highest level of evidence.

Management of Polypharmacy

Despite the evidence of preventable morbidity and mortality from adverse drug reactions (Baker et al. 2004; Field et al. 2005), in Canada for example, the majority of patients with multimorbidity who are taking multiple medications have never had a formal drug review (CIHI 2011). Trials of stopping medicines indicate that stopping or reducing doses of diuretics, anti-hypertensives, antipsychotics and proton pump inhibitors can be successful and their effectiveness is often increased by tapering (Iyer et al. 2008; Nelson et al. 2002; Campbell et al. 1999). Trials of multiple medication discontinuation also indicate that this can be done successfully and without adverse consequences for the patient (Garfinkel and Mangin 2010; Garfinkel et al. 2007).

A pragmatic prioritisation framework on which to base discussion with a woman with several comorbidities and on multiple medications has been suggested as covering (Holmes et al. 2006):

1. Medicines for symptom control (e.g. diuretics for heart failure). These are generally short terms benefits and efficacy is easy to judge in the individual based on their experience of the illness.
2. Medication proven to prevent future morbidity (e.g. warfarin in atrial fibrillation to prevent stroke). These may lack short term benefits but have possible longer term benefits. It is not possible to judge which patients will and will not reap the benefit.
3. Medication to treat numbers (e.g. treating high cholesterol or HbA1C levels). This is an often longer term benefit, is not calibrated against symptoms of illness and relies on assumptions that these intermediate outcome indicators are associated with improvements in outcomes that matter to women – namely, improvements in mortality and morbidity. A recent study compared effect sizes using intermediate outcome indicators and later studies of patient relevant outcomes and found the treatment effect estimate was 47 % higher in the trials using surrogate outcomes than in the trials using final patient relevant outcomes (Ciani et al. 2013).

Assessment of individual potential to benefit is important (if the medication has to be taken for 5 years to realise benefit and the patient is unlikely to live 5 years then benefit will not be realised) and this must be judged against the risks. For example, pravastatin must be taken for prevention of stroke in those at high risk for 5 years to realise 1.4 % absolute risk difference in stroke. If a woman is likely to die in the next year or two then the potential for benefit will be markedly reduced and must be measured against the risks which ensue from the outset of taking the medication.

In avoiding the harms of polypharmacy a rule of thumb is to aim for five medications. Beyond this, the risk of increasing morbidity with side effects rises substantially (Steinman et al. 2011; Buck et al. 2009). There are a variety of tools available to support medication prioritisation and suggest drugs to avoid if possible in older age, such as the Beers list, STOPP and START criteria, the Medication Appropriateness Index (Hanlon et al. 1992), the Drug Burden Index (Hilmer et al. 2007), as well as process guides to considering priorities (Ostini et al. 2011; BPAC 2010; Gallagher and O'Mahony 2008; Scott et al. 2012; Alexander et al. 2006; Mangin and Kerse 2010; Garfinkel and Mangin 2010; Cross 2013).

'Legacy Drugs'

There are a group of 'legacy drugs' (drugs that efficacy data suggest should have a time limited prescription duration, but are often carried on indefinitely) the prescription of which is only indicated for 1–5 years with no evidence of additional benefit beyond this period to offset against the ongoing potential harms. These drugs can add to the polypharmacy burden unnecessarily. Drugs such as

antidepressants, osteoporosis drugs, statins and proton pump inhibitors are examples of legacy drugs, and as previously detailed, many of these are prescribed much more frequently to women. Hormone Replacement Therapy (HRT) is another important example of a medication that should have a planned stop date. A detailed review of HRT – more correctly known as Menopause Hormone Treatment (MHT) – and the evidence and recommendations for use is included in Chap. 11. Prescription of drugs such as antibiotics is self-limiting, as usually only a single prescription is given, however the groups of legacy drugs require repeat prescribing, usually in primary care, and most systems in primary care do not provide a stop date alert. It is likely that multiple prescribers contribute to this legacy effect, and primary care clinicians are best placed to assess and address this issue.

A good prescriber is one who regularly pays attention to stopping and reducing the dose of medicines. Almost all drugs are eligible for a trial of discontinuation and equally importantly, it should not be regarded as a failure to have to restart a paused medication after such a trial. Regular recall to review the medications of women with multiple comorbidities should be a scheduled part of primary care. To prescribe well: adjust, watch, listen and adjust again.

New Is Not Necessarily Better: The Implications of Marketing Drugs to Women in Primary Care

The United States and New Zealand are the only countries allowing direct to consumer advertising. Many other countries have 'disease-oriented ads' and advertorials disguised as articles in women magazines with checklists for diagnosing disease, that are generated from the PR campaigns of pharmaceutical companies. Women are targeted more in advertising of new drugs. Women's magazines and daytime television are the most common places for presentation of drug advertising (Brownfield et al. 2004; Bell et al. 2000). Advertising targeting women is problematic for a number of reasons: it medicalises normal human experience, contains stereotyped portrayals of women, provides unrealistic expectations of effectiveness and minimises safety concerns (Mintzes 2010).

In one study of advertising in medical journals, 57 % of the advertisements for psychoactive drugs featured women and older women were targeted more (67 % of those directed at age 20–40 were for women, as were 90 % of the advertisements directed at women over 80) (Munce et al. 2004). Physicians are responsive to patients requests for advertised medicines – a study using actors as 'female standardized patients' trained to present with either depression or emotional responses to a stressful life situation, and asking or not asking for an antidepressant advertised on television, found that a woman's request for an antidepressant predicted whether she was likely to leave the office with a prescription much more than whether she had a condition an antidepressants drug would be useful in treating (Kravitz et al. 2005). In a New Zealand survey 18 % of the population had asked for a

medicine advertised on television and over half of these patients had received it, and 29 % of women had used a magazine or newspaper as a source of health information compared to 15 % of men (Toop et al. 2003b). Advertisements such as those for sibutramine (Reductil©) and the oral contraceptive pill Diane 35©, specifically targeted at women, have had to be withdrawn for inaccuracy of claims (Toop et al. 2003a; Mintzes 2004).

Rarely do new medicines offer substantial benefit. The French Independent Drug Bulletin *La Revue Prescrire* evaluates all new drugs coming onto the market using systematic review of all available evidence from clinical trials and using both published and unpublished data. Over a 5 year period they evaluated nearly 1,000 medicines and found only 2 % as clear treatment advances and 9 % as having some advantages (Mintzes and Mangin 2009). Less is known about the safety in the general population of drugs new to the market. Furthermore, clinical trial populations include less women, less people with comorbidities or concurrent medications and less primary care participants (whose illness encompass the less sever end of the spectrum) than 'real life' populations of patients. One group have recommended a safe approach is refraining from prescribing a new medicine until 7 years after introduction (Wolfe 2012). It takes even more time for differential and preferential adverse effects in women to filter through after introduction to market.

New drugs to the market are very visible: they are the drugs you are most likely to see in primary care medical journals, and presented by drug representatives and at commercially sponsored continuing medical education events and conferences for primary care clinicians. They are the most likely to come with free gifts and 'free' samples for patients attached.

I suggest the following principles: Have a higher threshold for prescribing drugs new to the market to women. Be cautious with dosing if a decision to prescribe is made. The information about efficacy, dose and side effects in women is likely to be less certain than the data provided.

Mind that Drug: Psychoactive Drug Prescription and Women

There are reasons for higher rates of stress in women. Women are more likely to suffer from poverty and economic deprivation, stressful role changes and a higher proportion of women work in stressful jobs. There is also evidence that if a woman and a man go into a primary care office with the same condition, the woman is more likely to emerge with a prescription for a psychotropic agent (Hausken et al. 2007). In addition, the changing stages of reproduction make a woman more likely to have contact with the medical system (for example, consultations for menstrual issues, screening for cervical and breast cancer, pregnancy-related appointments, attending with babies and children and also menopause) and therefore more likely to receive a prescription.

Twice as many psychotropic drugs (drugs that affect the mind) are prescribed for women as for men, and this holds true for the selective serotonin reuptake inhibitor (SSRI) antidepressants, the most common antidepressant class prescribed (Ashton 1991). Women are 70 % more likely to be recorded as experiencing depression in their lifetime than men (Kessler et al. 2003). As well as increased psychological stress, the promotion of screening also contributes to these high rates of prescription, despite evidence that screening for depression is of no benefit (Gilbody et al. 2005). Depression screening tests such as the Edinburgh Postnatal Depression Scale (EPDS) are promoted to assess women during the postpartum period. The range of false positives from this test ranges from 30 % to 70 %. It is designed to pick up minor depression that would benefit from time and support but Oates suggests a lack of counselling resources and skills results in many women with postnatal depression receiving antidepressants rather than non-drug assistance (Oates 2003). There is no evidence for benefit from screening for depression in primary care yet it is widely promoted by commercial interests.

A review of spontaneous adverse drug reaction (ADR) reporting in the US found that during a 10-year period the SSRI fluoxetine was associated with more hospitalizations, deaths or other serious adverse effects reported to the FDA than any other drug in America (Spigset 1999). The most common problems reported with SSRIs are neurological (22 % of ADRs), psychiatric (19.5 %), gastrointestinal (18 %) and dermatological (11.4 %) and women experienced a higher rate of the most harmful of these effects in comparison with men (Spigset 1999).

The rate of SSRI antidepressant prescribing is growing steadily in women and the proportion of women taking an SSRI in most developed countries is now over 10 % and much higher in subgroups in some countries – 30 % of women over 65 in Iceland in 2008 were taking an antidepressant (Pratt et al. 2011; OECD 2013). The evidence shows limited efficacy in the overall primary care population even in short 12 week trials (Arroll et al. 2005). In this meta-analysis by Arroll et al. the absolute difference in response between the antidepressant medication and placebo was 13.5 %, there being 44.5 % remission with placebo versus 58 % with antidepressants at 12 weeks, so nine patients need to be treated for one to benefit (Arroll et al. 2005).

There is also evidence that some of the rise in antidepressant use is driven by patients going on antidepressants and staying on them (Moore et al. 2009; PHARMAC). As discussed in the ‘legacy drugs’ section above, this is likely a combination of failure to review after the maximum 12 months of prescribing for a single episode (Kennedy et al. 2009; NCCMH 2010), reinforced by withdrawal symptoms misinterpreted as recurrence by the patient. Legacy drugs such as SSRIs which have time limited value, should have dates set for active discontinuation when prescribing is first initiated and these should be discussed with the patient.

Mortality and Morbidity from Prescribed Medicine Overdose

Although men still fall victim to prescription drug overdose more often than women, the number of women losing their lives from overdose of prescription drugs rose 400 % between 1999 and 2010 (compared to 250 % for men), according to recent US data from the Centers for Disease Control and Prevention (CDC). Eighteen women die per day of a prescription drug overdose in the U.S. – five times more than 10 years ago. Prescription painkillers have been a major contributor to increases in drug overdose deaths among women. In the United States alone, more than 6,600 women died from a prescription painkiller overdose in 2010 and this accounts for nearly half of all drug overdoses among women. This is four times as many deaths in women than from heroin and cocaine use combined. In 2010, there were more than 200,000 emergency department visits for opioid misuse or abuse among women in the United States; about one every 3 min (CDC 2013).

Prescription Drug Abuse and Women

Forty years ago, pain was widely under-treated with prescription painkillers reserved primarily for cancer pain. Now the scales have tipped the other way and, in some scenarios, pain is being over-treated with addictive medications even when non-addictive approaches would be effective. There are cycles of overprescribing of drugs with addictive potential in women – in previous decades diazepam and other benzodiazepines were over-prescribed to women for stresses that were environmentally generated – labelled in the popular press ‘suburban neurosis’.

Women are more likely to suffer from chronic pain than men and prescription painkillers are now commonly prescribed among women (Nicholas et al. 2011). Women are more likely to be prescribed painkillers as men for the same level of pain (Simoni-Wastila 2000; Chilet-Rosell et al. 2013), against the background that women are 50 % more likely than men to leave their doctor’s office with a prescription, even if they have the same condition (Currie 2003). A UK study found that women who have been abused by their partners have almost double the primary care consultation rate, together with a sevenfold prescription rate of pain medication in the youngest and middle age categories and threefold in the oldest age group (Wong et al. 2007). As discussed above, data from the CDC indicate that women aged 45–54 years have had the most dramatic increases in drug overdose deaths in the United States. Women are also more often prescribed painkillers and for longer periods of time than men.

Health care providers and women can take steps to protect against prescription painkiller overdoses among women by using non-narcotic alternatives for non-cancer pain as well as non-pharmacological modalities. There are some excellent resources freely available as illustrated in Box 14.2:

Box 14.2: Non Pharmacologic Resources for Managing Non-cancer Pain
"Pain: Understanding what to do about it in less than five minutes"
http://www.youtube.com/watch?v=4b8oB757DKc.
"Low Back Pain – Mike Evans Video"
http://www.youtube.com/watch?v=BOjTegn9RuY
"Be the Doctor not the Dealer"
https://www.youtube.com/watch?v=QMIHTliEuNk

Reproductive Age Prescribing

The examples of diethylstilboestrol, thalidomide and sodium valproate demonstrate that any medication has the potential for unintended and unknown harm when used in the reproductive age group if pregnancy should occur and important and often rapid informed decisions have to be made about medications by a woman when she becomes pregnant. However the even greater responsibility for the primary care prescriber occurs when prescribing in the reproductive age group, before pregnancy occurs. This responsibility covers three main areas: ensuring timely stop dates for legacy drugs to reduce overall drug exposure, warning re the need for pre-pregnancy discussion and duration of any likely tapering required for any women taking long term medication, and ensuring adequate and effective contraception for any woman taking known teratogens or where data is uncertain (this represents a large group of medicines). Informed discussions should include both what is known but also important unknowns. This is an example of the 'absence of evidence is not evidence of absence' principle – for example absence of, or unclear evidence on, effects of drugs taken during pregnancy on subsequent child development should be addressed as an important unknown rather than as reassuring that there is no effect.

Case Study Carey's story (Box 14.3) illustrates not just the slippage that occurs in prescribing with 'legacy drugs' that are only indicated for limited time periods but also issues around providing the opportunity for informed decision making in the reproductive age group Antidepressants are a good example of a legacy drug mentioned above and are common in younger age groups of women, proton pump inhibitors are another. In the reproductive age group polypharmacy is less of an issue but reducing unnecessary medicine use and reducing the risk of accidental exposure in the first trimester are important aspects of prescribing.

Multiple prescribers, and often withdrawal effects experienced by the patient (as described by Carey in Box 14.3, these are more likely to explain how she felt off the medicine, rather than the return of the indication for which the drugs were prescribed) combine to facilitate ongoing prescribing well beyond the duration of benefit. This has particular implications for women, as it widens the window for exposure during pregnancy. Around a third of pregnancies are unplanned and there

Box 14.3: Case Study: Carey
Carey is 26 and comes to see you as she did a pregnancy test at home the previous week that is positive. Her last menstrual period was 8 weeks ago – she did the pregnancy test when her period was 10 days overdue and this was 7 days ago. You look in her notes and see she is taking an SSRI. Looking back further you see she has been on this for some years, and had repeat prescriptions written by three of the doctors in the practice. You talk to her and she says she was started on it after the death of her father. It was her first episode of low mood. She says she kept on taking it as she thought it kept her well. "I know I need it still as I forgot it once when I went away for the weekend and I felt terrible, really awful. . ."

are data indicating planning of pregnancy predicts later cognitive and behavioural outcomes in children, independent of a variety of cofactors. This is likely to represent unwitting environmental and drug exposures.

A simple and regularly repeated pregnancy warning to the patient on long term medicines is important but will not suffice. When prescribing such medicines in primary care, explicit attention must be paid to effective contraception and instruction about its use (see section "Reproductive Age Prescribing") as well as warning when medications will need a significant taper period. A woman who presents for discussion of medication and pregnancy after she is pregnant has already had opportunity for informed shared decision making reduced.

Pertinent to Carey's case is that fact that, while some studies indicate higher recurrence rates in women with more severe, frequently recurrent (4 or more) episodes of depression (Cohen et al. 2006), the most recent studies indicate that in the kind of population normally treated in primary care there was no higher recurrence rate of depression among well women taking long term antidepressants in those who stop in pregnancy compared with those who continue (Yonkers et al. 2011). However it is not as simple as just stopping as soon as possible. Some drugs such as SSRIs need tapering, so given the lag time between conception, awareness of missed period, testing and primary care visit, as in Carey's case, it is likely that, by the time she has finished the taper period, the first trimester would be complete. Her capacity to make an informed choice about taking medication in pregnancy is reduced.

Enabling Informed Choice for Women in the Reproductive Age Group

General practitioners have an important role to play in helping prevent inadvertent fetal exposure to medicines. 11.7 million women of childbearing age are prescribed FDA Category D or Category X medications each year (Schwarz et al. 2005; Andrade et al. 2006). A systematic review of studies in other countries found the

proportion of women who were prescribed a drug with positive evidence of fetal risk varies: Denmark (18.7 % of 15,756 women), the Netherlands (21.0 % of 7,500 women) and Canada (6.3 % of 109 344 women) (Daw et al. 2011). In the United States, approximately 6 % of US pregnancies occur in women taking medications with known teratogenic risk (Schwarz et al. 2005; Andrade et al. 2006). The most frequently prescribed Category D and X medications in the primary care setting are anxiolytics, anticonvulsants, antibiotics and statins. Prescriptions for these medications occurred at 1 in 13 visits for women aged 14–44 years (Schwarz et al. 2005). Contraceptive counseling was documented during less than 20 % of these visits and occurred at equally low rates whether category A or category X.

The most common contraception used in these women is the combined oral contraceptive. Ensuring the adequacy of contraception when given, and especially in women taking other medications that are known or unknown teratogens is important, as 40 % of unintended pregnancies occur in women using contraception and 90 % of these are due to inconsistent or incorrect use (Kost et al. (2008), Steinkellner et al. (2010). A survey of hospital doctors in the US identified that barriers to contraceptive counselling when prescribing included a lack of reimbursement for such counselling, as well as poor knowledge of both teratogens and contraceptives (Eisenberg et al. (2010).

Contraceptive status should be recorded with the prescribed medicines and strenuous efforts made to maximise the efficacy of oral and other contraception where it is used. Women should be warned regarding pregnancy on the initiation of any prescribed medicine, and this should be recorded in the medical record. Women using any prescription medicine should be strongly advised to re-consult their primary care doctors regarding medicine use before contemplating pregnancy.

Prescribing hormonal contraceptives is covered in some the detail in other chapters of this book: here I will only focus on issues relating to providing contraceptive advice and medicines/devices in primary care in these (and any) circumstances. Two general principles apply. The first is to maximise efficacy of contraception when taking other prescription medicines long term by adequate instruction and reminders. The second is to minimise risk. Prescribing contraceptives would be one of the most common prescriptions provided for women in primary care, and illustrates a general principle that is extremely important. Where the decision is made to prescribe hormonal contraception, or any medicine to women, it should be done from a perspective of comparative safety. While justification of the risk of venous thromboembolism (VTE) using hormonal contraception is made on the basis of the risk of VTE in pregnancy, this cannot be used to justify using a product with excess risk compared with those that carry less risk. Useful resources are available and should guide these decisions, for example in this case those that group contraceptives by comparative risk of venous thromboembolism (Table 14.2).

Fragmented prescribing by multiple prescribers increases the risk of potentially teratogenic drugs being prescribed – with multiple drugs prescribed and dilution of responsibility, and the prescriber of a potentially teratogenic medicine may not feel it is their responsibility to provide the contraceptive advice needed – in a survey of

Table 14.2 Risk tables: birth control pills: venous thromboembolic risks

	Birth control pill[1]	Estrogen	Progestin	Adjusted annual relative clot risk vs. non use (95 % CI)[2]	Adjusted annual relative clot risk vs. Levonorgestrel-containing pills[3]
Progesterone-only pills	Micronor (28)	–	Norethindrone 0.35 mg	0.6 (03–1.1)	–
Levonorgestrel-containing combined estrogen-progestin pills	Alesse (21 + 28)	20 mcg	Levonorgestrel 0.1 mg	2.2 (1.7–2.8)	–
	Aviane (21 + 28)	20 mcg	Levonorgestrel 0.1 mg	2.2 (1.7–2.8)	–
	Min-Ovral (21 + 28)	30 mcg	Levonorgestrel 0.15 mg	2.2 (1.7–2.8)	–
	Portia (21 + 28)	30 mcg	Levonorgestrel 0.15 mg	2.2 (1.7–2.8)	–
	Seasonale/ Seasonique	30 mcg	Levonorgestrel 0.15 mg	2.2 (1.7–2.8)	–
	Triquilar (21 + 28)	30/40/30 mcg	Levonorgestrel 0.05/0.075/ 0.125 mg	2.3 (1.9–2.8)	–
Norethindrone-containing combined estrogen-progestin pills	Brevicon 0.5/35 (21 + 28)	35 mcg	Norethindrone 0.5 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS
	Brevicon 1/35 (21 + 28)	35 mcg	Norethindrone 1 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS
	Loestrin 1.5/30 (21 + 28)	30 mcg	Norethindrone acetate 1.5 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS
	Minestrin 1/20 (21 + 28)	20 mcg	Norethindrone acetate 1 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS
	Ortho 0.5/35 (21 + 28)	35 mcg	Norethindrone 0.5 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS

	Ortho 1/35 (21 + 28)	35 mcg	Norethindrone 1 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS
	Ortho 7/7/7 (21 + 28)	35 mcg	Norethindrone 0.5/0.75/1 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS
	Synphasic (21 + 28)	35 mcg	Norethindrone 0.5/1 mg	1.6 (0.8–2.9)	0.8 (0.4–1.6), NS
Norgestimate-containing combined estrogen-progestin pills	Cyclen (21 + 28)	35 mcg	Norgestimate 0.25 mg	2.6 (2.2–3.0)	1.2 (0.9–1.6), NS
	Tri-Cyclen (21 + 28)	35 mcg	Norgestimate 0.18/0.215/ 0.25 mg	2.6 (2.2–3.0)	1.2 (0.9–1.6), NS
	Tri-Cyclen Lo (21 + 28)	25 mcg	Norgestimate 0.18/0.215/ 0.25 mg	2.6 (2.2–3.0)	1.2 (0.9–1.6), NS
	Apri (21 + 28)	30 mcg	Desogestrel 0.15 mg	4.2 (3.6–4.9)	2.2 (1.7–3.0), $p < .001$
	Diane-35 (acne)	35 mcg	Cyproterone acetate 2 mg	4.1 (3.4–5.0)	2.1 (1.5–3.0), $p < .001$
	Linessa (21 + 28)	25 mcg	Desogestrel 0.1/0.125/ 0.15 mg	4.2 (3.6–4.9)	2.2 (1.7–3.0), $p < .001$
	Marvelon (21 + 28)	30 mcg	Desogestrel 0.15 mg	4.2 (3.6–4.9)	2.2 (1.7–3.0), $p < .001$
	Ortho-Cept (21 + 28)	30 mcg	Desogestrel 0.15 mg	4.2 (3.6–4.9)	2.2 (1.7-3.0), $p < .001$
	Ovral	50 mcg	D-norgestrel 0.25 mg	3.5 (2.5–5.1)	Data not available
	Yasmin (21 + 28)	30 mcg	Drospirenone 3 mg	4.5 (3.9–5.1)	2.1 (1.6–2.8), $p < .001$

(continued)

Table 14.2 (continued)

	Birth control pill[1]	Estrogen	Progestin	Adjusted annual relative clot risk vs. non use (95 % CI)[2]	Adjusted annual relative clot risk vs. Levonorgestrel-containing pills[3]
	Yaz (28)	20 mcg	Drospirenone 3 mg	4.8 (3.2–7.3)	2.1 (1.6–2.8), p < .001
	Demulen 30 (21 + 28)	Data not available (sometimes classified as lower risk)			
Non-oral hormonal contraception	Transdermal combined *contraceptive patches			7.9 (3.5–17.7)[4]	2.3 (1.0–5.2)***
	Vaginal ring**			6.5 (4.7–8.9) p < .001[4]	1.9 (1.3–2.7)****

Adapted with permission from Mintzes B, Monk T www.pathwaysbc.ca

Notes

Baseline clot risk for woman under 35 on no bcp: 2.2/10,000[5]

Baseline clot risk for woman age 35–49 on bcp: 14.8/10,000[5]

Baseline clot risk during pregnancy (age not specified): 7–27/10,000[6]

Baseline clot risk, early postpartum (age not specified): 40–65/10,000[6]

Non oral contraceptives:

*When compared with oral contraceptives containing the corresponding progestogen (norgestimate), the adjusted rate ratio was 2.2 (1.0–5.0)

**When compared with oral contraceptives containing the corresponding progestogen (norgestimate), the adjusted rate ratio was 1.8

***Before adjustment for length of use 2.3 (1.0–5.2)

****Before adjustment for length of use 2.0 (1.4–2.9)

1. Brand names are Canadian and may differ between countries

2. Lidegaard et al. BMJ 2011; 343: d6423; based on full population data for Denmark, 2001–2009; eight million women-years of exposure, adjusted for age, year, and education levels

3. Lidegaard et al. BMJ 2011; 343: d6423; based on full population data for Denmark, 2001–2009; eight million women-years of exposure, adjusted for age, year, education levels, and length of use

4. Lidegaard et al. BMJ 2012; 344: e2990; based on all non-pregnant women from Denmark, free of previous thrombotic disease or cancer, 2001–2010

5. Lidegaard et al. BMJ 2011; 343: d6423; rates derived from Table 14.1, crude incidence per 10,000 women-years

6. US FDA Drug Safety communication: updated information about the risks of blood clots in women taking birth control pills containing drospirenone, (4-10-2012), available at: www.fda.gov/Drugs/DrugSafety/ucm299305.htm

internal medicine specialists in the United States most (88 %) felt it was the responsibility of primary care physicians to provide contraceptive advice and counselling (Eisenberg et al. 2010). 'Most Responsible Provider' is a fashionable term and it is the primary care clinician who is usually the patient's Most Responsible Provider. General advice and warnings are needed from the primary care clinician. This is despite the origin of prescriptions from a different source as the medication prescriber may not perceive it to be his/her responsibility and the woman may think an absence of warning and counselling implies safety.

Treatment of Urinary Tract Infections in Women in Primary Care

Women also suffer in greater proportion from some short term illnesses commonly treated in primary care where medicines are prescribed. Urinary tract infection is one example. In this case there are wider community responsibilities to consider. Prescribing antibiotics for UTI is for reducing symptom duration rather than microbiological 'cure'. Around 10 % of women will suffer from a lower urinary tract infection in a year, 50 % in a lifetime, with around a third of these occurring before age 24 (Foxman 2003). This exposes a large proportion of the community to whichever antibiotic is chosen first line. The risk of driving antibiotic resistance in the chosen class is high so responsible choice is important.

Research indicates that empiric prescribing is justified on the basis of symptoms (Richards et al. 2005). It also indicates that the resistance rates quoted in laboratories overstate the true resistance rate (Richards et al. 2002). Low side effect, narrow spectrum antibiotics such as notrofurantoin and the most appropriate, with efficacy measured in terms of clinical symptoms (BPAC 2011). A recent paper indicates that in older patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers, co-trimoxazole is associated with an increased risk of sudden death. This is probably related to trimpethoprim-induced sudden hyperkalemia. Other drugs such as nitrofurantoin should be chosen first line where a woman is taking an ACE or an ARB, or potassium should be monitored (Fralick et al. 2014). This preserves broader spectrum and more risky drugs for more serious infections. Drugs such as fluoroquinalones are increasingly used, however they have side effects more significant than the symptoms they treat in this instance – the risk of tendon rupture increases with even short term use (Movin et al. 1997; McGarvey et al. 1996).

Medicines for Healthy Women

There are many medicines that can be and are given to currently healthy, asymptomatic women. Some of this kind of prescribing is medically driven, for example for primary prevention of future disease such as cardiovascular disease, and some

generated by requests from women, often from pressure to weigh less or look younger. In countries where direct to consumer advertising is allowed these requests for 'lifestyle' medicines may be generated by advertisements, in other countries more subtle media presence of commercial interests in magazines and newspaper press releases or advertorial articles may stimulate requests as detailed previously.

It is important in discussions on these medicines to separate the pressure to prescribe for social or commercial or even state driven reasons (springing from a desire to reduce the economic burden of health care) with a population based approach to prescribing, from what the evidence suggests is in the best interest of the woman sitting in the consultation room. As discussed earlier in this chapter, publications assessing the evidence for benefit in women indicate that statins are of no benefit in primary prevention and less benefit generally to women (Redburg and Roberts). Similarly anti-hypertensives may carry more risks for women as detailed.

Archie Cochrane's comments on such screening and subsequent treatment of the healthy provide a succinct summary of the primary care practitioner's responsibility:

> We believe that there is an ethical difference between everyday medical practice and screening. If a patient asks a medical practitioner for help, the doctor does the best he [or she] can. He [or she] is not responsible for defects in medical knowledge. If, however, the practitioner initiates screening procedures he [or she] is in a very different situation. He [or she] should, in our view, have conclusive evidence that screening can alter the natural history of the disease in a significant proportion of those screened. (Cochrane and Holland 1971)

Overactive bladder for example was a condition name invented by a public relations campaign for a pharmaceutical company (Toop and Richards 2003) with demand stimulated by a planned campaign targeting women and physicians with checklists and advertisements. The drug advertised offers no clinically significant benefit (Therapeutics Initiative 2005) and going to the toilet frequently is not a medical condition.

Almost all medications for weight loss have had subsequent safety concerns about stimulating effects on the cardiovascular system and, in the case of 'Fen-Phen', structural abnormalities (Drolet et al. 2007; CDC 1997). Some weight reduction medicines such as sibutramine (Reductil©) and Fen-Phen have been withdrawn from the market due to an unacceptable risk benefit profile (Drolet et al. 2007; CDC 1997). Few, if any, have offered sustained weight loss. This experience ought to stimulate prescriber caution with any new products in this group.

A woman is better served in addressing lifestyle issues by lifestyle modulation before chemoprevention where the evidence is less certain. Healthy public policy is the best way to address unhealthy environments and health problems that result from economic disparity.

Non-pharmacological Approaches to Treatment: The Safest Prescribing

The practice of medicine is increasingly synonymous with the giving of medicines. This is further amplified in the prescribing patterns for women. For most common complaints and diagnoses, women receive prescriptions more often than men (Verbrugge and Steiner 1985).

The safest prescribing is of effective non-drug alternatives. It is easy to forget the efficacy and safety of alternate strategies among the flooding of the literature and hype to doctors and patients associated with pharmaceutical company research on their products. It is also easy to forget that most people taking long term medicines are not benefiting from them (in order for half to benefit the NNT must be two or less and there are few drugs for chronic disease or risk that meet this threshold). This means that most patients are taking risks without hope of benefits.

According to a CDC report summarising US data sources, 15 % of women in the reproductive years suffer from depression and 7 % from 'hypertension', while 49 % get insufficient exercise and 32 % are obese (CDC 2011). For these women, exercise and healthy eating is likely to offer greater gains at less risk than pharmacological treatment. If all women were of normal weight, exercised daily, and maintained a healthy diet, this report estimates number of women with hypertension could be reduced by approximately 50 % (CDC 2011).

Exploring effective and safe non pharmacological approaches to treatment seems warranted. This would seem even more justified where there are multiple morbidities that might be reduced, or the medication burden reduced. Unfortunately the nature of primary care means that the more medical conditions there are to discuss, the less likely routine health maintenance is addressed (Katerndahl et al. 2011). This creates a paradoxical effect where patients who are most likely to benefit from strategies such as improved diet and exercise across their multiple conditions are least likely to receive support with this. This is not because of a fault of their doctor, but rather the fault of a system that does not allow for adequate time to be given to complex primary care that is needed.

Improving the Data for Prescribing for Women

Given the paucity of evidence from RCTs for differential effects of medicines in women, one of the key tools primary care clinicians have is in contributing to the evidence base to inform prescribing for women. Doctor and patient reporting of adverse drug effects is the main way the evidence on side effects is gathered once a drug is on the market. Most countries allow direct reporting by doctors, other health professionals and the pharmaceutical industry to the regulator through such agencies as the FDA (US), Health Canada (Canada), the MHRA (the Yellow Card

system in the UK). Many other countries, including Australia and New Zealand, also have long-standing spontaneous reporting systems in place.

Patient direct reporting to the national pharmacovigilance centre and/or regulator is also allowed in a few countries and two reviews have concluded it is equally reliable, though more time consuming to report, and that patients are more likely to directly report drug adverse reactions when they feel their health care provider has not listened to their concerns (Herxheimer et al. 2010; Blenkinsopp et al. 2007). One paper on patient reporting of statin side effects enquired about physician response, and found many patients experienced physician denial of the side effects indicating that doctor reporting may contain ascertainment bias (Golomb et al. 2007).

Patient direct reporting of side effects can also be made online through RxISK.org, a global pharmacovigilance website that has a searchable central database that combines direct patient reports with publicly accessible pharmacovigilance datasets including the FDA and Health Canada. Entering information does double duty – providing a clinical resource by giving an individual assessment of the likelihood of causality when a woman presents with symptoms that may represent a drug side effect using a causality algorithm and automatically searching the databases for similar reports. At the same time this data is recorded in the RxISK searchable dataset and prepopulates forms to be sent to individual country regulators such as the MHRA, FDA, Health Canada and others. This alertness to and recording of the observations of women and those who treat them is essential, especially in the absence of specific and publicly available raw data from clinical trials. Pharmacovigilance data is available disaggregated by sex and clinicians and women contributing to them increase the data to inform prescribing for women,

Direct observation and reporting of the effects of drugs on patients in the community such as this is how the effects of thalidomide were discovered, and thalidomide provides an illustration of why these post-marketing data are so important, beyond the data from RCTs that are sufficient for licensing: Thalidomide was the first drug ever to be pronounced effective on the basis of randomised controlled trial (carried out by a pharmacologist named Louis Lasagna who was later responsible for pushing for the inclusion of randomised controlled trials as a basis for licensing of drugs by the FDA). The serious side effects were not detected.

Conclusions

Women are more likely to be prescribed medicines, and more likely to suffer from their side effects. Most trials are not carried out in the primary care population, where benefits are generally less than in secondary care populations with more severe disease or risk. Many medicines have not been extensively tested on women and most trials that do include women do not report efficacy and safety broken down by gender.

In the primary care environment of prescribing multiple medicines for women based on an uncertain evidence base, the best adjunct to providing the best care for women is clinical observation. New drugs to the market should be prescribed even more cautiously in women than in the general population. Screening and investigation likely to result in possible over-diagnosis and subsequent prescription of a medicine should be avoided. Dosing should start at the lowest possible dose of a medication – lower than the standard recommendation and titrated up according to effect where possible. This requires vigilance in monitoring both beneficial and harmful drug effects and titrating the dose for the individual to levels that may not reflect the 'standard dosing' but may be most appropriate for that individual woman.

Contraceptive status should be recorded with the prescribed medicines and strenuous efforts made to maximise the efficacy of oral and other contraception where it is used. Women should be warned regarding pregnancy on the initiation of any prescribed medicine, and this should be recorded in the medical record. Women using any prescription medicine should be strongly advised to re-consult their primary care doctors regarding medicine use before contemplating pregnancy.

When prescribing in comorbidity, efforts should be made to limit the numbers of medicines to five or less. This decision should be guided by patient priorities for care, potential for benefit and potential for adverse effects and interactions. Women are more vulnerable to polypharmacy and its adverse effects. There is evidence for benefit of trials of stopping or reducing the dose of medicines in this case. Legacy drugs such as SSRIs and bisphosphonates, which have time limited value, should have dates set for active discontinuation when prescribing is first initiated and these should be discussed with the patient. When prescribing multiple medicines in comorbidity, regular planned review and monitored drug pauses should be trialled to determine ongoing need and to uncover any adverse effects. Prescribing effective non pharmacological treatments should be done wherever possible.

Prescribing medicines is one of the most common and dangerous things we do in medical care. Adverse drug effects are among one of the leading causes of death in most countries in the developed world: for example a Swedish population based study indicates they are the seventh most common cause of death in Sweden and hospital based studies in the US suggest they are the fourth to fifth leading cause (Wester et al. 2008; Lazarou et al. 1998) in most countries in the developed world. This fact is largely lost amidst the highlighting of disease epidemics causing death. Around a third of these adverse drug effects are avoidable. To provide good care in prescribing medicines for women we must be careful, and prescribe from a position of comparative safety.

Take Home Messages

- Women are prescribed more medicines than men, and are more susceptible to adverse events, yet there is less evidence for safety and efficacy of prescription medicines in women than in men, and even less in the primary care setting.
- Dose information is usually not differentiated by sex, yet there is evidence that the equivalent dose may differ for women and men – starting at the lowest possible dose and titrating up if necessary is the safest approach in this circumstance.
- In healthy asymptomatic women a high level of certainty for benefit should be required before initiating a long term medicine. Prescribing in the best interests of the individual woman presenting to a primary care prescriber requires awareness of social, commercial and state pressures to prescribe on both prescribers and patients.
- Legacy drugs such as SSRIs, PPIs and bisphosphonates, which have time limited value, should have dates set for active discontinuation when prescribing is first initiated and these should be discussed with the patient.
- Primary care prescribers need to be alert to the fact that prescription drug overdose and abuse are substantial and increasing problems among women.
- When prescribing multiple medicines in chronic comorbidity, regular planned review and monitored drug pauses should be trialled to determine ongoing need and to uncover any adverse effects.
- When prescribing in comorbidity, efforts should be made to limit drugs to 5 or less
- Women taking medicines should be warned regularly regarding pregnancy and any need for tapering medication when stopping, and this should be recorded in the medical record.
- Women using any prescription medicine long term should be provided adequate effective contraception and strongly advised to re-consult before contemplating pregnancy. Contraceptive status should be recorded with the prescribed medicines and strenuous efforts made to maximise the efficacy of oral and other contraception where it is used.
- The safest prescribing is not to use medicines where there are effective non pharmacological treatments.

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Chapter 15
A Medicines Regulatory Perspective on Women's Medicines

June M. Raine and Janet M. Nooney

Introduction

No effective medicine is without risk. Furthermore not all hazards can be known before a medicine is marketed, and knowledge of a medicine's benefits and risks can and does change over time. Medicines regulatory systems exist in most, though not all, countries with the objective of promoting and protecting public health. Regulation generally achieves this objective via a legal framework controlling marketing of medicines according to standards of safety, quality and efficacy; with provision of information for healthcare professionals and patients on the benefits and risks to inform their decisions. Regulatory authorities also decide whether medicines can be safely supplied other than on a doctor's prescription, when the safety profile of a medicine is sufficiently well known.

Since women's lives tend to be more medicalised than other special populations, it is hardly surprising that the evolution of medicines regulation has been closely intertwined with the drug safety issues which have most affected women. Drugs affecting fertility, taken during pregnancy, to help manage the effects of the menopause and to treat cancers of the female reproductive system, all have significant public health as well as societal interest.

At the heart of regulatory decisions on how medicines may be accessed and used lies the challenge of balancing the available evidence on benefits and risks in order to provide up to date information which supports safe use. Robust decisions balancing benefits and risks are even more important when the population in which the medicine is used is essentially healthy or, in the case of pregnancy and

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lactation, when adverse effects may be sustained by the fetus or breast feeding infant.

This chapter aims to give a regulator's perspective on the issues concerning women's medicines which have most shaped and influenced regulation – in particular in the UK and Europe – while linking these with some of the principles which underpin medicines regulation, in the past, present and future. It considers how women, together with those clinicians and researchers concerned with women's health, increasingly can contribute to strengthening regulation, optimising the benefits from medicines and minimising their risks.

Medicines Regulation and Women's Medicines

The Beginning

The tragedy of thalidomide use by pregnant women in Europe, Australia and Japan during the late 1950s and early 1960s was the main precipitant for the introduction of the regulatory controls on marketing medicines which are in place in many countries today. When the link between thalidomide use in pregnancy and the associated limb deformity (phocomelia) in babies was identified (McBride 1961), politicians, healthcare professionals and the public awoke to the fact that anyone could commercialise a medicine without any independent review of its safety. Moreover, the extent of usage of thalidomide in many countries before the link was made with its effect in pregnancy ran to about 10,000 affected pregnancies.

Importantly for medicines regulation, the thalidomide tragedy reinforced the vital nature of having mechanisms to receive the observations of clinicians, to enable early detection of signals of potential drug hazard. This principle remains embedded in the notification systems (such as the Yellow Card scheme in UK and the WHO Programme for International Drug Monitoring) found in medicines regulation today. Nowadays, an unusual pattern of adverse effects associated with a medicine may be identified by notification systems from as few as four or five reports (MHRA 2011), and this means that regulatory action can be taken to protect the public much more quickly.

A second key learning point was that the animal studies conducted with thalidomide prior to marketing were only conducted in rodents, species which turned out to be incapable of identifying the specific type of thalidomide embryopathy in humans (Kim and Scialli 2011). Although debate continues on the precise mechanism by which thalidomide caused teratogenicity in pregnancy (WHO 2014), the nature of regulatory requirements for testing new medicines means that the potential for teratogenicity is thoroughly evaluated prior to marketing.

Thirdly, the belief that thalidomide was very safe compared with other sedatives and hypnotic agents then in use, led to its general availability without medical prescription in the UK and Germany. The lack of any controls on advertising of medicines at that time, together with the promotion's focus on the safety of thalidomide in overdose and in children (see Fig. 15.1) further increased its use

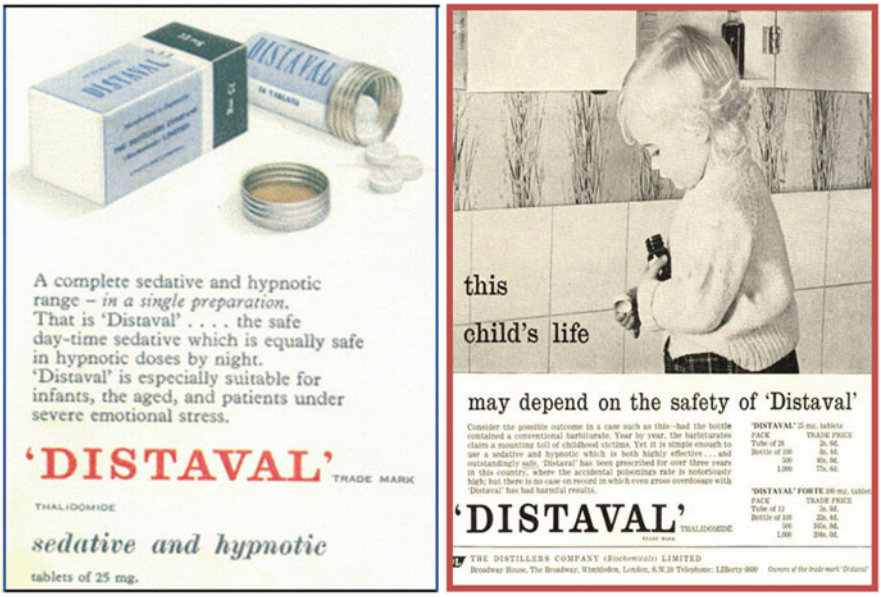


Fig. 15.1 UK advertisements for Thalidomide, c1961

by pregnant women across Europe. As a result, central to the responsibilities of regulators today is control of medicines' advertising to prevent misleading prescribers and the public, even in countries such as the USA and New Zealand where direct advertising of all medicines to consumers is allowed (see Chap. 14).

The legal framework for medicines regulation introduced across Europe in 1965 built on the lessons learnt from thalidomide, and made provision for national decisions to take into account therapeutic practice in different countries. Most countries set up committees or other structures to involve independent expert pharmacologists and specialist healthcare professionals in their licensing and safety decisions. Despite the fact that thalidomide was by no means the only medicines safety issue to have profound implications for women over many years (other examples of these issues are detailed throughout this book), expert advice was sought and regulatory action taken on an ad hoc basis as each issue arose (Armitage and Nooney 2004). It was not until 2006 in the UK that a dedicated standing Expert Advisory Group on medicines for women's health was established specifically to provide expert advice on medicines for women, and even then this has operated on an informal rather than a statutory basis.

Moving Forward: Developing Modern Regulatory Systems

Following the introduction of medicines regulation in Europe, in the 1970s regulators had to get to grips with medicines already in established use, for which in many cases the evidence of efficacy and safety were minimal. For some of these

older products, the process of review was protracted because of "accepted" medical practice and an absence of systematic critical benefit risk review. For example, a medicine for management of menopausal flushing, veralipride, introduced in some EU countries in the 1960s was only removed from the market in 2007 after a review by the European Medicines Agency (EMA) of serious adverse reactions affecting the central nervous system (EMA 2007). The challenges of evaluating older medicines are still apparent in the continued availability of some medicines for which there is a relative absence of robust data. In 2013-14, European reviews of the evidence for use of the short acting beta agonists, including salbutamol, in the management of premature labour (EMA 2013a) and bromocriptine in the suppression of lactation (EMA 2014b) resulted in safety communications and prescribing restrictions across Europe.

As medical practice moves forward, new evidence is generated while medicines are in clinical use. For example, although hormone replacement therapy had been in use for prevention of osteoporosis since the 1980s or earlier, the Women's Health Initiative trial was the first trial actually to demonstrate efficacy in prevention of fractures in post-menopausal women (Rossouw et al. 2002). European pharmaceutical legislation was updated in 2014 to make provision for post-authorisation efficacy studies in specific circumstances. Nonetheless, it seems that more drivers for change are needed. Here the informed voice of women, asking for information on benefits and risks of medicines on which to base their decisions, will be a key lever.

A key theme of medicines regulation over time, which is well illustrated by women's medicines, is that "old" medicines may gain new therapeutic uses. Table 15.1 lists some medicines for which important new uses have been developed in women's health.

Not all of these new uses are licensed (at least in the UK) although evidence of efficacy and safety may be accepted by clinicians. For example, bromocriptine is not licensed for treatment of post-partum cardiomyopathy, but there is some evidence to support its use, including biomarker data (Haghikia et al. 2013; Halkein et al. 2013). For more general information about "off label" use of medicines, see Raine (2014).

Some of the key events in the history of medicines regulation in UK with implications for women's medicines are shown in Fig. 15.2 which illustrates in a schematic picture the timeline from thalidomide onwards.

Table 15.1 Medicines for women which have developed new uses

Drug	Original use	Extended/new use
Thalidomide	Nausea, insomnia	Myeloma
Prostaglandins	Induction of labour	Termination of pregnancy
Levonorgestrel	Oral contraception	Emergency contraception
Minoxidil	Hypertension	Male-pattern alopecia
Bromocriptine	Hyperprolactinaemia	Post-partum cardiomyopathy
Aspirin	Analgesia	Recurrent miscarriage
Hydroxyprogesterone caproate	Threatened miscarriage	Risk of pre-term birth

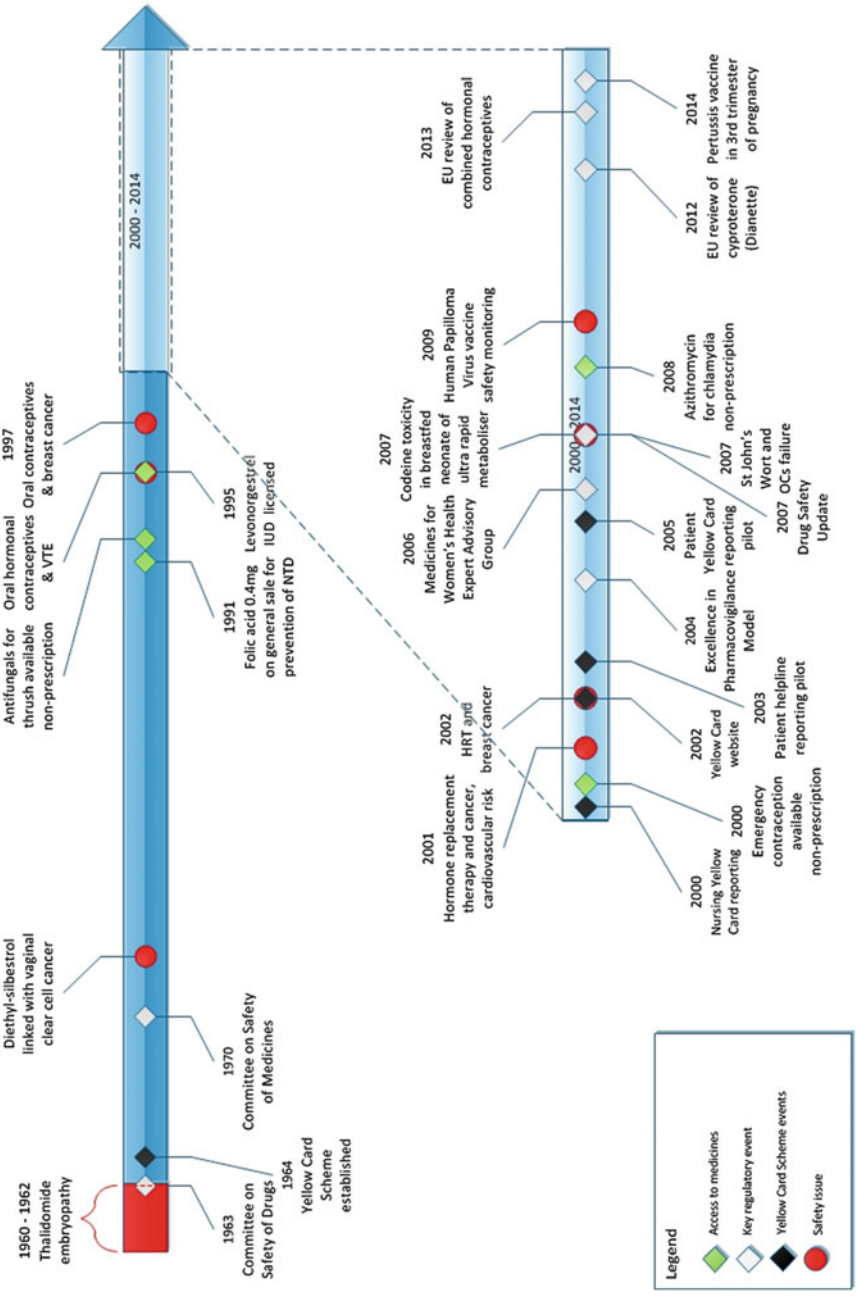


Fig. 15.2 Key events in UK medicines regulation related to women's health

It is often said that regulation follows science, and what is striking from the diagram in Fig. 15.2 is not only the lengthy timescale for regulatory progress, but that concerns about "old" safety issues can re-emerge. In 2013 the European review of combined hormonal contraceptives was undertaken in response to media concerns in several EU member states about the risk of venous thromboembolism (see Chap. 6), which were much the same as the "Pill Scare" in UK in 1995 (see Chaps. 6 and 19). This major review resulted in better information for women and healthcare professionals on the nature of the risk of venous thromboembolism and on approaches to minimise it (EMA 2014b; summary tables including data from this report are included in other chapters). The aphorism that those who fail to learn from the past are condemned to repeat it seems particularly appropriate for women's medicines.

Medicines Regulation Today: An Outline of Working Practice

Regulatory systems for medicines are built around the principle of granting a product licence once there is evidence to show that standards of safety, quality and efficacy have been met and that the balance of benefits and risks can be considered favourable.

What is a Medicine?

To be considered a medicine, a product needs to exert its effects by pharmacological, immunological or metabolic action. Thus levonorgestrel-releasing intrauterine systems (LNG-IUS, Mirena®) are regulated as medicines, since their contraceptive effect arises from the release of levonorgestrel into the uterus, whereas copper intrauterine devices (Cu-IUDs) are regulated as medical devices, since their contraceptive effect is considered to be largely due to their physical presence in the uterus.

Medicines and medical devices are regulated under different legislative systems in Europe and the USA. All medicines are subject to a detailed pre-authorisation review, with specific legal requirements for pre-licensing data, labelling and packaging, information that must be provided to the user, together with restrictions on their advertising. By contrast, medical devices need to conform to safety and performance requirements (CE marking in Europe). The requirements for demonstrating safety and performance are the same for all devices but the degree of intervention by a third party depends on the nature of the medical device and the inherent degree of risk it carries. For example, a breast implant would be subject to the highest degree of scrutiny, but a vaginal speculum would be subject to the

lowest degree of scrutiny. Systems for reporting adverse incidents with devices may also differ.

Developing a New Medicine: Data Requirements

New medicines, whether a new chemical entity or a biological product (e.g. a monoclonal antibody; see Branch and Agranat 2014), are required to be supported by a full programme of non-clinical and clinical tests to establish the main safety profile and efficacy of the product for the intended indication (see next sections) and a pharmaceutical development programme that establishes the suitability of the formulation (quality) of the product. Figure 15.3 shows a schematic outline of the key stages in development of medicines.

The main data requirements for medicines are agreed through the International Conference on Harmonisation (ICH) which was established in 1990 to harmonise the technical requirements across the regulatory regions of Europe, USA and Japan. The ICH issues guidelines on safety, quality, efficacy and multidisciplinary topics (see www.ich.org), which are then adopted into the regulatory provisions of each region for implementation.

'Generic' versions of a medicine may be licensed and marketed after a period of data protection (during which the original manufacturer seeks to maximise the return on investment), provided the generic "copy" is manufactured by methods which do not contravene any remaining patents and is shown to be 'equivalent'. Generic medicines are licensed on the basis that, if they are shown to be bioequivalent in terms of their pharmacokinetic profile, they will have the same safety and efficacy profile as the innovator medicine. However, bioequivalence is not suitable for some products, such as the LNG-IUS, where the product's pharmacological action occurs locally to its site of administration. In such cases, applications for licences for 'generic' medicines need to be supported by clinical data to establish 'therapeutic equivalence'.

If use of an active substance is 'well established' (i.e. medicines which contain it have been on the European market for at least 10 years) published scientific literature can be used to provide evidence of the non-clinical and clinical efficacy and safety of the product. Similarly, products which contain active substances that have been licensed for some time can rely on published data to satisfy some of the data requirements, with new clinical data to address the new features of the product (e.g. a new active ingredient in a combination, new combination of established active ingredients, new formulations, new indications or new patient populations). Thus medicines can evolve over time (see case study in Box 15.1).

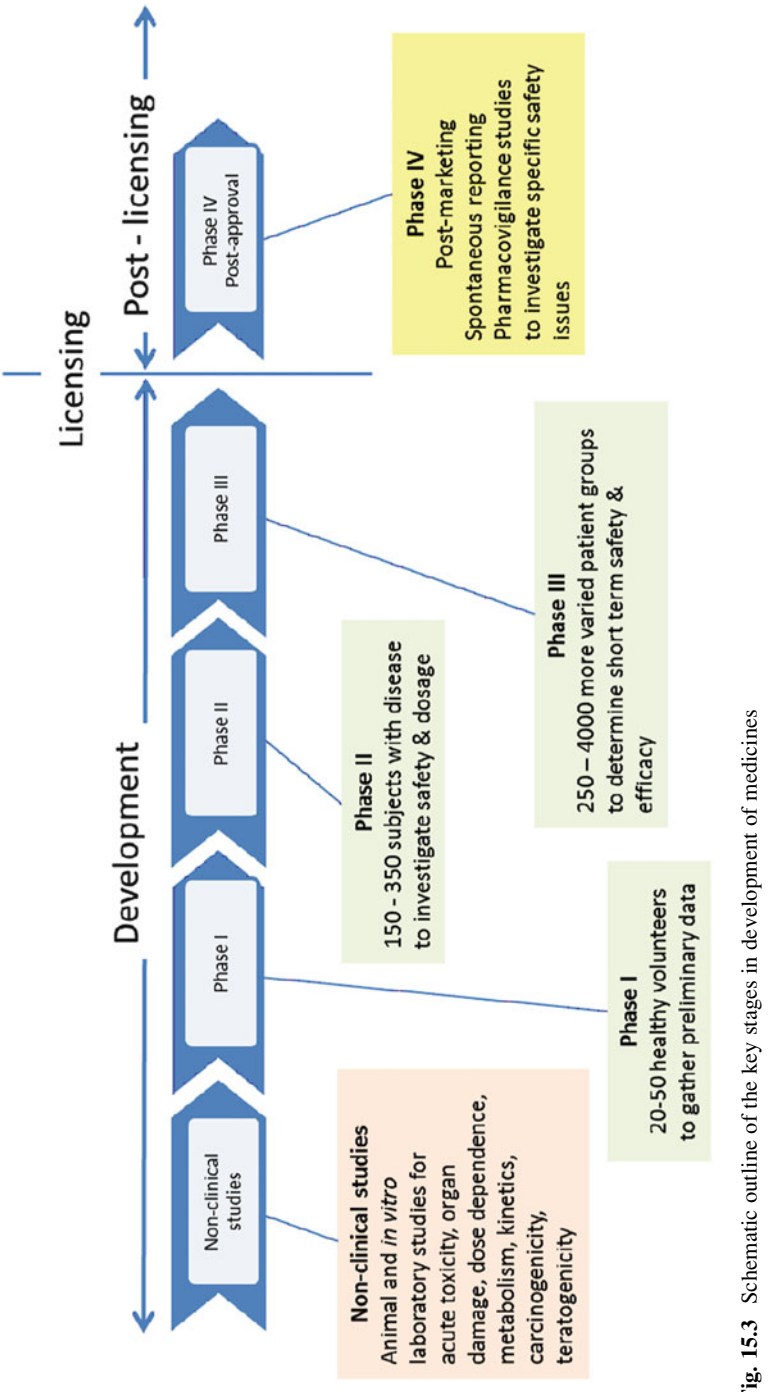


Fig. 15.3 Schematic outline of the key stages in development of medicines

Box 15.1: Case Study: Life Cycle of a Product: Levonorgestrel-Releasing Intrauterine System (LNG-IUS) in the UK

Life cycle of LNG-IUS use		
1995	Mirena® licensed in UK for contraception for 3 years use	**Risk: benefit assessments for different indications:** the extension of indications for LNG-IUS use from contraception to heavy menstrual bleeding (HMB) and endometrial protection as part of HRT, involve different health status and risks, e.g. age, menopausal status, and gynaecological pathology **Duration of use**: level of LNG release over time in situ determines the duration that the product can be used for each of its licensed indications. However physical presence may play a role in the contraceptive effects in later years and LNG release may be more critical for post-menopausal endometrial protection. Extrapolation from data on contraceptive use is not appropriate in this situation, so Mirena is licensed for 5 years contraceptive use, but 4 years HRT use Pharmacoepidemiological approaches have been used to investigate risks of perforation and breast cancer Points to consider when evaluating data are switching indication, menopausal status and duration of use
1998	Use for contraception extended from 3 to 5 years	
2001	Indications extended to include treatment of idiopathic menorrhagia for 5 years use	
2004	Indications extended to include protection from endometrial hyperplasia during oestrogen replacement therapy for 4 years use	
2012	1st generic LNG-IUS (Levosert®) licensed in UK for heavy menstrual bleeding for 3 years use	
2013	Reduced size LNG-IUS (Jaydess®) licensed in UK for contraception for 3 years use	

Non-clinical Testing of New Medicines

Non-clinical testing (i.e. animal and in vitro laboratory studies) of new medicines is designed to elucidate the mechanism of action, gain information on dose and predict likely safety issues in clinical use (Jacobs and Hatfield 2012). Most, though not necessarily all, of the non-clinical testing of a medicine occurs during the early stages of product development.

Pharmacokinetic (PK) and pharmacodynamic (PD) studies aim to establish both the desired (on-target) actions of the active component(s) and the undesired (off-target) actions of the active component(s). These help to identify both the selectivity of the product's actions and potential areas of safety concerns due to the toxicological properties and/or excessive pharmacology of the medicine through the identification of the target organs of toxicity and undesirable pharmacodynamic effects on essential organ systems, (cardiovascular toxicity, CNS toxicity, immunotoxicity, haematological effects etc.). Evaluation of carcinogenic potential (genotoxicity and carcinogenicity), and adverse effects in pregnancy and lactation to the mother and infant (reproductive toxicity and teratogenicity) (ICH 2010) may also be required. The specific studies conducted and their design will vary depending on the individual properties and intended uses of the medicine. For instance, the potential of a new medicine to cause cancer will be explored in non-clinical tests for medicines intended for long-term use.

Assessment of Risks of Medicines During Pregnancy

Unintended effects on offspring are a potential concern with all new medicines. These can occur directly, via in utero exposure, or indirectly, via effects on sperm or oocytes. It is not possible, ethically or logistically, to test for these in humans. Consequently, reproductive toxicology data are needed from animal or in vitro studies on most new medicines (ICH 2010).

Reproductive toxicology studies include:

1. effects on male and female fertility and early embryonic development (up to the stage of implantation in the womb)
2. effects on embryo-fetal development during the first trimester (through to the fusion of the embryonic hard palate)
3. effects on the second and third trimester, on birth (including effects on gestation length and stillbirths) and the neonatal period (through to the age equivalent to that of a 2 year old child).

Which of these studies is needed depends on the product and its intended clinical indication and patient population. For example, use for a male-only indication, or for a paediatric indication in a pre-pubescent population would require some, but not all studies. By contrast, use in women of child bearing potential would require all of the above studies, whereas use by post-menopausal women only would not require any of them.

Even with these studies, potential risks from exposure to a medicine of an unborn child are avoided during development of a new medicine by either excluding women of child-bearing potential, or requiring vigilant contraceptive use. Consequently, safety during pregnancy is largely unknown for most new medicines when they are first launched. Also, these methods are not appropriate for some

medicines aimed specifically at women's health, e.g. contraceptives, or products to support assisted reproduction.

In 2004, the FDA issued draft guidance on studying pharmacokinetics in pregnancy (FDA 2004) and as a result, more information is available on use of some medicines which is unavoidable during pregnancy. Nevertheless, information on use in pregnancy is commonly missing at time of licensing a new product.

Clinical Trials of New Medicines

Early clinical trials for a new medicine focus on establishing the pharmacokinetic properties of the new medicine, that the new medicine has the desired pharmacological action (proof of concept), the likely dose range to achieve the desired effect (dose-finding studies) and, finally, that the action translates into clinical usefulness (proof of efficacy). The latter trials (known as therapeutic confirmatory trials) also establish the main safety profile of the product, so that the benefit-risk balance may be assessed. As a general rule, for medicines to be used long term, around 100 subjects are studied for a year, and around a thousand subjects are included in studies overall (Duijnhoven et al. 2013).

To pass regulatory scrutiny, clinical trials must be conducted ethically, with due regard to patient safety (i.e. in accordance with Good Clinical Practice (GCP) standards as set out in ICH guideline E6 (ICH 1996)). Efficacy trials are expected to be comparative trials, in which comparison to a placebo or to an established treatment (or both) is blinded. Clinically relevant surrogate endpoints can be acceptable to establish efficacy, however clinical relevance may change as medical knowledge advances (e.g. bone mineral density is no longer acceptable in the EU as a surrogate endpoint for fracture reduction in patients with osteoporosis (EMA 2006)). In addition, key elements of the trial (e.g. primary endpoint(s) and their size, statistical analysis, data handling etc.) are required to be defined prior to the start, in the trial protocol.

Whilst efficacy expectations can be defined in advance (and measures of efficacy are usually the primary endpoints/outcomes for most clinical trials), safety issues are usually harder to predict. Safety is carefully monitored throughout clinical trials by a combination of asking about a subject's well-being at regular intervals during the trial and monitoring of clinical parameters. Although the full safety data are often not included in papers published in the scientific literature, regulatory submissions include a full report (the final study report) of a trial which details the side effects of the treatment compared with those reported for placebo or the comparator treatment.

Specific anticipated side effects may be investigated as main outcomes if these have been identified earlier in the development programme, or due to experience with previously licensed medicines in the same class. For example, following observation of an increased risk of endometrial cancer with unopposed estrogens in post-menopausal women in the 1970s, endometrial safety needs to be actively investigated for new combined HRT products (EMA 1997).

Regulatory Assessment and Approval of New Medicines

Regulatory agencies (operating within government departments or in linked institutions) conduct pre-licensing assessments of data submitted from companies in order to grant approval of a product for use ("marketing") in that regulatory authority's jurisdiction (e.g. country or EU-wide). In addition to the data outlined above, in the EU, the applicant is also required to submit a summary of the safety issues, with proposals for investigating these further. Strategies for minimising risks, as appropriate, also have to be provided in *Risk Management Plans* (see below) for all products in the EU and for selected/high risk products in the USA. The *Product Information* (see below) and the packaging supplied with the product are both means of risk minimisation (e.g. by contraindicating use in particular circumstances; use of child-resistant packaging etc.). Consequently, proposed product information and packaging also needs to be submitted prior to licensing.

Within each regulatory agency, teams of toxicologists, pharmacists, physicians and statisticians rigorously review the data and produce a critical appraisal of benefits and risks. Regulators can also request further information from the applicant, as appropriate. In addition to the assessment performed by the regulator, expert opinion will usually be sought from advisory committees and sub-committees for specific areas (e.g. women's health) before the product is approved (or declined).

Risk Management Plans

From 2005, EU legal requirements included the provision of *Risk Management Plans* (RMPs) for newly licensed products. The RMP provides a summary of the safety issues for the product and specifies the important gaps in knowledge at the time of licensing (Blackburn and Raine 2014). For example, information on use in pregnancy is a common feature of RMPs as an area of important missing information. Proposals for further investigations may include, for example, long-term follow-up via disease or pregnancy registries or studies on specific clinical endpoints.

Product Information

The term "labelling" is often used to describe a medicine's licensed indication, posology, contraindications, warnings, precautions and side effects. In the EU, this information is captured in the *Summary of Product Characteristics* (SmPC) for prescribers and the *package leaflet* for patients.

The details in the product information and package leaflet are based initially on the results of the pre-licensing studies, but are updated as additional information

becomes available (e.g. interactions with other new medicines). The product information thus sets the 'terms of the licence' and any use of the product outside of these terms constitutes 'off-label' use. In such cases, the responsibility for the safety, quality and efficacy of the product is considered to be with the prescriber. In the EU, the SmPC also provides the basis for advertising and promotion of the product, as this must be consistent with it. Thus companies are not allowed to promote uses (i.e. further indications and/or patient populations) that are not included in the SmPC; and these would require further clinical trials for their addition to the product licence.

The *package leaflet* plays an important role in conveying key information on the risks of that medicine and is intended both to support informed decision making and, increasingly, to support the use of the medicines to optimise benefit and minimise risks. This is particularly important for 'over the counter' medicines used without medical input (i.e. diagnosis or prescription).

Post Market Surveillance and Women's Medicines

Clinical trials alone cannot be used to fully characterise all potential risks associated with a medicine. Some side effects only become apparent when medicines are used by large numbers of patients (because of the rarity of the side effect), for long durations (due to the slow onset of the side effect) or by wider ranges of patients than are typically included in clinical trials. In 'real-world' use, patients are more likely to have other medical conditions, to use other medicines concomitantly, to have differences in their genetic make-up, underlying disease or lifestyle, or to be younger or older than those included in trials.

Regulatory approaches to post market surveillance have evolved over time largely in response to some major public health challenges, many of which have been linked to medicines for women's health (see Fig. 15.2 for some of the key examples). These safety issues have driven a shift from a reactive approach based on individual case reports (known as "spontaneous" reports) from healthcare professionals, to more proactive approaches. This shift has been facilitated by conceptual work based on an appreciation of what more robust forms of evidence are available (moving up the evidence hierarchy) coupled with proactive generation of further information to fill the gaps in knowledge which inevitably exist when a medicine is licensed (Waller and Evans 2003; Rawlins 2008).

The current methodology which regulators use to monitor and review the safety of medicines in clinical use generally relies on concurrent use of different data sources, some of which are outlined below. Regulators operate using a framework of legally based tools, ranging from requirements on pharmaceutical companies to report adverse events, to post-authorisation safety studies sometimes within risk management plans. Regulators also conduct formal benefit risk reviews usually driven by significant new safety data.

Adverse Reaction Reports: Spontaneous Reporting Schemes

Individual case reports of suspected adverse drug reactions which are sent to regulators spontaneously by health professionals, pharmaceutical companies and patients are used to detect "signals" and generate hypotheses of a link between a medicine and an adverse effect. The UK's Yellow Card Scheme is an example of a spontaneous reporting system where reporting forms (available widely in paper form, in formularies and electronically via the MHRA website) may be completed by healthcare professionals, patients and carers with information on the suspected adverse drug reaction. Similar schemes are operated in most other countries. The Yellow Card forms collect details of the reporter, patient identifier, and suspect medicine (Foy et al. 2014). The information is regularly screened by teams of scientists, pharmacists and physicians, who may need to contact reporters for additional medical information about the cases. Good quality reports include information on relevant medical history (or its absence) and concomitant medications. This is facilitated by well-designed forms, for example to capture information on an adverse effect in a child following drug exposure during pregnancy (MHRA 2014a, in press). Information on the adverse reaction should also include, if appropriate, information on dechallenge (outcome when the medicine is withdrawn) and rechallenge (outcome when the medicine is re-administered at the same dose).

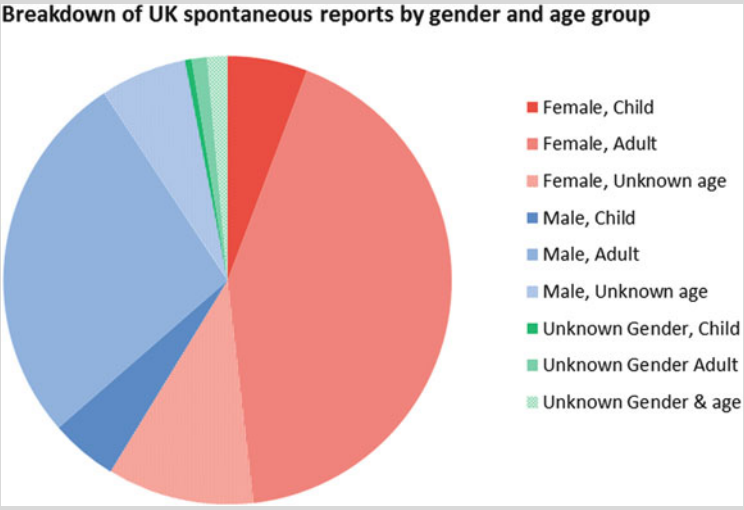
The spontaneous reporting "early warning" function remains the mainstay of pharmacovigilance world-wide. However, its role has been the subject of increasing debate as more sophisticated tools and larger databases have become available to identify reporting trends quickly. The limitations of spontaneous reporting include under-reporting (it is generally believed that only around 10 % of suspected adverse drug reactions are ever reported), biases in reporting (due to media interest in a medicine or the natural focus on newly introduced medicines), and importantly, the lack of a "denominator" (the number of patients who have received the medicine). Information on the number of patients exposed is needed in order to assess the frequency of an adverse reaction. This can be challenging to assess since, although prescription data may be readily accessible, these alone do not reflect whether prescriptions have been dispensed and/or the medicine actually taken. In addition, in some instances, it is necessary to know the background rates of events in the treated population in order to calculate the risk attributable to the medicine.

Most spontaneous reporting schemes make provision for reports of adverse reactions to be made by patients themselves. Initial concerns by some EU regulators, that reports from patients would lack sufficient detail to be scientifically valid, have proved to be unfounded. Research has shown that patient reports are of a similar level of seriousness as healthcare professional reports. Interestingly, substantially more reports are received for women than for men for both healthcare professional and patient reports (Box 15.2). A comprehensive review of patient reporting following its introduction in the UK (Avery et al. 2011; Hazell et al. 2013) demonstrated that patient reports may add valuable information, particularly on the

impact of a medicine on quality of life. For example, a signal of hair loss associated with a combined hormonal contraceptive containing drospirenone, was detected from Yellow Card reports where the first report was from a patient. After confirmation, this resulted in updates to the product information for health professionals and patients.

Box 15.2: More Adverse Drug Reports Are Received for Women than Men

Review of all the data held in the Yellow Card database (approximately 750,000 UK reports in August 2014 accrued since 1964) has shown that 59 % reports of adverse drug reactions are for females compared with 38 % for males (in 3 % gender was not known). The breakdown of Yellow Cards according to gender and age group is shown in the figure below:



When evaluating only patient reports in the Yellow Card database, the proportion of ADRs reported for females is 64 %, compared with 35 % for males (with 1 % unknown gender) – an even more striking difference than for all reports. It is of interest to note that reports relating to pregnancy, puerperium and perinatal conditions amount to 1.2 % of all female Yellow Card reports, with congenital, familial and genetic disorders amounting to 0.4 % of reactions. These categories of ADRs alone therefore do not account for the differences between reports of ADRs for males and females. It should be emphasised again that great caution should be exercised in drawing conclusions from dynamic spontaneous data, whose function is detection of signals of new or changing drug safety issues.

Intensive Monitoring of New Medicines

For new medicines, there is more to learn to establish whether the safety profile reflects that seen in the clinical trials, and new knowledge to gain from 'real life' use. There is an added urgency when this involves rapid uptake of a new medicine into clinical practice. In the EU since 2013 an intensive monitoring system has been in place, using a 'Black Triangle' to identify those medicines for which all adverse reactions should be reported. These include new drugs, biological medicines and those for which specific risk management measures are in place. The 'Black Triangle' is a simple way to highlight to health professionals and patients where reports are especially encouraged for particular medicines. Signal detection is carried out more frequently on EU black triangle medicines compared with non-black triangle.

As discussed above, whilst spontaneous reporting schemes are very valuable, their use is limited because of the lack of information on patient exposure. Exposure data may be collected through prescription event monitoring programmes, such as operated by the Drug Safety Research Unit in UK (Layton et al. 2011) and formerly by the Intensive Medicines Monitoring Programme in New Zealand (Clark and Harrison-Woolrych 2006, Harrison-Woolrych, 2014). These active surveillance schemes have performed nationwide prospective cohort studies which have generated valuable safety evidence for many new medicines. The IMMP also conducted several studies of IUDs.

Additional Pharmacoepidemiological Approaches

Appreciation of the limitations of spontaneous reporting has led to regulators adopting additional pharmacoepidemiological tools and approaches. The enormous value of studying medicines in large populations has been demonstrated par excellence in relation to hormone replacement therapy. Large studies such as the Women's Health Initiative in US (Rossouw et al. 2002) and the Million Women Study in UK (Beral et al. 2003) have characterised and quantified important risks, enabling evidence-based decisions with resulting public health benefit. These studies enabled quantification of important risks associated with HRT in real world use and supported regulatory action in Europe (Armitage and Nooney 2004; MHRA 2007a, b, see Chap. 11). Nonetheless, there remain important areas for further research including the risks of HRT in women with premature menopause.

Regulatory data sources for monitoring benefit and risk in clinical use include health record databases such as the UK's Clinical Practice Research Datalink and for particular products or populations, formal registries. Pregnancy registries are of special importance for investigating possible links between medicines and congenital abnormalities. An example of a novel approach to networking registries was a Scandinavian study examining the risk of cardiac defects with SSRI antidepressants (Kieler et al. 2012).

Identifying the risks of medicines in large populations of users requires not only well-designed and robust methodologies, but prompt evaluation, especially when scientific studies reach the public domain rapidly via 24 h media coverage and internet access. This is particularly true for vaccines, where the success of mass immunisation depends on public confidence in safety. The availability in 2007 of Human Papilloma Virus (HPV) vaccines for teenage girls to prevent cancer of the cervix (see Chap. 9) required a step-change in regulatory surveillance approaches. As a result of careful planning and tailored statistical methods, new signals for HPV vaccines were assessed in real-time in the context of age-appropriate rates of expected events in this population. This approach demonstrated that the rate of reporting of chronic fatigue syndrome following vaccination was what would have been expected in this population of adolescent girls (Donegan et al. 2013). This enabled the signal to be refuted and the media scare on chronic fatigue syndrome in UK to be managed, thus enabling continuation of the vaccination programme.

Personalised Medicines for Women

The science of pharmacogenomics has taken an increasingly prominent role in regulation, supporting better targeting of medicines to the population most likely to benefit. A good example of this is trastuzumab (Herceptin®) and breast cancer, where Herceptin should only be used when the tumour has been demonstrated to over-express the HER2 protein – which is the case in about a quarter of breast cancers (EMA 2014c). Importantly, pharmacogenomics has increasingly contributed to risk minimisation strategies, by enabling exclusion of the population of patients most at risk of adverse reactions. Regulatory action may range from mandatory testing to raising awareness in safety bulletins. For instance, robust evidence from randomised clinical trial data of the genetic basis for abacavir and hypersensitivity reactions supported genetic testing (Mallal et al. 2008). By contrast, a single case report of codeine-related morphine toxicity in the breastfed infant of an ultra-rapid metaboliser (Koren et al. 2006), resulted in regulatory action to raise awareness of a potential risk of codeine as a post-partum analgesic. Growing experience in pharmacogenomics in pharmacovigilance has supported the production of EU regulatory guidance (EMA 2014d).

Continuous Monitoring of Benefits and Risks

One of the most important regulatory roles is continuously monitoring the benefits and risks of medicines in post-marketing clinical use, and assessing the impact of new information. A standard regulatory approach is to require the company to submit a regular report (known as a periodic safety update report or PSUR) at

particular time points during the post-marketing period, generally every 6 months during the first 2 years on the market, then annually up to 5 years. Since 2012 in EU the requirements on companies have been specifically extended to data on the benefit of the medicine, so that PSURs have become periodic benefit risk evaluation reports. This has supported a shift in the regulatory approach from progressive addition of safety information to product labelling, to permitting an overall assessment of benefit risk balance, with the potential for major regulatory action. An example of a benefit risk assessment conducted in the context of a periodic safety update report was the review of strontium ranelate and increased risk of cardiovascular events, with the result that the use was restricted in the EU by excluding patients at high risk of cardiovascular disorders (EMA 2013b).

Regulatory Communications on Women's Medicines

The regulatory approach to communicating information about medicines for healthcare professional and women has traditionally depended on statutory labelling – in the EU via the SmPC and package leaflet. The growing expectation of women to be involved in decisions concerning their health has encouraged a fundamental change in delivering comprehensible information on risk. Many aspects of risk communication relating to medicines for women are covered in Chaps. 18 and 19 of this book.

For regulators, communicating the availability of improved and updated information in a timely way is a prevailing challenge. There is now evidence to show that Direct Healthcare Professional Letters (letters containing drug safety information sent by marketing authorisation holders at the request of regulators) have often failed to make the desired impact (Plening et al. 2012). Information for prescribers (which patients may now access via the internet) and patient information leaflets remain long and complex. An EU requirement for companies to test leaflets with patients has supported a drive for improved user-friendliness (Raynor et al. 2007, Raynor 2013). The European Commission has undertaken to take further steps to address the shortcomings of product information (MHRA 2013).

A climate of increased transparency has resulted in regulators making available public assessment reports, which provide more details on regulatory decision making for a number of issues, including those affecting women's health, for example the reviews of HRT (MHRA 2007a) and HPV vaccine safety (MHRA 2012).

Drug safety bulletins tailored to national needs and therapeutic context may have greater impact since these can provide useful prescribing advice and the supporting evidence. The impact may be enhanced by linking with other publications and the media. In UK, patient versions of the Drug Safety Update Bulletin have been well received, with one patient version for statins being the MHRA's most viewed web-page for the month after publication.

Advertising of women's medicines is subject to regulatory controls, as for all medicines. In the EU, as in many jurisdictions, this relies on a system of self-regulation by the industry. However, there are particular aspects relating to use of

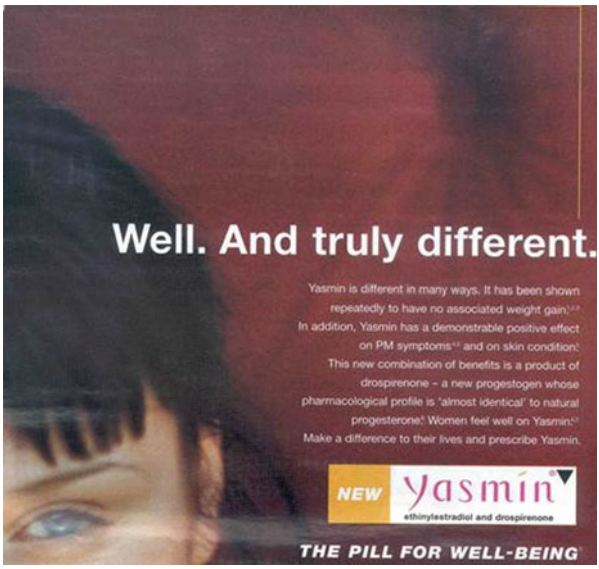


Fig. 15.4 Advertisement for Yasmin, c 2002

medicines in healthy people and where a therapeutic area contains many options, which merit a more interventionist regulatory approach. For example, claims made for effects of particular combined hormonal contraceptives on wellbeing in healthy women withdrawn after regulatory review, illustrate why proactive scrutiny is necessary to protect public health (see Fig. 15.4).

Regulatory Decisions on Access to Women's Medicines in the UK

As the safety profile of a medicine becomes well understood, and its place in therapeutics established, regulators keep under review the level of medical supervision needed to ensure safe use. The level of supervision may vary from restriction to specialist prescription (for example, isotretinoin for resistant acne, where the known teratogenicity merits a robust pregnancy prevention plan) to pharmacy availability, where the pharmacist's knowledge and skills ensure appropriate purchase (such as for orlistat for weight reduction in individuals of BMI equal to or greater than 28 kg/m^2 in combination with a low calorie diet) and to general retail availability for analgesics for dysmenorrhoea.

The public health considerations of widening availability of medicines are particularly pertinent when prompt access and administration may impact on efficacy. In the UK, one of the earliest reclassifications from prescription-only to pharmacy availability in 1992 was for topical imidazole antifungals for vaginal candidiasis. The regulatory decision was that, following medical diagnosis, a

woman with recurrent infection who recognises the symptoms may safely self-manage. Other examples where early access is important are tranexamic acid for menorrhagia (reclassified in the UK in 2007) and emergency contraception (EC) (reclassified in the UK in 2000). For levonorgestrel EC, although the licence permits use up to 72 h after unprotected intercourse, much of the evidence suggests that efficacy in preventing pregnancy is optimal the sooner it is taken (see Chap. 7).

The potential impact on public health was also a consideration when azithromycin was reclassified from prescription-only to pharmacy availability in UK in 2007 for the treatment of sexually transmitted chlamydia infection. The risk of antimicrobial resistance was considered small in light of the single dose administration. Given the potential for long-term sequelae from chlamydia infection leading to infertility, the change of legal classification therefore made provision for anonymous contact tracing and treatment.

Over time there have been calls by some healthcare professionals for non-prescription access to combined hormonal contraceptives for regular use, on the grounds that this would remove barriers to initiation and maintenance of safe and effective contraception (Grossman 2008). Given their efficacy in pregnancy prevention balanced against the extensive record of safety in use, and the widespread introduction of local systems for access via suitably skilled non-medical personnel, there seems to be a reasonable basis for this to be seriously considered by regulators. An important barrier to such a step would appear to be a lack of evidence that the deregulation would promote public health in the way predicted.

Complementary Therapies and Women's Health

The increasing willingness of women to take a role in their own healthcare has not surprisingly resulted in a growing uptake of complementary therapies: herbal, homeopathic and other traditional therapies such as Ayurveda and Chinese medicines. Herbal medicines used by women are discussed in Chap. 13 of this book. A survey of the UK public in 2009 found that usage of herbal medicines is higher among women and among those from higher social groups AB (higher or intermediate managerial, administrative or professional occupations), compared with men and those in lower social groups D and E (semi and unskilled manual workers and those on a state pension) (MHRA 2009a).

Regulatory approaches to herbal medicines in the EU have been based on demonstration of quality and safety in the context of evidence of traditional use. Safety surveillance nonetheless needs to be conducted for complementary medicines to the same standard of public health protection. This was shown in relation to the interactions of St John's Wort (widely used in the UK for mild depression) with a range of important medicines including oral contraceptives (Henderson et al. 2002). Reports of contraceptive failure were received in the UK from 2000 and continue to be received, both for concomitant use with oral contraceptives and with contraceptive implants, despite repeated regulatory communications (MHRA 2014b).

A public assumption that 'natural' means safe was abruptly, if temporarily, dispelled in 1999 when the effects of a Chinese herb, aristolochia, taken for skin conditions and known to have carcinogenic potential, was linked with renal failure in case reports (Lord et al. 1999). This herbal remedy has now been banned in most countries. Despite this, the assumption amongst the public that 'natural' means safe seems to persist. However, as detailed in Chap. 13, Black Cohosh, a product commonly used to relieve menopausal symptoms, is known to cause abnormal liver function, jaundice and hepatitis, and herbal products for the treatment of eczema have been found to contain corticosteroids (MHRA 2009b). In addition, Chinese herbal medicines have been reported to have effects on fertility, including reversible ovarian failure (Edmonds and Montgomery 2003), which should be borne in mind when investigating premature menopause.

Importantly, whilst 67 % of respondents in the UK survey quoted above who used herbal medicines in the last 2 years agreed that it was necessary to tell your GP if you are taking herbal medicine, 22 % of this group felt that telling their GP was not necessary. A key message for healthcare professionals is therefore to always to ask about self-treatment with any natural or herbal remedies.

Special Regulatory Challenges for Women's Medicines

There are a number of special regulatory challenges relating to women's medicines.

Medicines in Pregnancy

It is widely recognised that a key priority for regulators is to strengthen the regulatory provisions for monitoring drug safety in pregnancy. Existing registries have shown capability particularly in the area of anti-epileptics, and collaborative initiatives such as EuroCAT have facilitated identification of teratogenic exposures (Dolk 2005). In the 50th anniversary year of medicines regulation in Europe the time is right to refocus on improving detection of medicine harms in pregnancy. This is particularly important for women who need medicines for long-term conditions, such as multiple sclerosis, epilepsy, rheumatoid arthritis and psychiatric illness, which persist during pregnancy. Conversely, better information is needed on the safety of medicines to manage conditions which occur during pregnancy and the puerperium.

Use of Medicines by Healthy Women

For many medicines, the assessment of benefits and risks relate to use by healthy women wishing to manage or control normal aspects of their reproductive life. In such circumstances, medicines need to be very safe; their risks appropriately quantified and clearly communicated; and risk minimisation steps need to be supported by good evidence of their effectiveness. Such evidence must be comprehensibly expressed to support joint decision-making between women and their advisers. Moreover, the growing willingness by regulators to involve women in decisions about benefits and risks needs to be supported.

Quantifying Benefit Versus Risk

When medicines are used prophylactically and especially in the long term, regulation needs better tools to quantify benefit:risk, including in the context of duration of exposure. A step forward in communicating risk was achieved in the UK in 2002, relating to quantifying potential harms associated with long-term use of HRT, which expressed the risks in terms of baseline and excess risk over a period of use (MHRA 2007b). The main challenge now is in expressing benefit as well as risk. The work of the European Innovative Medicines Initiative PROTECT consortium has made important progress in expressing risk and benefit not only quantitatively but using visual and graphic tools (Mt-Isa et al. 2014).

Impact of Regulation of Women's Medicines

To date, the impact of regulation on women's medicines has not been assessed systematically. Questions such as *"how are regulatory decisions affecting women using medicines in real life*?" need to be evaluated in order to maintain confidence that the systems for identification, investigation, management, communication and monitoring of risk in the context of benefit are robust and demonstrably promote and protect public health. There have been some efforts to evaluate the impact of widening access to emergency contraception without prescription, both in UK (Marston et al. 2005), and internationally (Raymond et al. 2007). A good example of outcomes measurement was the collaboration between regulators and public health scientists following the introduction in the UK of pertussis vaccine in the third trimester of pregnancy to tackle an emerging problem of whooping cough in infants. Using robust regulatory approaches to monitor the main safety questions of interest, including premature labour and stillbirth, it was possible to demonstrate a favourable benefit risk of the vaccine and a sharp decline in neonatal infection and deaths followed introduction of pertussis vaccination in pregnancy (Amirthalingam et al. 2014; Donegan et al. 2014).

Future Regulatory Prospects for Women's Medicines

The discipline of regulation has been profoundly shaped and influenced by women's medicines, and there seems no reason to suppose that this will not continue to be the case in the future. The dynamic evaluation of benefits and risks of medicines in women together with prompt and proportionate regulatory action, are essential for public health promotion and protection. The understanding by healthcare professionals and women of the working of regulation and how they can interact with regulation effectively is of fundamental importance to optimise the benefits of the medicines they use and to minimise risks.

Involvement of Women in Regulatory Decisions

Regulatory efforts to incorporate women's perspectives into decision-making have progressed but need to go further. The European review of combined hormonal contraceptives undertaken in 2013 gained insight into expression of the risk of venous thromboembolism associated with combined hormonal contraceptives from the involvement of patient and consumer groups. The routine involvement of women in regulatory decisions which affect their health is the logical next step.

Improving Access to Innovative Medicines

Finally, the recognition that regulatory demands for new medicines can inadvertently hinder the introduction of new medicines, has lead to new approaches to advance the licensing of innovative new medicines. These include the *Breakthrough Medicines* programme in USA, *Adaptive Licensing* scheme in the EU and the *Early Access to Medicines* scheme in the UK. These schemes are all at an early stage, but have the potential not only to facilitate access to new treatments for patients with unmet medical need, but also to change the face of medicines' regulation.

Take Home Messages

- Regulators serve public health by taking evidence-based actions to optimize benefit:risk and providing up to date information to support decisions by healthcare professionals and women on medicines taking.
- Benefit:risk evaluations take into account clinical use. As no medicine is without risk, benefits of medicines used by healthy people are must be clearly favourable and risks minimal.

(continued)

- Evidence on benefit:risk of medicines in "special" populations, in particular in pregnancy, is limited prior to authorisation.
- Healthcare professionals and women can play an important part by reporting suspected adverse drug reactions to regulatory authorities without delay – every suspected adverse reaction report can make a difference.
- Healthcare professionals should always ask about self medication including any complementary therapies.
- As regulatory systems develop in the future, it is hoped that there will be routine involvement of women in regulatory decisions which affect their health.

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Chapter 16
Political and Religious Perspectives on Managing the Risks and Benefits of Women's Medicines

Brian Edwards and Veronika Valdova

Introduction

Pharmacovigilance systems for regulating and controlling safety of medicines do not differentiate between those exclusively for women and those for men. And yet, the societal circumstances for certain women's medicines – especially where such medicines affect reproduction – are so obviously different from other medicines, we wished to examine what evidence exists to define how religion, cultural traditions, politics, economics, history and a society's view of science impacts the safe use of medicines by women. This is a large and complex subject which cannot be covered completely in this one chapter, but we aim to give an overview and to draw on specific examples from around the world to illustrate some of the many interesting issues.

Historic Development of Reproductive Rights for Women

Avoiding pregnancy has been a serious concern for women and men for many years. For example, prior to the nineteenth century, information about human reproduction was widely available to the American public, even though we do not know how well it was understood. However, it was the efforts of Anthony

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Comstock that drove the manufacture and distribution of a wide range of contraceptive devices underground, due to the 1873 passage of the so-called Comstock Act which outlawed this merchandise in the broad category of 'obscenities' (Berger 2010).

As Vancaillie explained, cultural, religious, and political context makes all the difference in reproduction-related decision-making (Vancaillie 2013). Control over one's own fertility has shifted from secular and religious authorities to the individual. Over the last 50 years 'Reproductive Rights', which refer to the right to decide freely and responsibly the number and spacing of children, and to have the information, education and means to do so, have received increased prominence. They were first recognized as a human right at the International Conference on Human Rights in Teheran in 1968 (United Nations 1968). With reference to Paragraph 7.12 of this document, it states that the right to reproductive health now includes the concept that individuals have the right to attain the highest standard of sexual and reproductive health and to make reproductive choices free from coercion. The success of population education and family planning programs in a variety of settings has shown that informed free choice is essential to the long-term success of family planning programs. Any form of coercion has no part to play.

Indeed, the origin of the right to decide on one's reproductive activity and coercion-free decision-making with regards to reproductive matters dates back to Article 2 of the Convention on the Prevention and Punishment of the Crime of Genocide (Office of the UN Special Adviser on the Prevention of Genocide (OSAPG) 1948) which defines genocide as 'any of the following acts committed with intent to destroy, in whole or in part, a national, ethnic, racial or religious group, including imposing measures intended to prevent births within the group' (Office of the UN Special Adviser on the Prevention of Genocide (OSAPG) 1948). As we will see later, discussions about controlling reproduction can quickly be linked to one of the most sensitive issues in human existence.

The 1994 International Conference on Population and Development (ICPD) in Cairo was another milestone in the history of women's rights (UNFPA 1994; International Conference on Population and Development – ICPD – Programme of Action 1994). ICPD delegates reached a consensus that the equality and empowerment of women was a global priority for stabilizing population growth. A woman's ability to access reproductive health and rights is central both to this empowerment and is key to sustainable development.

A total of 179 governments signed up to the ICPD Program of Action which set out to:

- Provide universal access to family planning and sexual and reproductive health services and reproductive rights;
- Deliver gender equality, empowerment of women and equal access to education for girls;
- Address the individual, social and economic impact of urbanization and migration;
- Support sustainable development and address environmental issues associated with population changes.

Following on, it was hardly surprising that women's health was one of the UN Millennium Development Goals (MDG) with a target of 75 % reduction in maternal mortality by 2015 (Oppenheim 2014; UN Department of Public Information 2008).

The 1994 ICPD concluded that the availability of safer methods of modern contraception permitted greater opportunities for individual choices in reproduction matters throughout the world. As of 1994, about 55 % of couples in developing regions were using some method of family planning, a fivefold increase since the 1960s. Although fertility rates in developing world dropped in the same period from six to seven children per woman to three to four, at least 350 million couples worldwide still lacked access to family planning methods. These numbers did not include sexually active unmarried individuals (UNFPA 1994, point 7.13).

Surveys from more than 60 developing countries indicate that more than 100 million women who are not currently using a contraceptive method want to delay the birth of their next child or to stop childbearing altogether (The United Nations Population Fund 1999). Each year during the decade that followed, the number of couples in their reproductive years will increase by about 18 million. Thus the global impact of actions taken in Western countries concerning women's medicines such as contraception must always be considered (UNFPA 1994).

In an ICPD report in 2010, it was stated that use of any contraceptive methods among currently married women aged 15–49 years was around 75 % in the 15 of the EU Member States and Non-EU advanced countries. Similar high levels were observed in the Russian Federation (80 %) and Turkey (73 %). Low levels were seen in the Balkans, the Caucasus and Central Asia, except Uzbekistan where the proportion was 65 %. In most of these countries, there was a decline in contraceptive use prevalence from 2000 to 2010 (Unmet need for family planning is defined as the proportion of women who have regular sexual intercourse, do not want to get pregnant, and do not use contraceptive methods. The value of this indicator was at about 2–3 % in France (2004/2005), 10–15 % in about a dozen other European countries, Armenia and Georgia, 23 % in Azerbaijan (2006), and 30 % in Bulgaria (Wittich and Philipov 2013, Chapter 1 Section C).

The ICPD Program of Action focuses on population policies at a macro level and addresses demographic situations to achieve sustainable growth and development. Unlike the outcomes of previous World Population Conferences, the Program of Action of the ICPD aims for a holistic approach to reproductive health in context with socio-economic and environmental factors, not just the absence of disease. According to the 2010 ICPD report, fertility changes in Europe and especially countries in transition, encompass several important trends: significant increase in childlessness, drop in overall birth rate, proliferation of non-marital cohabitation, and increase of births out of wedlock (Wittich and Philipov 2013, Chapter 1 Section A). Increase in life-expectancy further worsens the trend of population aging. The ICPD Program of Action clearly linked individual reproductive health to societal and environmental factors, namely delaying of important life decisions such as childbearing because of increased economic uncertainty due to factors such as globalization (Wittich and Philipov 2013).

Against this back drop emphasizing the global importance of contraception for future sustainability of society, are new ways of thinking about health and the place of medicines. The Commission on Social Determinants of Health (CSDH) was set up by the World Health Organization (WHO) to better understand the complexity of health (WHO 2012). They were tasked with summarizing the evidence on how the structure of societies, through myriad social interactions, norms and institutions, are affecting population health, and what governments and public health systems can do about it. Having health framed as a social phenomenon places it more broadly as a topic of social justice. Consequently, health equity (described by the absence of unfair and avoidable or remediable differences in health among social groups) becomes a guiding criterion or principle, and influences the use of all medicines, in particular medicines for the well-woman. Understanding health from a socio-cultural perspective is now as important as traditional science.

Medicalization of Women's Sexuality

Understanding socio-political factors is linked to the phenomenon of 'medicalization' which is the process of defining an increasing number of life's problems as medical problems. This can impact what is regarded as 'benefit'. Some medicines developed for women are a rich area for medicalization because of the difficulty we have in knowing what is 'normal'. For example, it has always been difficult to state what constitutes 'too much' or 'too little' sexual activity. However, researchers have now defined and classified a new medical disorder of 'female sexual dysfunction' and commonly cited prevalence estimates indicate that 43 % of women suffer from it (Quasha 2006). This was thought to be causally linked to testosterone deficiency, and a product, Intrinsa (Procter & Gamble), was developed (unsuccessfully) for this indication in surgically oophorectomised women. A E.U. license was refused because of a negative balance of benefit and risk (European Medicines Agency 2010a, b, c; Food and Drug Administration 2004).

Controversy surrounds current attempts to medicalise sexual problems and establish 'normative data' for a range of physiological measurements of female sexual response. The regulation of women's bodies by controlling their sexual expression and reproductive capacity is now conducted through medicine, whereas in the past religion played this role as we discuss further below.

The concerns are that medicalisation has extended to those life events that are natural to women, including menstruation, pregnancy and childbirth, which impacts the meaning of 'benefit' when balanced against risks. However, more recently some commentators such as Anita Clayton, the interim chair of the Department of Psychiatry & Neurobehavioral Sciences, University of Virginia School of Medicine, have criticized gender inequality in society when it comes to approval of medications for 'female sexual dysfunction', or FSD. She says that although 'sexual dysfunction is more common in women than in men (43 % vs. 31 %), the FDA has

approved 24 treatments for sexual dysfunction in men', with none for 'hypoactive sexual desire disorder', or HSDD, the 'most common form of FSD' (Clayton 2014).

Religious Influences on Women's Health

Managing the risks of female fertility, reproduction, and sexual behavior has a history which has an origin located in many religious doctrines. Some cultures have interfered with female fertility and reproductive medicines through influencing social attitudes and practices. For example, in Judaism at least a sixth of the Oral Tradition's volume is dedicated to women, with a substantial amount dealing with female health and fertility. It is the earliest source for ethical guidance, of which we are aware, about fertility and contraception, as well as physiology and pathology on the subject. Jewish law is the first which authorized emergency abortion (Chalik 2014, Personal communication; http://www.jogc.com/abstracts/full/200802_womenshealth_1.pdf).

In Judaism, a whole section of Talmud, called Nashim, is dedicated to women, and additional sections, Kiddushin, to the law of marriage, and Gittin, to the law of divorce. Women's obligations and responsibilities differed from those of men but were considered as important. The equality begins at the highest possible level: in Judaism, unlike Christianity, God is both masculine and feminine. Whilst in Christianity the right to sex is that of man, in Judaism this counts as a woman's right (The Mamre Institute 2014).

With regards to contraception, any methods that destroy the 'seed' or its passage are not permitted for birth control under Jewish law. Thus condoms are not permitted whilst the pill and IUDs are acceptable methods. One of the more mysterious Jewish laws (observed only by orthodox Jews) is the law of Niddah that is a ban on intercourse with a menstruating woman. This period of 'impurity' continues another week afterward and extends the "impure" status to 12–14 days. Whilst use of the term 'impure' in this context could be disputed the fertility benefits of this practice are relatively consistent with modern because a woman is likely to become pregnant having intercourse on day 14 at the time of typical ovulation.

In another difference from Christianity, under Jewish law a fetus has the status of "potential human life" until it has emerged from mother. That is, fetal life does not have as much value as life in existence, which is the mother's life. Jewish law not only permits, but requires abortion in circumstances when the mother's life is in jeopardy (The Mamre Institute 2014).

The position of Catholic Church is encapsulated in the key Catholic text, the 'catechism' which does not place a mother's life before that of a fetus. Moreover, it eliminates the distinction between an unborn child and its mother and in fact prioritizes life of a child because of its innocence (Speake 2012). This position was confirmed by the encyclical letter Humanae Vitae of 1968 and is the basis for the view of the Catholic Church that abortion, even if for therapeutic reasons, is to

be absolutely excluded as a 'licit means of regulating birth'. In addition, it refers to the natural rhythm method as the only acceptable form of contraception. (Paul VI 1968).

Islam does not have organized clergy, or a central authority; and there is no single interpretation of the faith. Different Muslim communities distinguish themselves by schools of Islamic law to which they adhere. *Fatwa* is a non-binding pronouncement issued by religious jurists or *muftis*, around which Islamic medical ethics are formulated, including female reproductive rights. Islamic law may coexist with secular states, and variety of interpretations exists, creating significant ambiguity. Fatwa was issued in favor of abortions as well as to support the practice of female genital mutilation in order to contain women's sexuality and preserve marriageability (Speake 2012).

The issue of female reproductive behavior in the Middle-East and North African region is closely linked to inheritance laws which grant males twice the share of inheritance of females, making them economic assets of the family; while placing the responsibility for family honor on daughters. The most important causes of suicide among unmarried adolescents in Egypt and Iran are loss of virginity and unplanned pregnancy. The resurgence of fundamentalist Islam brings back arguments that women, as the bearers of life, culture, and tradition, belong to society; and control over their behavior including reproductive capacities and choices is essential to preservation of moral authority and values of the society they belong to (Speake 2012).

Iran, the most conservative theocracy in the world, abandoned its family planning program after the Iranian Revolution of 1979, and the Ayatollah Khomeini's regime became overtly pro-natalist. In 1988, with the end of war with Iraq, a family planning program was reintroduced to slow down rapid population growth. The International Reproductive Rights Research Action Group (IRRRAG) spent 4 years researching women's reproductive rights in Egypt, in both urban and rural areas (International Reproductive Rights Research Action Group II). Women interviewed often interpreted Islam as fundamentally forbidding the use of contraception (although it specifically does not), and yet they continued to use it, showing much more pragmatism than theologians. Some authors argue that without economic justice and equality Muslim women in the Middle-East and North Africa cannot achieve recognition of their reproductive rights (Speake 2012).

Interpretation of Islamic Beliefs Regarding Contraception

Widespread belief that Islam bans contraception comes from interpretation of officially issued fatwa by local tribal, religious, and community leaders. Due to illiteracy and limited access to these texts, women especially in rural areas have no choice but to trust people around them with regards to legal and religious matters. Although Muslim women in the Middle East and North African region generally hold the same belief – that Islam does not allow contraception – their behavior is

often more pragmatic, which may also be due to better informal availability of contraception and better socio-economic status than for those in Afghanistan and Pakistan (Speake 2012).

The impact of the Taliban on women's health and reproductive rights is an extreme example of the deleterious impact of religious and political dogma on women's health. This is most notable in Afghanistan and some parts of Pakistan, specifically Federally Administered Tribal Areas (FATA) – the home of the Taliban. The influence campaign builds on a blend of tribal Pashtun values such as independence, personal honor, inviolability of his person, property and women, revenge, hospitality and Islamic creed (Cassidy 2012).

One of the most high profile implications of Taliban rule has been the ban on polio vaccines which they allege will render the next generation impotent. As a result of this campaign, together with the intimidation effect of several dozen health workers, about 4,000 parents refused to have their children vaccinated (Cassidy 2012). The Taliban agenda is prejudiced against women, separating them from men in word and deed. As a result males are not allowed to treat female patients or rescue women even during natural disasters. The interpretation of sharia offered by the Taliban is very narrow and its application is very rigid. Marginalization of educated women has made their contact with western influences difficult. This means that female doctors or other healthcare professionals in areas of Taliban rule would be very rare indeed. However, since 2010, women in Helmand, Jalalabad, and Nangarhar Provinces have been asserting their rights and economic independence with availability of educated professionals to deliver women's health programs (Ibid).

Socio-political Issues for Women in Former Soviet Union Countries

Countries in Central and Eastern Europe and Asia, which were part of the former Soviet Union, have been in transition at varying pace (DHHS 2003). Services developed specifically for women are often limited to their reproductive needs, especially childbearing. Services addressing other women's health problems have been underdeveloped, and are non-existent or inaccessible within public health care. Thus, girls, elderly women, the disabled, the unemployed and others with special needs have had limited access to medical services. Women from rural areas throughout the region have particularly limited access to health services. Many rural areas suffer severe shortages of health personnel, medical equipment, and other supplies. Women often must travel long distances to health centers as in the developing world (see Chap. 18).

The inadequacy of health services to meet women's needs can be observed best with respect to reproductive health. Moreover, the lack of or inadequate access to sex education in schools or other forms of family planning contributes to

insufficient contraceptive use. In short, family planning counseling and services usually still do not constitute an integral part of reproductive health services in many countries in this region. Women in most countries have easier access to free abortion services (with the exception of Poland where, with the most stringent medical exceptions, abortion is illegal) while contraceptives, when they are available at all, are usually not reimbursed (WHO 2014).

In Romania, according to the Romanian Reproductive Health Survey published in 2005, only 43 % of women stated that their most recent pregnancy had been planned, whereas 14 % said that the pregnancy was ill-timed and 49 % said it was unwanted. The proportion of women with unwanted pregnancies rose with greater number of living children. Women with low levels of education were more likely to say that their last pregnancy was unwanted (Ministry of Health, Romania 2005).

Romania is a good illustration about how policy impacts use of contraception. There used to be pro-fertility policies from the late 1960s to the 1980s that banned modern contraceptive use. When this policy was reversed, contraception prevalence rates rose for women from 40.5 % in 1993 to nearly 60 % in 2004. Men's rates of contraception use also rose – from 51 % in 1999 to more than 60 % in 2004. Popularity of condoms increased especially among men who were not married or cohabiting. This was accompanied by marked falls in abortion rates, lower incidence of STDs, and decreased maternal mortality (Ministry of Health, Romania 2005; Horga et al. 2013).

Global Perspective on Reproduction

According to the report of the Guttmacher Institute from 2013, most individuals and couples in the U.S. want to plan the timing and spacing of their childbearing and to avoid unintended pregnancies, for a range of social and economic reasons. In addition, because unintended pregnancy has a significant public health impact, the U.S. Department of Health and Human Services aims to reduce the number of unintended pregnancies (U.S. Department of Health and Human Services 2010). In 2006, the last year for which national-level data are available, 49 % of all pregnancies in the United States were unintended including eight in ten teen pregnancies (Guttmacher 2013). Pregnancy rates for women in the United States continued to decline in 2009, reaching the lowest level in 12 years (102.1 per 1,000 women aged 15–44). This level is 12 % below the 1990 peak (115.8) (Curtin et al. 2013). Increase in illegitimacy is also associated with numerous societal consequences of life without a father, which further worsens prospects of children who already may start life as disadvantaged (Wood and Gell 2014).

The health consequences of illegitimacy for U.S. children are striking: they are three-times more likely to commit suicide and 20–33 times more likely to become victims of child abuse than their peers from low-income households with married parents. The risks to children living outside a two-parent home include higher risk of infanticide (Mac Donald 1998). Thus the consequences of 'contraceptive failure'

for an unmarried mother can be profound not only for her but also for her child later in life.

The situation can be worse elsewhere in the world. For example, although Muslims must 'treat orphans with compassion and equity', Saudi Arabia's tribal society has tradition of stigmatizing orphans and illegitimate children who may end up abandoned or face life in an orphanage. Even if they are adopted, they are traditionally 'not marriageable' and their future is never discussed (Wagner 2011).

Demographic Consequences of Individual Choices

Demography is the statistical study of human populations and their changes (such as the number of births, deaths, marriages, and illnesses) that occur over a period of time especially with reference to size and density, distribution, and vital statistics. Individual choices have effect on demographic trends. In turn, the demographic situation of the environment in which individuals and families live has an impact on maternal health and reproductive decisions, by offering choices or imposing constraints. These circumstances include, among other factors, presence or absence of grandparents or wider family available to provide support to allow woman to continue being economically active; general acceptance of working mothers by employers; presence or absence of healthcare and childcare facilities and logistical networks; and economic and cultural pressure imposed on women in childbearing age. Individual reproductive behavior then translates into trends which can be observed at a population level. Sustainable population growth includes healthy fertility rates. Fertility, together with mortality and immigration, are important demographic drivers.

At the global level, total fertility rates have been falling over the last decades of the twentieth century, largely due to the availability of modern methods of contraception and the choices made by individuals and couples. The average number of children born worldwide fell from 5 in 1950 to 2.7 in 2005: In Africa the total number of children per woman decreased from average 6.7 in 1950 to 5.1 in 2005; in Asia, Latin America, and the Caribbean from 5.9 to 2.5 and 2.6, respectively; and from 3.5 to 2.0 in North America over the same time period. The decline was most marked in Europe where fertility rates have fallen over the last 55 years from 2.7 to 1.4 children per woman. The effect of fertility rates have to be also taken in context of average age at birth which shows generation interval, which determines how long it takes for a daughter to have a child. Currently the highest fertility rates persist in 35 poorest countries in the world. The population of Afghanistan, Nigeria, Uganda, and Yemen, are likely to triple by 2050 (Nugent and Seligman 2008).

The fact that contraception in Eastern Europe is mostly available only with prescription, and is not usually reimbursed, has little effect on overall demographic development which itself ranks as the lowest in the world (Bradatan and Firebaugh 2007). After the end of the Cold War, as a consequence of political, cultural, and economic changes in the region, as well as internal inter-generational tensions, the

demographic development in the region took a marked turn downwards. The relationship between demographic trends, reproductive behavior, per-capita income, and economic growth is complex; and the causative factors include shift in values, profound cultural change, inter-generational conflicts, income insecurity, and disintegration of state support system for families (Brainerd 2010; Thornton and Philipov 2007). Thus despite being within the EU, there are distinct demographic differences between Eastern and Western Europe that will impact the environment within which medicines for women will be used.

Socio-political Issues for Women in Russia

In Russia, a tremendous unmet need for family planning exists with abortion still remaining the main method of birth control (Denisov et al. 2013). But Russia's reproductive troubles do not stop with abortions being used as a method of birth control. By various measures, Russia's demographic indicators resemble those in many of the world's poorest and least developed societies (and the figures for males are far worse than those for women). Family formation trends are a further cause for concern. Between 1987 and 1993, the number of births in Russia dropped from 2.5 million to 1.4 million per annum. The all-time low was reached in 1999 when just 1.2 million people were born in Russia. A slight turnaround in 2010 was still below the 27 % replacement level required for long-term population stability (Eberstadt 2011).

In the late 1980s in Russia, births still exceeded deaths by an average of 800,000 births a year. But the collapse of communism brought a series of demographic changes with declining birth rates and rise in deaths. According to Eberstadt's analysis, this population decline was caused by excess mortality among adults, mainly due to accidents, poisonings including alcohol intoxication, injuries, suicides, homicides, and other unnatural deaths, infectious diseases such as HIV/AIDS and drug-resistant tuberculosis, in combination with an average birth rate of about 1.5 per woman (Eberstadt 2011).

According to the Federal State Statistics Service, over the last 20 years since 1992, Russia became a net mortality society (FSSS 2013). This trend was only reversed in 2012 when the total number of births equaled total mortality (see Fig. 16.1). Part of the population decline in the mid to late 1990s is explained as the consequence of high mortality. The changes in Russian society are so complex it is difficult to identify specific reasons to explain the decline in birth rate. It may be linked to the increased cost of living exceeding income, so that giving birth to a child is perceived as an irrational or irresponsible act. This perception is consistent with a prevailing negative influence of the media in combination with a traditional disregard of Russian culture for women – all of which shape attitudes toward women in childbearing age (Eberstadt 2011).

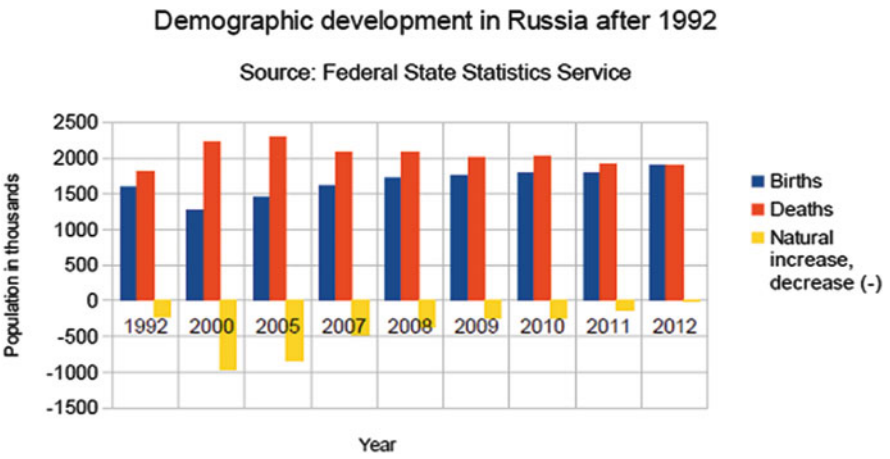

Fig. 16.1 Demographic development in Russia during economic transformation following collapse of the Soviet Union (FSSS 2014)

Cuba

In contrast to other Communist countries and other Latin American countries, Fidel Castro, as the Communist dictator of Cuba, placed a special emphasis on women's health and well-being because of how he viewed their role in building an egalitarian society. Castro instructed the health department to set up women's clinics, Sanitary Brigades, and a network of hospitals to specialize in feminine care. Contraception and abortion became widely and readily available to all women and provided for free by the State. In 1965, Castro's public health department officially decriminalized abortion to reduce maternal morbidity and mortality rates. This action made Cuba's abortion policy the most liberal policy in the region and most of the world (Croll 1981; Keck and Reed 2012).

Western Europe and the European Union

The birth rate in Western Europe has been in decline since the 1960s and this trend has been only partially reversed in some EU countries because of a higher birth rate among immigrants and more women giving birth later in life.

European Demographic Transition

Clark and Alter (Clark and Alter 2010) explained demographic transition in European societies in the period from 1700 to 1870, and described some phenomena which are still relevant today. By 1870, at the height of the industrial revolution, much of Europe was experiencing economic growth. At that time, fertility levels declined to current levels even in the absence of reliable contraception.

The demographic transition to modern fertility rates only started in the 1870s in England (as shown in Fig. 16.2 below) as in the rest of Europe, and then progressed rapidly. By 2000, the average English woman had fewer than two children over her lifetime. The European Marriage Pattern which kept fertility low was based on delayed marriage, marriage choices and family structure. While fertility within marriage was high, typically about 10–25 % women remained unmarried and therefore excluded from reproduction. At the same time, the illegitimacy rate was low, typically 3–4 % of births, mainly due to social exclusion and limited opportunities and life choices for those affected. This illustrates that individual reproduction behavior is inseparable from cultural, economic, and social environment (Clark and Alter 2010).

"Zero Population Growth"

In 1967, demographer Kingsley Davis introduced the term 'zero population growth' by defining the population fertility goal as replacement levels, of about 2.1 child per woman in developed countries and 3.0 in developing countries. This fertility rate was supposed to ensure sustainable development (Population Research Institute, Grimes 1994). The movement became greatly popular in the late 1960s and 1970s.

One of the main supporting arguments was that investment in education, health and family benefits would fall, freeing up resources to be used for improvement of quality of life because of more favorable ratio between economically active individuals and dependents. The early 1970s enthusiasm for economic advantages of zero population growth waned, however; because of long-term adverse consequences of such development. In reality any advantages of zero growth vanish as

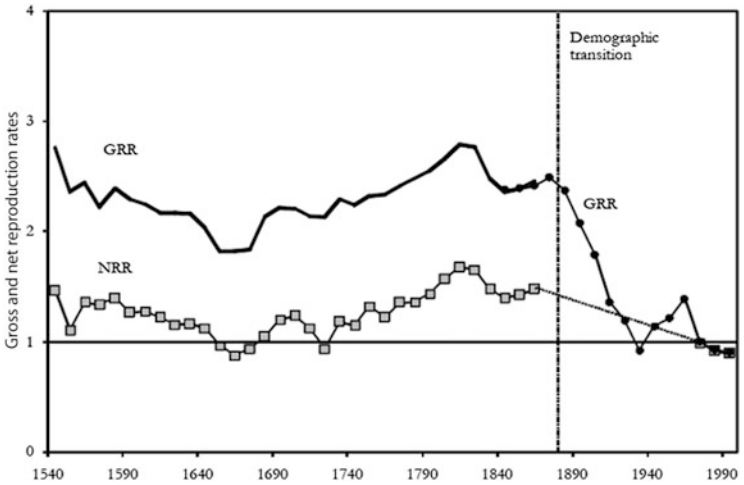

Fig. 16.2 The first demographic transition in England. The Fertility History of England, 1540–2000 (Clark and Alter 2010). Notes: *NRR* net reproduction rate, *GRR* gross reproduction rate

the population ages due to increased number of dependents who retired from economically active life (Grimes 1994) (Fig. 16.3).

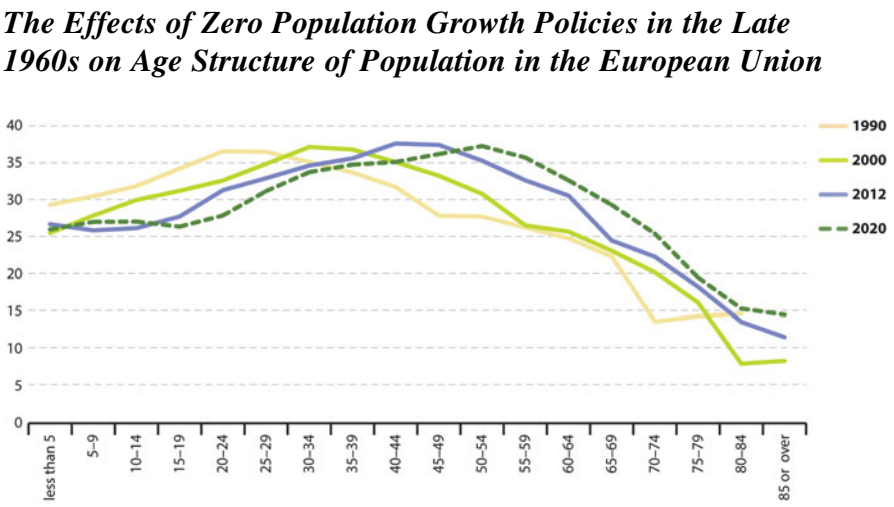

Fig. 16.3 Data from Eurostat showing the EU population is rapidly aging (Eurostat 2013)

Political Influences on Reproductive Behavior in the Czech Republic

The situation in Czechoslovakia illustrates well the effect of policy on reproductive behavior (Fig. 16.4). After the Soviet invasion of 1968, many pro-population measures were implemented to compensate for the decline in birth rates since the 1960s. The era of political 'normalization' started with pro-population measures intended to calm down an explosive political situation and ease public unrest. The generation born during this peak was named after then president Gustav Husák – 'Husák's children'. People with small children living in confined conditions with their parents only received independent housing from the state if they showed loyalty and gratitude toward the state. The decline in birth rates following the Velvet Revolution in 1989 parallels changes in Russia and other former Warsaw Pact states after the fall of Soviet empire. This has yet to be fully explained because of the enormous complexity of the change. Profound change in economic environment, devaluation of currency combined with sudden surge in prices of property in the early 1990s, coupled with temporary and long-term migration abroad, economic insecurity, in conjunction with lower willingness of parental generation to repeat the experience of multi-generational households with their own children and

Fig. 16.4 Demographic development in Czechoslovakia showing effect of pro-population policies in the early 1970s and drop in birth rate during economic transition after 1989 (Czech Statistical Office 2013)

grandchildren, led to procrastination of starting families, and increased popularity of less formal forms of cohabitation, often considered a 'temporary solution' only. Although it is difficult to speculate what role reproductive medicines might have played, it is self-evident that increased availability of contraception meant this generation of women has more control over their own reproduction than their mothers ever had, so that the number of abortions significantly dropped.

China's One Child Policy: A Case Study of Political Impact on Reproductive Behavior

Probably the most extreme case study of policy impact on reproductive behavior of individuals and couples comes from China's one child policy. Thomas Scharping in his study "Birth Control in China 1949–2000" (Scharping 2003) meticulously researched all aspects of Chinese population policy from 1949. A large number of primary and secondary sources such as national and international statistics, laws, directives, internal documents and conferences were used to compile valid data sets.

The political debate around birth control at the Chinese Communist Party (CPP) level is particularly enlightening. After World War Two and takeover of the country by Communists, population growth was seen as essential for national security and defense, especially by Sun Yat-sen and Mao Zedong. But resources required for population growth were obstructing economic development, and scientists and politicians like Zhou Enlai and his wife Deng Yingchao advocated measures which would allow tighter population control already in the mid-1950s. It was not until the late 1970s when the leadership gradually imposed limits on reproduction of the population and implemented its one child policy in response to economic crisis (Allès 2006).

These policy measures greatly accelerated otherwise normal demographic transition toward smaller family size. Because of strong son preference in China the government policies did not always work as intended; and the sex ratio became seriously skewed due to selective abortion practice and female infanticide, reaching 111.8 boys to 100 girls in the census of 1990. Although abortion itself is not illegal in China, and despite little ethical or moral debate about it, prenatal screening and sex selective abortion are still forbidden (Davin 2004).

Between 1979 and 1999, the proportion of women using contraceptive methods in China increased from 60–70 % to 80–90 %, with IUDs and female sterilization being the most widespread methods. Reclassification of nationalities between 1982 and 1990, together with exemptions for some regions, provinces, and minorities, led to major increases in the Mongol, Manchu, and Tijua populations. The author concludes his book by showing the near-impossibility of effectiveness of all these measures, and consequent hiding of illegitimate births from statistics. Scharping's estimate is that the population under-assessment for the years 1953–1980 is about 11–12 %, and as much as 5–12 % for 2000 (Allès 2006).

Access to Oral Contraceptive Medicines

The requirement for a prescription is an important barrier to access to oral contraceptives, even in developed countries. Over-the-counter access may improve uptake and continuity of protection (Grindlay et al. 2013). Grindlay and colleagues compiled results about contraceptive access from 147 countries between April 2011 and September 2012, and proceeded to analyze regional patterns. About a third of screened countries allowed access to oral contraceptives with prescription only, 8 % required some sort of screening, and 24 % required no prescription at all. In almost 40 % of screened countries oral contraceptives were at the time of this survey available informally without prescription (Grindlay et al. 2013) (Fig. 16.5).

Access to contraceptives is greatly influenced by religious, political, and cultural environments. The primary purpose of contraceptive medicines is not to stop women from having children altogether, but to empower them to better time and space their pregnancies. At a population level, access to contraceptives and their responsible use becomes a public health issue because of direct impact of individual behavior on demographic trends. This is illustrated by the US where about half of

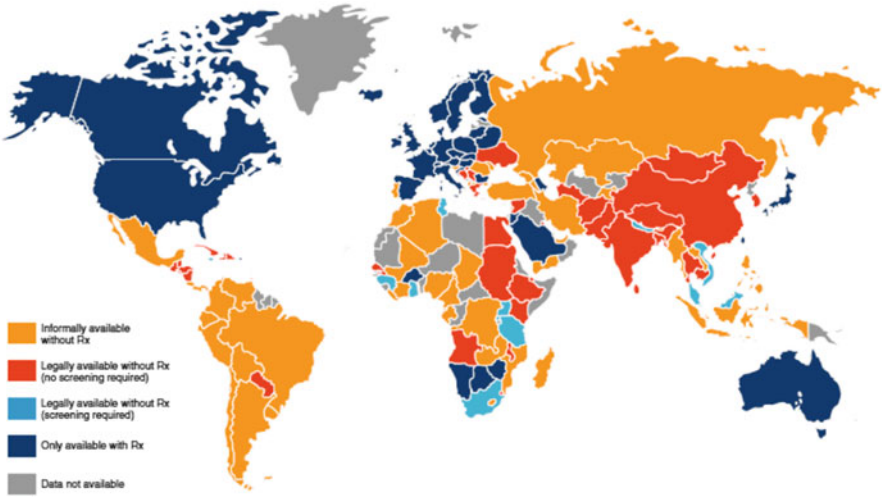

Fig. 16.5 World map of oral contraception availability (Reprinted with permission from Ibis Reproductive Health (Grindlay et al. 2013))

pregnancies are reported as unintended, either ill-timed or unwanted. About four out of ten of these unintended pregnancies end in abortion (Guttmacher Institute 2013).

Overview of Abortion Laws in the U.S.

The overall U.S. unintended pregnancy rate increased slightly between 1994 and 2008. Although the abortion rate decreased 8 % between 2000 and 2008, there was an 18 % increase among poor women, and 28 % decrease among higher-income women. Some 1.06 million abortions were performed in 2011, down from 1.21 million abortions in 2008, a decline of 13 %. The number of U.S. abortion providers declined from 1,793 in 2008 to 1,720 in 2011. The number of clinics providing abortion services declined from 851 to 839 (Guttmacher Institute n.d.).

Figure 16.6 below shows an overview of abortion laws in the U.S. (Guttmacher Institute 2014a, b). Of the 41 U.S. states which prohibit abortions, exceptions generally apply when it is deemed medically necessary to protect the woman's life or health (Guttmacher Institute n.d.). According to the Guttmacher Institute, 39 U.S. states require an abortion to be performed by a licensed physician and 20 states require an abortion to be performed in a hospital after a specified point in the pregnancy (Guttmacher Institute 2014a, b).

STATE	MUST BE PERFORMED BY A LICENSED PHYSICIAN	MUST BE PERFORMED IN A HOSPITAL IF AT:	SECOND PHYSICIAN MUST PARTICIPATE IF AT:	PROHIBITED EXCEPT IN CASES OF LIFE OR HEALTH ENDANGERMENT IF AT:	"PARTIAL-BIRTH" ABORTION BANNED	PUBLIC FUNDING OF ABORTION		PRIVATE INSURANCE COVERAGE LIMITED
						Funds All or Most Medically Necessary Abortions	Funds Limited to Life Endangerment, Rape and Incest	
AL	X	Viability	Viability	20 weeks*	▼		X	
AK	X				▼	X		
AZ	X	Viability	Viability	Viability	X	X		
AR	X		Viability	20 weeks†	X		X	
CA				Viability		X		
CO	X						X	
CT		Viability		Viability		X		
DE	X			Viability			X	
DC							X	
FL	X		24 weeks	24 weeks	▼		X	
GA	X			Viability	Postviability		X	
HI	X			Viability		X		
ID	X	Viability	3rd trimester	Viability‡	▼		X	X
IL			Viability	Viability	▼	X		
IN	X	20 weeks	20 weeks	20 weeks*	X		X*	
IA	X			3rd trimester	▼		X	
KS	X		Viability	20 weeks*	X		X	X
KY	X	2nd trimester		Viability	▼		X	X
LA	X		Viability	20 weeks*	X		X	
ME	X			Viability			X	
MD	X			Viability§		X		
MA	X	12 weeks		24 weeks		X		
MI	X			Viability‡	X		X	X
MN	X	20 weeks	24 weeks	24 weeks		X		
MS	X¶				X		X§	
MO	X	Viability	Viability	Viability	▼		X	X
MT			Viability	Viability*	Postviability	X		
NE	X			20 weeks*	▼		X	X
NV	X	24 weeks		24 weeks			X	
NH					X		X	

Fig. 16.6 (continued)

NJ	X[‡]	14 weeks			▼	X		
NM	X				Postviability	X		
NY			24 weeks	24 weeks[‡]		X		
NC	X	20 weeks		20 weeks			X	
ND	X			20 weeks[*]	X		X	X
OH	X	Viability	Viability	Viability[*]	X		X	
OK	X	2nd trimester	Viability	Viability	X		X	X
OR						X		
PA	X	Viability	Viability	24 weeks[*]			X	
RI				24 weeks[‡]	▼		X	▼
SC	X	3rd trimester	3rd trimester	3rd trimester	X		X	
SD	X	24 weeks		24 weeks	X		Life Only	
TN	X			Viability	X		X	
TX	X			20 weeks[*]			X	
UT	X	90 days		Viability[†,Ω]	X		X[*]	X
VT						X		
VA	X	2nd trimester	Viability	3rd trimester	X		X[Ω]	
WA				Viability		X		
WV					▼	X		
WI	X	12 weeks		Viability	▼		X[*]	
WY	X			Viability			X	
TOTAL	39	20	18	41	19	17	32+DC	9

Fig. 16.6 Guttmacher Institute (2014a, b): An overview of US abortion laws

Availability of Hormonal Emergency Contraception in the USA: A Curious Case of Political and Religious Influence

The United States celebrates free markets and yet the competitive forces of medicine and religion have featured in the American social landscape since the nation's beginnings (Prescott 2011). The complex intertwining of religion, politics and science has been well illustrated by the story surrounding emergency contraception which has been written about at length but will be summarized here.

Emergency contraception (EC) in the form of Plan B has been available by prescription in the United States since 1999. Plan B consists of two 0.75 mg levonorgestrol tablets to be taken 12 h apart as soon as possible and within 72 h after an act of unprotected or inadequately protected intercourse. Efficacy decreases with time so any delay in taking the therapy is critical. In October 2002, three States (Alaska, California and Washington) had made EC over the counter in pharmacies. However, even then many pharmacies were unwilling to advertise this service. Evidence then suggested that 93–97 % of a representative sample of women understood the main purpose of EC (Raymond et al. 2009).

The American College of Obstetrics and Gynecology (ACOG) supported the change to over the counter status (OTC) and provided guidance (American College of Obstetricians and Gynecologists, Committee on Health Care for Underserved Women 2012; American College of Obstetricians and Gynecologists 2010). Opposition came from the National Right to Life Committee some of whose members objected and Pharmacists for Life who claimed EC was an 'abortifacient'. In response to a submission by a product license holder (Barr Labs), the FDA convened an Advisory panel who voted 23-4 in favor of Plan B being made available without a prescription (Food and Drug Administration 2003).

There was widespread coverage in the main media outlets which was by and large very supportive. However, organizations such as Christian Science Monitor claimed such a decision would lead to more irresponsible sexual behavior and spread sexually transmitted disease. In February 2004, the FDA said it would delay decision until May. The FDA requested further evidence about experience in those aged 16–17 years. A coalition of conservative lawmakers led by Republican Dave Weldon (R-Fla) claimed easier access would increase unsafe sex particularly amongst teenagers. The Catholic Medical Association stated that without medical advice, use of Plan B would be disastrous. The American Life League submitted a petition of 20,000 signatures objecting to Plan B as an abortifacient. In May 2004, the FDA rejected the application on the grounds that girls less than 16 years of age could not use safely Plan B unsupervised. The FDA suggested that OTC status might be granted for women over 16 whereas those younger than 16 would require a prescription. The ACOG (at its 52nd Annual Meeting on May 4th 2004) and

Physicians for Reproductive Choice and Health accused FDA of caving into political pressure and disregarding science (Grimes 1994).

Wisconsin introduced an emergency hotline for EC and Plan B was becoming increasingly available through the Internet and social media. A further three states had legislated to permit OTC use: Hawaii, New Mexico and Maine. The FDA repeatedly denied influence from the Bush administration although some external commentators suspected that 're-election' concerns and influence of the right may have been significant. In August 2005, the FDA announced that it had indefinitely deferred Barr's application for Plan B – a move which was strongly supported by the Secretary of Health Human Services (HHS). Shortly after, Susan Wood, FDA Assistant Commissioner Women's Health, resigned in protest (Wood et al. 2012). The mainstream media were deeply critical of the FDA position and both the American Medical Association and American Academy of Pediatrics supported OTC Plan B without age limits (Wood et al. 2005).

In February 2011, Teva Women's Health Inc. (who had taken over Barr Labs) submitted to the FDA a supplemental new drug application for Plan B One-Step, which was the same single dose product and active ingredient as submitted 8 years previously. In December 2011 the FDA inferred that it was ready to grant approval without age restrictions. There then followed an unprecedented intervention by Kathleen Sebelius, Director of HHS, who announced that she believed that the evidence did not conclusively establish that Plan B One-Step should be made available over the counter for all girls of reproductive age (Johnson 2011). Of note, a further Presidential election was due in 2012.

Meanwhile, a legal application to challenge the FDA's decision had been filed in 2005 by the Center for Reproductive Rights. On April 15th 2013, District Judge Edward Korman overturned the HHS and FDA decision and ordered the FDA to approve the application for Plan B with no age restrictions within 30 days. His argument was based on the premise that age restriction is a barrier to access by those on low income and teenagers, because all would have to show age identification. His ruling was severely critical of the interference by Sebelius in the regulatory process. There were considerable attempts by the US Department of Justice, through the 2nd Circuit Court of Appeals, to delay or even the overthrow the decision (US District Court for the Eastern District of New York 2013).

On June 10, 2013, the FDA notified Judge Korman of its intent to comply with the court's April 5, 2013 order. To comply, the FDA had asked Teva Women's Health, to submit a supplemental application seeking approval of the one-pill product to be made available without any restrictions. The FDA fulfilled its commitment to the court by promptly completing its review and approving the supplemental application. The press statement from FDA stated that "over-the-counter access to emergency contraceptive products has the potential to further decrease the rate of unintended pregnancies in the United States (Food and Drug Administration 2013).

This year, in 2014, the FDA expanded access to generic and cheaper versions of Plan B so that these products can now be sold over the counter without age restrictions. Generic versions of the emergency contraceptive were restricted to

women ages 17 and older, but those restrictions have now been lifted. The FDA has stated that the only stipulation now is that generic forms of the drug must say they are intended for "women 17 years of age or older," but no ID check is required. So this ends a decade of wrangling over the accessibility of Plan B in the US (Uhl 2014).

However, this did not mean ready availability of emergency contraception. For example, some hospitals in the U.S. had not been routinely offering emergency contraception to the patients even when they had been victims of sexual assault. Two studies from Illinois and North Carolina found that emergency contraception was offered to victims of sexual assault only in 51 % and 40 %, respectively (Cremer et al. 2010).

Meanwhile, levonorgestrel emergency contraception had become available over-the-counter in Norway (2000), Sweden (2001), The Netherlands (2004), India (2005), Canada (2008), and Spain (2009). Another 45 countries now allow access from a pharmacist without a prescription. The regulatory review in general is that the physical and medical risks are few and the main concern is awareness, availability, and privacy. Formal availability does not mean the medication will be accessible though. In Italy, many doctors refuse to prescribe it, and many pharmacists refuse to sell it, arguing with their right for professional self-determination and conscience. Given the very low risks of harm, it has been suggested that availability without prescription at general sales outlets, such as supermarkets, would remove the legal duty of physician and pharmacists to provide the medication and relieve them of moral dilemmas leaving provision to market forces and personal choice (Ceva and Moratti 2013). Thus it is unlikely that we will have heard the last of how best to manage the benefits and risks of emergency contraception.

The Impact of Religion

Religion may impact on the use of women's medicines, especially contraception by either creating barriers or facilitating use. Unfortunately, studies of such questions are hampered by methodological limitations such as cross-sectional approach to data collection, non-representative samples and limited measures of religion.

Religion affects the formation of sexual attitudes, behaviors, and ethics of teenage sexuality. Mark Regnerus, a professor of sociology at the University of Texas, in his book Forbidden Fruit explored the relationship between religious discourse and sexual behaviors of American teenagers (Regnerus 2007). The research was based on several outstanding national data sets. About 97 % Americans believe in God, about 80 % claim that religion is fairly important to them, and more than half regularly participate in religious services. The vast majority of youth also participate in some sort of sexual activity. Prior to this book, research concerning religiosity and sexual behavior of American teenagers was considerably limited. The topics had indeed been studied but always separately from each other. Regnerus delivered a comprehensive presentation of religion's effects on teen

sexual behaviors, perceptions of risk, motivations, and attitudes. Religiosity, more than religious affiliation, influences adolescent decision-making. The core message religious parents tend to communicate to their children is more related to morality and values rather than sexuality.

The attitudes of Christian youth, especially those who declare themselves as Protestants, are rather conservative, and the pledge of abstinence does have delaying effect on start of sexual activity. Regnerus's findings suggest that teen sexual life is nowhere near as rampant as presented by the media. The use of contraception by teens is unreliable not because of religious attitudes but because of their flawed risk perception, reliance on unproven techniques and lack of planning (Davidson 2011). This is discussed further in Chap. 3 (Prescribing Medicines to Adolescent Women, p. 69).

Issues Influencing Use of Women's Medicines in Developing Countries

Perspectives on women's medicines in developing countries are discussed in some detail in the following chapter (Chap. 18, p. 531) but we would also like to comment here on issues in these countries, particularly in relation to political and religious influences.

We know that in some cultures when it comes to contraceptive use and family planning, women lack decision-making power to negotiate about sex, childbearing and contraception, as husbands assume sexual access and control. While a husband can, and often does, refuse to use contraceptives despite his persistent sexual demands, women find themselves caught in their conflicting roles as solely responsible for family planning, and at the same time to be sexually available to their husbands.

In some developing countries, ill women still need their husbands' approval before they can go out to seek medical treatment or health care. Or, when they do arrive at the hospital, there are numerous medical procedures that require their husbands' signatures. Thus, in such countries gender roles and male-female power relations have a more important role in influencing how women's medicines will be used compared with traditional medical practice.

Although, as we mentioned earlier, since 1994 some governments have been obliged to provide access to means of control over one's own reproduction, some countries still have a long way to go. Rashid conducted research among adolescent married women in urban slums of Bangladesh (Rashid 2011). She described and contrasted in detail the irrelevancy of international agreement on human rights when young women are intimidated by the patronage structure of local gangs who fill the vacuum created by the failure of government involvement to providing essential women's health services (Rashid et al. 2011).

Not all people think that having fewer children is a blessing and some get deeply suspicious about genocidal agendas of 'birth control missionaries'. Family planning was introduced in Malawi in the 1960s but was banned shortly afterwards and it took 20 years of dialogue to reintroduce a child spacing program as part of the country's population management. The people of Malawi were extremely unhappy about the whole idea of contraception and understood it as a post-colonial conspiracy to wipe out the black population. Policy guidelines were first introduced in Malawi in 1992 and amended in 1996 to remove barriers such as spousal consent, age, and parity. Total fertility declined only slowly from 6.7 children per woman in 1992 to 6.0 in 2004 and about 5.6 in 2010. African society is constructed in such a way that high fertility and a large surviving family is economically and socially rewarding. This is in stark contrast to western societies where many women who want to have a family postpone their children till later or limit the size of a family below what they actually want because of socio-economic pressure (Palamuleni 2013).

The situation was similar in other African nations, too. After gaining independence in 1980, Zimbabwe received worldwide recognition for its effective family planning programs. But, Zimbabweans took a hostile position to the idea because of concerns over conspiracy to control the black population. Pro-birth tribal politics in Kenya in combination with religious concerns shaped fierce opposition against governmental family planning efforts to slow down population growth in the 1960s and 1970s. Governmental involvement in family planning programs, especially in low-income countries generates deep suspicions over genocidal efforts among the population, especially when funded from high income countries. Sentiments and clashes over family planning may be so powerful that they can bring down entire governments.

Shiffman and Quissel (2012) make a good case for full consideration of political and religious objections in newly reintroduced family planning policies in low-income countries. A report in the Lancet arising from the London Family Planning Summit in July 2012 indicates that the efforts to provide men and women in low-income countries methods to control their own fertility are gaining momentum once again (Shiffman and Quissell 2012).

In Pakistan (which is discussed in some detail in Chap. 18), as many as 60 % women believe that family size is determined by God (Farid-ul-Hasnain et al. 2013). The frequency varies between rural and urban areas. Religious figures are both spiritual and community leaders so their influence is ubiquitous and hard to evade. Premarital and extramarital sex is forbidden by both religion and culture, marriage follows only a few years after the onset of puberty and illiteracy and limited access to information excludes any possibility of informed autonomous decision-making. Most young women learn about sex on their wedding night and only learn that sex leads to pregnancy when they learn they are pregnant (Ibid).

About 32 % of Pakistani students believed use of oral contraceptives was against Islamic philosophy (Ajmal et al. 2011). Illiteracy rates remain high especially in rural areas and access to healthcare is very difficult as described in Chap. 18.

In 2006–2007, less than a quarter of Pakistani married women use contraception, up from 9 % in 1999. In a survey conducted in 2006–2007, 96 % of ever-married and currently married women age 15–49 knew of at least one method of family planning. This had increased from about 62 % in 1984–1985 (National Institute of Population Studies, Islamabad, Pakistan, and Macro International Inc., Calverton, Maryland USA 2008). However, there are significant barriers to contraceptive use in Pakistani society, due to numerous cultural factors such as son preference and high prevalence of misinformation and misconceptions about contraceptive products and their side effects (Farid-ul-Hasnain et al. 2013). In the 2006-6 survey, 28 % of married non-users attributed single causes for non-use as "up to God" and 10 % because their husband opposed use (National Institute of Population Studies, Islamabad, Pakistan, and Macro International Inc., Calverton, Maryland USA 2008).

Religious, Moral and Ethical Objections to Provision of Women's Medicines

Based on the Ethical and Religious Directives for Catholic Health Care Services (ERD), Catholic hospitals have refused to provide emergency contraception, perform abortions and sterilization procedures, as well as in vitro fertilization (IVF) treatment.

The Catholic argument is that IVF goes against natural conception, and that infertility is God's will. Another argument relates to the number of created embryos to give the couple best chance of pregnancy, and the consequent discarding of embryos which were not used, among other reasons for their poor quality and low chances of survival. Disposal of non-viable embryos is thus seen in the same light as abortion. Objections can come from secular quarters, too, where the main resistance is against unwed and same-sex couples. The treatment is typically not reimbursed so the poor are excluded by default.

Religious issues have profound impact on access of vulnerable populations to reproductive medicines in the developed world as well. This can be illustrated by the history of a long religious battle over a healthcare facility in Austin, Texas. In May 1965, Seton Medical Center entered into an agreement with the city manager of Austin, the then owner of the Brackenridge hospital. Seton was a Catholic facility owned and operated by the Daughters of Charity of St. Vincent DePaul which would take full management and control of the public hospital, Brackenridge. The declared purpose was to continue essential health care services including women's reproductive, children', and trauma, for all citizens of the Austin and Travis County, regardless of their financial means. This public/private partnership was not unusual.

The main complication of the deal was Seton's requirement to adhere to the Ethical and Religious Directives for Catholic Health Care Services developed by

the U.S. Conference of Catholic Bishops (USCCB) in 1994 which banned the facility from direct involvement in reproductive services such as contraception, sterilization, abortion, and fertility services, namely in vitro fertilization and insemination to which the Catholic Church morally objected. The directives did permit an indirect role in the delivery of some of these services should a Catholic institution affiliate with a non-Catholic institution.

The conflict which followed lasted 7 years, involved all the aspects of national debate, including intense discussion over the provision of emergency contraception. The Catholic Church is a major stakeholder in the health care field in the U.S. and exerts enormous influence over the provision of health care services. More than 600 Catholic hospitals function in 47 states with 1 in 6 patients being taken care of by a Catholic Church health care facility. The Daughters of Charity National Health System had an excellent record in nursing and managing successful hospitals throughout the nation. The restrictions from Rome; however, and increasing secularization of society, created new challenges for them. The Second Vatican Council, which met through 1962–1965, emphasized social justice and human dignity. The Daughters redefined their governance and ministry and renewed their commitment to the poor and the oppressed. The mission was redefined from 'bringing students and patients into the nuns' world' to 'nurses entering the patients' world', to share their experience.

Secular influences at Seton grew through the 1970s due to appointment of lay administrators, nursing supervisors, and trustees who played a significant role in negotiations with Brackenridge. In cases where a Catholic facility sought affiliation with a non-Catholic institution, it had to ask the local bishop for approval. The bishop in Austin was not normally involved in hospital policy decisions, but it was his responsibility to communicate directly with the Vatican's Congregation for the Doctrine of the Faith, which was responsible for ensuring that Catholic teachings were implemented in all church facilities. The National Conference of Catholic Bishops, a church policy-making body in the U.S., got involved in the debate on issues of abortion and reproductive services (Wall 2010).

In 1968 the Catholic Church through its Encyclica 'Humanae Vitae' (Paul VI 1968) came up with an answer to all this turmoil, which was as much a religious stance as it was political one: it confirmed its position that abstinence is the only acceptable contraception method. With some regional variations, the Church insists on this stance to this day. The 1968 Encyclical Humanae Vitae caused a serious divide between Church hierarchy and laity and caused a split among Catholic clergy. Particularly controversial was the exclusion of reproductive services including family planning from Catholic hospitals which merged with non-Catholic institutions.

The partnership was vital for Brackenridge for several reasons. A significant number of uninsured patients were denied access to healthcare, not only in Austin but nationwide. Brackenridge employees and management were worried that removal of the institution from public scrutiny would allow decision-making behind closed doors. Austin's bishop John McCarthy, one of the country's moderates, aggressively supported the deal between Seton and Brackenridge and in July

1995 he wrote a letter to Vatican with background information on the proposed lease. The bishop signed the lease in October 1995, assuming Vatican's consent. The Vatican responded in March 1996 and again in 1997, with a request that all reproductive services should be ceased. Any breach of contract with the city regarding reproductive services would subject Seton to a multimillion dollar fine.

The Texas Family Planning Association was very uneasy about the whole situation because they were not allowed to be involved. In 2000 the situation dramatically changed after McCarthy's retirement and appointment of more conservative bishop Gregory Aymond, a supporter of Vatican teachings, by John Paul II. Aymond was the representative to the USCCB 2001 meeting when the bishops developed new Ethical and Religious Directives and agreed to especially focus on Part Six 'Forming New Partnerships with Health Care Organizations and Providers'. After considering several options, the city proposed to create a hospital within a hospital, which would handle all contraception and sterilization services and emergency contraception for women after a sexual assault. The Daughters of Charity resolved the conflict by offering an innovative compromise. In many ways, the resolution of this conflict serves as an example of strong and competent leadership focused on key goals, which were to maintain essential services for all people of Austin, including the poor (Wall 2010).

In the U.S. most states have 'conscientious objection' in their legislation which allows physicians to opt out from performing abortions. Meyers and Woods argue that physicians have an obligation to perform all socially sanctioned medical services, including abortions. The case study presented by Meyers and Woods outlines conflicting legal obligations between a state-mandated obligation to provide abortion services for two population groups – inmates from local penal facility and those deemed incompetent to make their own medical decisions – and the right of physicians to opt-out from providing abortion services. Of eight physicians qualified to perform the procedure only one was willing to perform elective abortions. As a result of this opt-out clause, as of 1991, 83 % of US counties had no abortion provider (Meyers and Woods 1996) compared to 89 % in 2011 (Guttmacher Institute n.d.).

Religious Beliefs About Blood Transfusion

A patient's refusal of blood transfusion on religious grounds is one of the most controversial examples of conflict between medical ethics and religion. Jehovah's Witnesses consider refusal of blood transfusions fundamental because acceptance of blood which is sacred would prevent them from entering Paradise. Members of the Church are required to observe this rule under threat of expulsion from the community. No other religion is so extreme in their view. Jehovah's Witnesses who accept blood and in this way revoke their membership in the organization are then ostracized by the community to the point that they are completely blanked by their

lifelong friends and family members who are still part of the Church, and essentially treated as outcasts.

The Watchtower Society introduced the policy of refusal of blood transfusion in 1945. Since 1961 it enforced zero tolerance towards those who wilfully accept blood transfusion. In 2001, Dr. Carl Saphier conducted a study with the purpose of determining the rates of obstetric haemorrhage and maternal mortality in women Jehovah's Witnesses. Death rate of 521 deaths per 100,000 live births among Jehovah's Witnesses constitutes a number approximately 44 times higher than the general US population. According to Dr Reed, former Witness and currently a widely recognised authority on the sect, the number of deaths worldwide caused by refusal of blood transfusion on religious grounds is estimated around 9,000 a year (Radomyski 2011).

Otherwise, Jehovah's Witnesses accept most medical treatments, surgical and anaesthetic procedures, devices and techniques, as well as haemostatic and therapeutic agents that do not contain blood, for example non-blood fluids such as crystalloids and colloids, erythropoiesis stimulating agents (ESAs), desmopressin, vasoconstrictors and recombinant clotting factors (Royal United Hospital Bath NHS Trust 2013).

Conscientious Objection to the Provision of Emergency Contraception

Wicclair argues that the refusal to provide emergency contraception to the victims of sexual assault based on conscience is unjustified, because an institution "cannot have a conscience", an attribute, as well as ethical and moral objections can only be expressed by human beings (Wicclair 2011). However, in some instances the hospital mission can be considered an analogue to the conscience of a physician, nurse or pharmacist. One way to explore moral identity of an institution is to explore its mission statement. Although it is disputable why staff of such an institution should be required not to make an exception on offering emergency contraception for rape victims, there are several reasons for enabling hospitals to maintain their identity and integrity by exempting them from general institutional obligations. First, it may be important to staff to work in institution which shares a commitment to a core set of goals, values, and principles, and violation of these values may at the very least to moral distress. The same principle applies to patients who seek care in such an institution (Wicclair 2011).

Human Papillomavirus Vaccine: A Case Study of the Issues Associated with Mandatory Vaccination in Michigan, USA

Compulsory vaccination against Human Papilloma Virus (HPV) became a hot political issue in the U.S. The vaccine (Gardasil) was first approved by the FDA in September 2006 (the HPV vaccine is discussed further in Chap. 9). Gardasil protects against four strains of HPV, the most common sexually transmitted disease in the U.S., including the strains which are linked to higher incidence of cervical cancer. Because the vaccine has the greatest benefit before a person becomes sexually active, the Advisory Committee on Immunization Practices recommended its application to girls between 11 and 12 years of age (Centrum for Disease Control and Prevention 2013).

Three months after approval was granted the vaccination became compulsory for all girls entering sixth grade in Michigan. Making vaccination mandatory in this way caused a furious political debate. Although Advocacy groups such as Focus on the Family did not object to availability of the vaccine, they certainly objected to its mandatory use. In their view, such a requirement by a secular state constitutes intervention which may be irreconcilable with the child's family's religious values and beliefs.

Groups which are recommending mandatory HPV vaccination have drawn an analogy with the success of breast cancer screening procedures which has saved many women's lives by enabling them to receive treatment earlier. A critical question is whether achieving a higher level of coverage justifies the infringement of parental autonomy that compulsory vaccination inevitably entails. Different ethical frameworks that accord varying weights to communitarian and individualistic values will lead to contrasting answers to this question. Ethical and epidemiological analyses are essential to decisions about mandating a medicine such as the HPV vaccine, as are political calculations and the possibility that additional mandates may inflame grassroots opposition, be it religious, philosophical, or ideological (Zimmerman 2006; Colgrove 2006).

Female Subjects in Clinical Research Studies

Following the guidance arising from Declaration of Helsinki in 1964, the restriction on participation of vulnerable subjects in clinical research originally referred only to pregnant women. It was later extended by the FDA in 1977 to all premenopausal women of childbearing age as the most effective way of minimizing this risk (FDA 1977; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). This was understandable following the thalidomide and diethylstilbestrol (DES) disasters. The former disaster is very well known, whereas the latter was relatively more recent and its consequences are still ongoing with concerns about adverse effects in the grandchildren of DES women.

Diethylstilbestrol (DES) is a synthetic form of oestrogen that was prescribed to pregnant women between 1940 and 1971 to prevent miscarriage. In the early 1950s research was conducted to assess the efficacy of this treatment and no benefit was found to substantiate its use. Despite this, DES continued to be prescribed. According to the CDC DES Update: Consumers 2014; only in the 1970s did it come to light that daughters of women who were taking this medication during pregnancy had a higher risk of clear cell adenocarcinoma of the vagina and cervix (Herbst et al. 1971). In 1971, the FDA advised that use in pregnancy was contraindicated (Editorial, Western J Med, 1971). In some European countries such as France, Netherlands and the UK the drug continued to be prescribed in pregnancy until 1977 under the name Distilbène®. However, it was not until 2000 that approval for use in humans was completely withdrawn by FDA in the US. There is a modestly increased risk of breast cancer and cervical cancer among women who had been taking DES during pregnancy (National Cancer Institute at the National Institutes of Health 2011).

Women make up over half over the world population but their health needs (except for reproductive concerns), as well as involvement in clinical research has lagged behind. Therefore, realization set in that not including women in developmental programs was becoming a significant safety concern in its own right because of the missing information about benefit-risk at the time of approval. The policy not to include women in research started to change in the US around 1986–1987 after the NIH issued guidelines urging inclusion of women for the first time in NIH Grants and Contracts (National Institutes of Health (NIH) 2003; National Institute of Health Office for Extramural Research 2014a, b). In 1990 the Women's Health Equity Act was passed and the Center for Disease Control and Prevention (CDC) established the National Breast and Cervical Cancer Prevention Program (Mikulski 1990).

In June 1993, the National Institute of Health (NIH) Revitalization Act (*An Act To amend the Public Health Service Act to revise and extend the programs of the National Institutes of Health, and for other purposes*, 1993) included the following key points:

- reauthorized certain expiring authorities of the NIH,
- mandated establishment of the Office of Research Integrity,
- lifted the moratorium on human fetal tissue transplantation research
- mandated inclusion of women and minorities in clinical research protocols
- created the Office of Research on Women's Health,
- created the National Center for Human Genome Research,
- mandated establishment of an intramural laboratory and clinical research program on obstetrics and gynaecology within The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

The law stirred much political controversy. This was particularly because the moratorium on research on human embryos from IVFs had been terminated by creation of the Human Embryo Panel. Until then, all IVF grant proposals had to be approved first by an Ethics Advisory Board and yet no such board had been reconstituted (S.1 – National Institutes of Health Revitalization Act of 1993 – Subtitle B – Clinical Research Equity Regarding Women and Minorities, n.d., p. 1).

In the Consolidated Appropriations Act of 2008, Congress provided the Department of Health of Human Services Office on Women's Health (OWH) with funds for the Institute of Medicine (IOM) to conduct a comprehensive review of the status of women's health research, summarize what has been learned about how diseases specifically affect women, and report to the Congress on suggestions for the direction of future research.

The committee focused on conditions that are specific to women, are more common or more serious in women, have distinct causes or manifestations in women, have different treatments and outcomes in women, or have high morbidity or mortality in women. The Committee identified breast cancer, cardiovascular disease and cervical cancer as conditions in which the research contributed to major progress (National Research Council 2010).

Regulation of Women's Medicines and Risk Management Plans

Current regulatory practice for maintaining a satisfactory balance of benefit and risk of medicines and ensuring proper use depends on a risk management plan involving all stakeholders. This is primarily governed by medicines legislation targeted to the pharmaceutical industry and regulatory agencies based on guidelines developed by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) ("ICH E2E" 2004). A medicines regulatory perspective on women's medicines is covered in Chap. 16 of this book and will therefore not be covered in detail here.

Call for a More Holistic Approach

From our review of the place of women's medicines, especially those for controlling reproduction, we suggest that a more holistic view of managing the risks of these medicines is needed. This should involve taking into account social, religious and political views, and long-term demographic consequences for the community and nation in case overall birth rate declines below replacement level, or exceeds limitations imposed by the community's resources.

This harks back to 1999 when the FDA produced a risk management framework for all medicines in the USA. The FDA had convened a Task Force which subsequently recommended that FDA take the opportunity to engage all stakeholders to re-examine the current system for managing the risks associated with the use of medical products. They encouraged public policy discussion that focused on defining more clearly the roles and responsibilities of all participants of the risk management system.

An activity often lacking in risk management models is risk confrontation: community-based problem solving that actively involves relevant stakeholders in the decision-making process (U.S. Department of Health and Human Services and Food and Drug Administration 1999). Even as far back as 1989, The National Research Council wrote that determining the acceptable level of risk should occur in a larger context. So even for medicines in general, social and community values are at least as important as the technical judgments of professionals and should be included in the determination of acceptable risk (National Research Council 1989).

Risk confrontation is not in ICH E2E and is not routinely part of the RMPs required by ICH agencies. Interesting, as of December 2013, there is no FDA published Risk Evaluation and Mitigation Strategies for contraceptive medicines. Given the important interaction between religious, political and social factors, we recommend for policy holders that a more robust approach is taken to managing the risks of reproductive medicines, taking all stakeholders – in particular women themselves – into account. A transparent approach to examining all concerns and sources of evidence is required. This means that concerns that were expressed about emergency contraception, as an example, could be captured as 'missing information' in a RMP. We should examine the root causes behind such a safety concern as they may need to be addressed.

Conclusions

Women with their specific needs and inevitably dependent status in certain stages of life are much more vulnerable to the effects of the political and religious environment which surrounds them. Religious beliefs of the society which surrounds them may affect their sexual and reproductive behavior at least to the same level as their own beliefs and values; and political and socio-economic environment determines choices they have with regards to reproductive behavior.

Any methods designed to control the level of human reproduction are a sensitive political as well as religious matter and a public health issue. The reproductive health of a nation is of key importance to public health. Therefore, risks associated with the use and misuse of women's medicines that control fertility and reproduction affect the health and well-being of the individual as well as long-term health of society and its sustainability.

Political decisions, socio-economic environment, culture, administrative measures, religious influences, and public policies profoundly affect decision-making of individuals and couples when and how they start a family, how many children they wish to have, how many children they do have; and spacing and timing of pregnancies. Thus we need to adapt our approach to risk management by adapting planning to social, religious and cultural variation. This will have implications for advising women about how to use medicines and for the design of educational programs about safe use of medicines for the advancement of women's well-being and health.

Take Home Messages

- Public health agencies need to understand how reproductive health of women is central to sustainable development.
- Healthy choices need to be made available to all women, including those who wish to pursue their education and career and have a family.
- Contraceptive medicines are intended to empower women to time their pregnancies better and are not intended to prevent pregnancy altogether.
- Although knowledge about contraception is expanding, as its use, there are still parts of the world where ignorance prevails.
- Even within the European Union, the social fabric of some Member States will mean that a risk management plan for a contraceptive or a plan that involves fertility control will vary. Indeed, the ability of some women to report suspected adverse reactions or other problems with women's medicines may be severely impaired.
- Risk management must adapt according to the prevailing social and religious attitudes and opinions of the time
- Clinicians/pharmacists need to understand how medicines for controlling reproduction are very different in that their benefit/risk depends on the political policies, social and religious beliefs and values within a society at any given time.
- Access to contraception and acceptability of methods depend on the cultural background of the women concerned and her set of beliefs.
- Treatments that control fertility can be an extremely delicate matter because individual circumstances even within a religious group may vary widely.
- In some political, religious or other environments safety issues may not be readily discussed or revealed and so must be sought using sensitivity and respect for an individual's cultural values.

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Chapter 17
Perspectives on Women's Health and Medicines in Developing Countries

Nighat M. Khan

To be a pregnant woman in Africa is to have one foot in the grave.

African Proverb

Introduction

This chapter takes a bird's eye view of complex health problems for women in low to middle income countries. It is important for us to first have some understanding of overall health systems, to comprehend the malfunctioning of drug manufacturing, drug registration, drug regulation and drug dispensation as part of general malady rather than a standalone problem. Although the example here is primarily of Pakistan, it can very well be reflective of the ordeals of citizens of any developing world countries. These problems range from poor country resources due to internal and external conflicts, poor governance, corruption and lack of transparency and accountability oscillating as common denominators.

This section borrows heavily its statistics from World Health Organization country profiles, regional comparisons and its Global Health Observatory. These provide the readers with a starting point. Many of these countries' problems have additional burdens of religious and socio-cultural factors and some of these aspects have been discussed in Chap. 16.

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Maternal Health Status in the Developing World

According to the United Nations (UN), health is a basic human right, yet 800 women die every day somewhere in the world due to pregnancy and child birth related causes (http://www.who.int/gho/maternal_health/en/). In 2010 a total of 287, 000 women lost their lives due to pregnancy-related complications, with 99 % of these women dying in the developing world (http://www.un.org/millenniumgoals/pdf/Goal_5_fs.pdf). According to this WHO report, out of 800 pregnancy-related deaths, 440 occurred in sub-Saharan Africa and 230 in Southern Asia, compared to five in high-income countries. The risk of a woman in a developing country dying from a pregnancy-related cause during her lifetime is about 25 times higher than a woman living in a developed country. Maternal mortality is a health indicator that shows very wide gaps between rich and poor, both between countries and within them. The precarious state of health in women in developing countries is not only due to non-availability of health care, or very limited access to health care facilities, but also whatever care is available is often substandard and unregulated.

At a recent meeting of the Commission for Status of Women (CSW 58 2014) at the United Nations (2015), the UN Secretary General Report on Millennium Development Goals (MDGs) indicated while many of its goals have been achieved – for example MDG-1 (Eradicate extreme poverty and hunger) has been on target and poverty rates have been halved between 1990 and 2010 – 1.2 billion people still live in extreme poverty (http://www.unwomen.org/~/media/Headquarters/Attachments/Sections/CSW/58/CSW58-agreedconclusions-advanceduneditedversion.pdf).

In combating HIV and malaria infection, MDG-6 is showing promise. The incidence of HIV is declining steadily in most regions but 2.5 million people are still newly infected each year (http://www.un.org/ga/search/view_doc.asp?symbol=E/CN.6/2014/L.7).

Achieving MDG-5, which has to do with maternal health, is still far from reaching its finishing line. There are several challenges in its way to success and they are as mighty as ever. The progress on achieving MDGs for women and girls is held back due to the persistence of historical and structural unjust power relations between men and women, poverty and inequalities and disadvantages in access to resources and opportunities that limit women's potentials and capabilities. Discriminatory laws, policies, social norms, attitudes, harmful customary and contemporary practices and gender stereotyping all contribute to our failure to provide rightful health to women and girls.

To develop an understanding of women health in the developing world, one has to review some maternal health statistics. There may be some variability in the quality of these statistics and they are largely determined by the health systems in each country, as well as by the methodology in obtaining these statistics. Causes of high maternal death rate are multiple, but share similar etiology in almost all developing world countries (http://apps.who.int/iris/bitstream/10665/112682/2/9789241507226_eng.pdf?ua=1; http://www.unicef.org/wcaro/overview_2642.html).

In 1990, 523,000 women lost their battle of life due to pregnancy related causes. By 2013, this figure reduced to 289,000. In 1990, MDG-5 aimed to bring down

Table 17.1 Leading causes of maternal mortality in the developing world

Cause of death	Percentage of maternal mortality
Severe bleeding	25
Infection	15
Eclampsia	12
Obstructed labour	8
Unsafe abortion	18
Indirect causes (AIDS, malaria etc.)	20
Other direct causes of maternal death	2

Source: http://www.who.int/whr/2005/en/

maternal mortality rates by 75 %. Although maternal mortality has been reduced by 47 % since the 1990s, it is a far cry from its original goal of reducing it by 75 %. Table 17.1 summarises the main causes of maternal mortality in developing countries.

Severe anemia occurs in 50 % women in the developing world. This becomes a major risk factor for maternal death when compounded by hemorrhage.

Improving maternal health is also key to achieving MDG-4 of reducing child mortality rates. Providing good and skilled care to women during pregnancy and childbirth is fundamental for saving maternal as well as children's lives. One of the sub-goals of MDG-5 was to make every pregnant woman attend at least four antenatal clinics during her pregnancy. Although births attended by skilled health personnel have increased, there are vast disparities in provision of these services within countries and within population groups.

Only 50 % women in developing nations have access to any antenatal care. Many women never attend antenatal clinics during their pregnancies. They have to rely on home birth attendants, no matter how complicated the pregnancy or labour is. This report also highlights a stark rural and urban divide in maternity care in developing nations. The rural and urban disparity statistics indicate that only 53 % rural versus 84 % urban women had access to skilled health personnel during delivery in 2011.

Postpartum hemorrhage (PPH) is still a leading cause of maternal mortality accounting for 24 % of maternal deaths despite the wide availability of uterotonics or oxytocins. Out of these, nearly half of PPHs occur within the first 24 h and 66 % during the first week of delivery (Nour 2008; Campbell and Graham 2006; Murray et al. 2012).

The figures in Table 17.1 show that indirect causes like anemia, malaria and heart disease are responsible for 20 % deaths in pregnant women in developing countries, while infection (15 %), eclampsia (12 %) and obstructed labor (8 %) are other major contributors to maternal mortality (Hogan et al. 2010; Ndola et al. 2010).

In developing countries, 46 million of 211 million pregnancies (22 %) resulted in induced abortions. The majority of these were carried out in unsafe places as 'back door' abortions, leading to 68,000 deaths annually (World Health Organization 2007; http://www.who.int/reproductivehealth/publications/unsafe_abortion/induced_abortion_2012.pdf?ua=1).

It is unfortunate that in 2008 more than 50 % of all maternal deaths worldwide were in only six countries including India, Nigeria, Pakistan, Afghanistan, Ethiopia, and the Democratic Republic of the Congo (Ndola et al. 2010).

Health and General Status of Pakistan

Any discussion on women's health care issues in a developing country would be incomplete without studying health indexes. As stated above, Pakistanis used as a model Lower to Middle Income Country. The statistics in many developing countries present similar pictures.

Pakistan with a population of 180 million is the sixth most populous country in the world. The total health budget has remained unchanged over decades and has remained at around 2 % of Annual GDP. The country has a per-capita annual income (PPP, current international $) of US$2,655.3 and is ranked 110 out of 186 countries in the Human Development Index (HDI) (http://www.unicef.org/infobycountry/pakistan_pakistan_statistics.html; http://data.worldbank.org/indicator/SH.XPD.PCAP).

Fifty-five percent of Pakistani females above 15 years of age are illiterate. Thirty-six percent of the population is under 15 years of age, with a life expectancy of 63 years. Only 48 % of the population has access to sanitation (http://who.int/gho/health_equity/countries/pak.pdf?ua=1; http://www.worldbank.org/mdgs/maternal_health.html). Pakistan remains impoverished and underdeveloped.

The Gender Inequality Index (GII) for Pakistan is 0.567 and ranked 123 out of 186. The GII is similar in method to the inequality-adjusted Human Development Index (HDI). Loss of HDI is reflected by the gender inequality in that country which is measured through use of GII metric (http://hdr.undp.org/en/faq-page/gender-inequality-index-gii). The GII is interpreted as a percentage loss to potential human development due to shortfalls in the dimensions included. Since the GII includes different dimensions than the HDI, it cannot be interpreted as a loss in HDI itself. Unlike HDI, higher GII values indicate lower achievements. The world average GII score is 0.463, reflecting a percentage loss in achievement across the dimensions due to gender inequality of 46.3 %. While Netherland has gender inequality loss of only 4.5 %, Yemen has 74.7 % loss of HDI due to gender inequality. The European average is 28 % while Sub-Sahara Africa stands at 58 %. Pakistan with a GII of 0.567 suffers a loss of 56.7 % which is regional average (56.8 %) for South Asia.

Pakistan has a multi-tiered and mixed health care delivery system that has grown exponentially during the past three decades, with an increasing number of programs, projects, interventions and facilities, many of them on a fragmented and time bound basis. These are supported by different levels of government and/or development partners with overlapping geographical and thematic areas, leading to duplication and wastage of resources.

Public sector spending on health is a mere 26 % of the total health budget. Seventy-four percent of outpatient care is catered for by the private sector. In 2011,

the federal Ministry of Health was abolished after introduction of the 18th constitutional amendment and health and education services were transferred to the provinces. The five provincial governments now have their individual health and education ministries. This resulted in fragmenting the health services even further and whatever central cohesion in health policy there was before devolution of powers, was fractured even more. The country's health sector is also marked by urban-rural disparities in healthcare delivery and an imbalance in the health workforce, with insufficient health managers, nurses, paramedics and skilled birth attendants in the peripheral areas (http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_pak_en.pdf; http://www.nips.org.pk/abstract_files/Priliminary%20Report%20Final.pdf; http://www.who.int/mediacentre/factsheets/fs348/en/). In many situations, access to social security health care centers has decreased in Pakistan, the brunt of which has been borne by women.

Tables 17.2 and 17.3 summarise the above facts: Table 17.2 summarises the WHO country profile in very general terms, while Table 17.3 is a comparison of Pakistan with other countries of South East Asian region

Table 17.2 Pakistan WHO country profile (2011)

Country population	**180, million (last official population census carried out in 1998)**
Population living in urban areas (%)	36
Gross National Income ($) (annual)	2,870.2
Life expectancy at birth in years (both sexes)	67
Life expectancy at age 60 in years (both sexes)	18
Total fertility rate per woman[a]	3.3
Maternal mortality ratio per 100,000 live births	260
Under 5 Child Mortality rate per 1,000 live births	72

[a]The total fertility rate represents the number of children that would be born to a woman if she were to live to the end of her childbearing years and bear children in accordance with current age-specific fertility rates (http://data.worldbank.org/indicator/SP.DYN.TFRT.IN)

Table 17.3 Regional comparisons of utilization of health services in Pakistan compared with other countries in South East Asia

Contraceptive prevalence	**27 % versus 45 % in South East Asia**
Antenatal visits (4+)	28.8 % versus 44 % in South East Asia
Birth attended by skilled personnel	45 % versus 63 % in South East Asia
Physicians/10,000 patient population	8.1 versus 10.8 in South East Asia
Nurses and Midwives/10,000	5.5 versus 15.9 in South East Asia

From the figures shown in this table it is quite obvious that Pakistan is even lagging behind her own neighbours in the delivery of women's health care

African Perspectives on Women's Health Care

Whilst this chapter focusses on South East Asia – and Pakistan in particular as a key example – there are similar issues for women in other developing nations in other regions of the world. Whilst writing the risk communication chapters for this book (Chaps. 18 and 19) Bruce Hugman spent some time in Ghana in West Africa and conducted some informal interviews with local women. He gained some interesting perspectives on health care and broader issues for women in Ghana and a summary of his findings are presented in Box 17.1.

Box 17.1: Impressions of Women and Risk in West Africa
Supplementary material from Bruce Hugman
During the writing of Chaps. 18 and 19, the author spent some time in Ghana. He spoke at length with three senior and experienced female workers in the fields of health and patient safety from Ghana and Togo. The issues that arose from these conversations were fascinating, radical and relevant to this book, risk communication and this chapter on developing countries. Though markedly different in detail, many of the fundamental questions raised here have resonance for women everywhere.

Women's health risks and risk communication issues for women in Africa were said to be determined by two major factors:

- The socio-economic position of women in Africa and their domestic subjection
- The general lack of communication of any serious kind between health professionals and their patients

In most matters regarding every aspect of women's lives, with the exception of a small percentage of educated and independent women, men call the shots – economically, socially, sexually, even with regard to access to health care, HIV testing, and so on. Women's relative lack of education and employment skills puts them in thrall to their men, and, by extension, makes them largely passive recipients of healthcare when they receive it.

There were instances quoted of wives who were HIV positive, even when pregnant, who were too frightened to tell their husbands, fearing a beating or outright rejection. Given that many African men despise condoms, and some, maybe many, are sexually promiscuous, women are at great risk of infections of all kinds in sexual relations over which they have little choice and little power of refusal. Cultural practices such as a man's obligation to pay a 'bride-price' – giving him a sense of purchase and ownership – and bride-inheritance – where a widow is forced to marry her husband's brother or nearest male relative – reinforce women's powerlessness in a male-dominated world.

(continued)

Box 17.1 (continued)

The Chief Pharmacist at a major hospital in Accra spoke of a male patient who had dismissed her medication advice out-of-hand as lacking credibility coming from a woman. Women, on the other hand, will listen passively to what a doctor may say, especially a male doctor, and not raise questions or doubts for fear of seeming disrespectful or of causing upset. One woman was found to be leaving the hospital after her monthly HIV consultation without collecting her medication, a fact that was not discovered for some considerable time.

While some practitioners withheld risk information for fear of discouraging or alarming their patients, local experience suggested that many women welcome clear and accurate information, yearn to know more and thus have greater control over their own health and that of their children. African women appear to have a strong preference for female health workers. Men, prone in some instances, for example, to dismiss serious symptoms of PMT as 'laziness' are not always natural counselors for women, even if they had more time. In Ghana, women do have the choice of a male or female gynaecologist.

The Lady Pharmacists Association of Ghana (Lady Pharmacists of Ghana), a branch of the Pharmaceutical Society of Ghana, was established more than two decades ago to address these issues. It has blazed a path of useful communication throughout the country. Their method is to make themselves available to groups of women in their communities and to girls in their schools and to engage with them on issues and questions of importance to them. It is evident that exchanges of this quality and depth rarely, if ever, take place in clinics or pharmacies. It is said that women have faith in health workers.

There are other major initiatives to improve the education and health of women, such as Camfed Ghana, and the UN-inspired campaign Every Woman Every Child. The importance of supporting girls in their general and health education and improving the status and skills of women is recognised worldwide as a vital step in social development. The gap between urban and rural communities remains enormous.

On the day of one of the conversations reported here, a 10 year-old victim of rape was brought to the hospital for emergency contraception and post-exposure prophylaxis for HIV – 2 full weeks after the incident. She and her mother had to be told that there was nothing that could be done. Shame, guilt, ignorance, fear, who knows what crippling emotions, had prevented action being taken when it could possibly have helped the child.

There are immense challenges to be met in overcoming irrational practices and their risks. There are widely-held beliefs, for example, that intense 'cleansing' of the body through vaginal douching (also believed to tighten

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Box 17.1 (continued)

the vagina), enemas (including shared enemas in public baths), or the frequent use of laxatives will lead to improved health. This echoes the belief that a medication that provokes vomiting must be strong and effective. There is profligate use of antibiotics, available on the streets everywhere, marketed illegally on local and long distance buses and from vans with loudspeakers touring villages. The risks of resistance, interactions and reduced effectiveness of oral contraceptives are commonly unknown. Women are under great pressure to be plump and rounded, leading to excessive eating and the use of non-prescribed steroids. The search for the illusion of beauty through skin-whitening, with often unapproved, toxic products has further put women's health at risk.

Spacing of children is a women's issue. Though urban African women are reducing the number and frequency of their pregnancies through assertion and conscious management, things are not so easy in rural communities where multiple pregnancies are real threats to women's health, strength and, of course, their potential to develop in any other role or activity beyond motherhood and housekeeping. Public health programmes, such as those distributing the quarterly-injectible contraceptive Depo-Provera have good intentions to address this and other issues, but it is reported that there is next to no risk information accompanying the distribution and that no kind of active, informed consent is involved at all. That such a contraceptive method leaves women vulnerable to infection is not widely grasped and it does nothing to affect male condom-aversion.

Many women consider pregnancy a private affair, not to be spoken of until it is evident. This leads to delay, often up to the time of labour, before professional, ante-natal support is sought. Delay in seeking healthcare may be for more immediate, practical reasons too: if a visit to a clinic means a day's produce can't get to market and will rot, there are strong incentives to neglect personal health for family income.

In a report for CNN, Steve Murigi adds support to many of these observations:

> For many women in Africa, an astounding lack of information means they simply do not see or understand the reasons for attending antenatal and postnatal health services, let alone see the value added by giving birth at a health center. Moreover, the absence of information has hampered initiatives designed to prevent mother-to-child infections, as well as immunization.
>
> For women in many rural communities, the norm is for a traditional birth attendant (TBA) to assist the delivery instead of making the trip. TBAs often have no formal training and deliver without sterilized equipment, if any, causing yet more risks for mother and baby.

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Box 17.1 (continued)

> Every year in sub-Saharan Africa, 162,000 mothers die needlessly because of complications during pregnancy and childbirth. That figure represents a staggering 56 % of the global total. (Murigi 2013)

Herbals and traditional medicines remain popular, probably prevalent in rural communities, and the services of fetish-priests and other traditional healers may be sought before orthodox help. A child suffering from convulsions, for example, was reported to have been critically ill by the time he had been on a long journey to hospital via several time-consuming and fruitless visits to traditional practitioners.

The risks of counterfeit, substandard and/or untested medicines remain very high in Africa. Ghana recently had a major scare with the promotion of an anti-malarial suppository for children containing amodiaquine and artesunate, a combination never subject to clinical trials as a suppository in any population in its country of origin, India, or anywhere else.

The rush to medication, whether prescribed or self-administered, poses real risks, especially during pregnancy and for menopausal women. Antidepressants and sleeping pills are widely prescribed and taken with little or no understanding of short-term effects and longer-term risks. It is not always understood that anti-hypertensive drugs must be taken for life, not just for the first batch, as appears to be the case from time to time. This is one aspect of a cultural disposition that does not focus on consequences beyond what is immediate or very close. Cost is a major issue in decisions about therapy and adherence.

So what are the remedies for these multiple problems and risks? Our contributors, The Lady Pharmacists Association of Ghana, and many other influential groups are convinced that only the education and empowerment of women will improve knowledge, effective rational behaviour and reduce the risks. This high-level, radical aspiration appears to be fundamental to progress. The face-to-face engagement of health workers – essentially female too – with women in the community seems to be a priority path to take. In countries where the prevalent languages have no written form, or none known to the majority of the population, the printed word is useless. The spoken word, with, maybe, the support of short texts and phone contact, visual images and pictograms, may be the most important channels.

Radically improving the quantity and quality of information at the point of prescribing and dispensing must be a priority. The widespread illegal dispensing of medicines without the presence of a pharmacist is a major challenge to safety and to regulation and enforcement.

The understanding and treatment of mental illness, though not exclusively women's issues, are seriously neglected in sub-Saharan Africa, with maybe

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Box 17.1 (continued)

two thirds of cases unrecognised and untreated (allAfrica 2013). Mental illness has an impact on all aspects of women's health and welfare. With mental illness regarded in many places with superstitious fear, women are particularly vulnerable to stigmatisation, exclusion from their families and communities, and to physical abuse and to rape (Otieno 2013). Such facilities as there are, often outside government regulation and control, can be primitive and abusive (Edwards 2014).

The issues that put women at risk are so many and so varied, that only their demand, the raising of their voices for full information and disclosure, and for just, non-discriminatory treatment will, eventually, afford them the protection they need. Only a revolution in relations between the sexes will free women in Africa to take charge of their own reproductive and general health and to become empowered, to manage the multiple risks to which they are vulnerable, and to become fully-contributing citizens.

Drug Availability and Dispensation in the Developing World

Having reviewed some of the health indicators for women in a developing country we will now look at the prevalent systems of drug availability and dispensation in Pakistan and give some comparisons with other low and middle income countries around the globe.

Inequity of access to modern medicines in developing countries is highly undesirable and demands urgent action. It is reported that only 15 % of world's population utilizes 91 % of pharmaceutical products worldwide, whereas only about of third of lower and middle income countries have access to essential drugs (Caldera and Zarnic 2004).

Regional socio-cultural factors in developing countries compound this inequality of access to medicines by women, as learned when access to human immune deficiency virus (HIV) epidemic care was investigated. Rural women were least likely to gain access to anti-retrovirus drugs in African countries (AFP Report 2001).

It is reported that out of nearly four million HIV infected people (both men and women), only 10,000 (0.25 %) can afford essential AIDS medication at the marketed prices. In Malawi, this figure is reduced even further to 30 out of a million (0.00003 %) HIV-infected population. In Uganda only 1.2 % of 820,000 HIV patients can afford anti-retroviral medicines. A similar scenario is repeated in most developing world countries. Brazil is one of few countries which have provided generic anti-HIV medication to HIV patients with a significant fall in HIV-related deaths (Ahmad 2005). Currently the state run '*Programa Nacional de DST e Aids*' use eight patented antiretroviral drugs. Under this program, 159,000 HIV infected people receive these drugs free of cost.

Some argue that generic drugs provide an economically viable alternative in the developing countries. However, average public sector availability of generic medicines ranged from 29.4 % to 54.4 % across WHO regions in Asia (Cameron et al. 2009).

Pharmaceutical Products and Their Distribution in Pakistan

As discussed above, drug regulation and drug dispensation are poorly controlled and regulated in most developing countries. Pakistan is no exception.

A report by the WHO on regulation of pharmaceutical products provides an insight to the state of affairs in Pakistan (http://www.who.int/medicines/areas/coordination/pakistan.pdf). Pakistan has 4,000 registered pharmacists and 25 times more merchants dispensing medicines illegally, according to the Pakistan Pharmacists Association (http://www.ppma.org.pk). The total number of licensed pharmacists is 0.43 per 10,000 people living in Pakistan.

The annual expenditure on health per capita was US$39 as compared to Denmark which spends US$6,304 during 2009–2013 (World Bank Report 2013) (http://data.worldbank.org/indicator/SH.XPD.PCAP).

On average the government spends only 29.7 % of total pharmaceutical expenditure; private health expenditure covers the remaining 70.3 % of the total pharmaceutical expenditure. There are only 0.92 per 100,000 pharmacies in the public sector. 67 % of pharmaceutical personnel are pharmaceutical assistants and technicians with only 33 % qualified pharmacists at present.

The total pharmaceutical expenditure (TPE) in Pakistan for 2007 according to a WHO report was 112,000 million Rupees (Pakistani currency currently equivalent to 0.0102 US dollar). The pharmaceutical expenditure per capita was PKR 683 (US$6.96). The pharmaceutical expenditure accounts for 1.29 % of the GDP and makes up 47.28 % of the total health expenditure.

Public expenditure on pharmaceuticals represents 27.1 % of the total expenditure on pharmaceuticals. The public expenditure on pharmaceuticals per capita in 2004 was PKR 118.6 (http://www.who.int/medicines/areas/coordination/pakistan.pdf).

Poor budget allocation by the state along with equally questionable regulation on dispensing and sales of pharmaceutical products has led to free availability of almost all drugs over the counter. Almost any pharmaceutical product can be bought over the counter and without prescription. Regulation and inspection of pharmacies and drug stores is contaminated with corruption and bribery. Even the regulation of manufacturing by local pharmaceutical companies is non transparent and corrupt. Although multinational pharmaceutical companies claim to have strict quality controls, there is no control over counterfeit medicines. The counterfeit culture has its own language to denote a counterfeit product and there are various degrees of spurious additions. The product can have fake quality number assigned to it. A 'good quality' fake will have some degree of impurity and is called

'deau-number' (in local language deau stands for two in Urdu or fake quality number 1). If there is a product which is of poorer quality or a step down from deau-number it is called 'teen-number' (teen stands for three in Urdu or fake quality number 2). These are available for virtually any medicinal product coming to market. These manufacturing units are present in many big cities of the country. The packaging and copying is done to the highest level. It is a multibillion dollar industry and Pakistan is one of the top ten countries exporting counterfeit drugs to the US (http://www.bloomberg.com/news/2012-05-17/stopping-fake-drugs-from-pakistan-is-too-late-for-victims.html; http://pakistancriminalrecords.com/tag/spurious-drugs/).

The Punjab Institute of Cardiology Tragedy

Dispensation of counterfeit products unfortunately led to loss of lives at the Punjab Institute of Cardiology Lahore (PIC) Pakistan in January 2012 (http://tribune.com.pk/story/326824/pic-free-medicine-as-deaths-soar-past-80-authorities-still-clueless/). The year 2012 had a very inauspicious start for many poor and unsuspecting patients in a northern city of Pakistan (Fig. 17.1).

Fig. 17.1 Queuing up for death. Women outside pharmacy counter at Punjab Institute of Cardiology Lahore Pakistan (Source: http://tribune.com.pk/story/326824/pic-free-medicine-as-deaths-soar-past-80-authorities-still-clueless/)

In January 2012, several patients attending a public health care institution the Punjab Institute of Cardiology (PIC) Lahore experienced unusually high fatal adverse events on taking a tablet by the name of Isotab. This medicine was dispensed without any cost to PIC patients and local pharmaceutical companies were given contracts to supply this public hospital (Arie 2012). It was reported that Isotab caused bone marrow suppression and aplastic anemia, resulting in generalized bleeding followed by death within few days. These patients had reached hospitals with complaints of non-stop bleeding from different parts of the body and dark spots all over. More than 200 patients lost their lives. The death toll could be higher as many deaths went unreported. In Pakistan it is a socio-religious norm to accept death as result of fate and post mortem examination is considered desecration of a dead body (http://paktribune.com/news/PIC-deaths-London-lab-declares-Isotab-as-contaminated-medicine-247196.html).

According to details which subsequently came to light when samples of Isotab were dispatched to a drug testing laboratory in London, this medicine was substandard and injurious to health. The results revealed that samples were heavily contaminated with dangerously high levels of Pyrimethamine, an antimalarial drug.

Noises in the media caused the government to have a knee-jerk response. The Federal Investigation Agency (FIA), seized a huge quantity of the suspected medicines during a raid on the warehouse of Pharmawise Lab (PVT) Limited, including 29,400 tablets of one the drugs. Three more pharmaceutical laboratories which supplied the medicines to PIC were raided too. This revealed large scale corruption in Drug Inspection. A protest was held outside the PIC by relatives of patients who had died, as well as by those who were not receiving sufficient free medicines from PIC since the scandal broke.

In a similar knee-jerk response to this tragedy, the Drug Regulatory Authority Pakistan (DRAP) act 2012 was announced with a mandate of regulatory drug registration and distribution and quality assurance. The DRAP act has a mandate to regulate manufacture, import, export, storage, distribution and sale of therapeutic goods (http://drap.org.pk/DRAP%20ACT.htm).

Sadly the manufacturers of these killer drugs, the main culprits of above incidence got away unpunished due to political connections and bribery. Had they been punished, many unfortunate killings by spurious drugs would have been avoided.

Box 17.2 opposite shows a press cutting from an English daily newspaper, the Express Tribune, published more than 2 years after the Institute of Cardiology tragedy in Lahore (http://tribune.com.pk/story/687276/bad-business-spurious-drugs-seized-two-arrested/) (Box 17.2 and Fig. 17.2).

Even with the DRAP act in action, there continue to be many reports in the local and international press about manufacturing and export of counterfeit drugs (http://tribune.com.pk/story/687276/bad-business-spurious-drugs-seized-two-arrested/; http://tribune.com.pk/story/686629/karachi-residents-arrested-for-allegedly-smuggling-fake-medicines-to-malaysia/).

Box 17.2: Bad Business: Spurious Drugs Seized, Two Arrested
By *Asad Kharal*: Published: March 26, 2014

Lahore: **Spurious drugs were seized from a factory in Kot Abdul Malik, Sheikhupura, on Monday.**

"Raw materials and machinery were also seized in a joint raid by the Federal Investigation Agency (FIA), the Health Department and police," FIA Director Usman Anwar told *The Express Tribune*.

He said the 'medicines' being manufactured included Exelza 3 mg (Z-Jans Pharmaceutical) and Penegra 100 mg.

"The machinery seized includes a tablet making machine, a packing machine and a mixer."

The FIA director said two factory workers had been arrested in the raid.

Separately, spurious drugs were seized from a factory on Bund Road, Lahore. FIA said the Lahore drug inspector helped the Federal Investigation Agency in the raid.

The 'medicines' seized include Lexotanil, Humulin, Neurobion, Vancomycin, Cefaxone, Cilapen, Acyclovir, Rasibid, Penro, Neuromed, Oxidil, Megodine and Hydro.

FIA said two workers had been arrested.

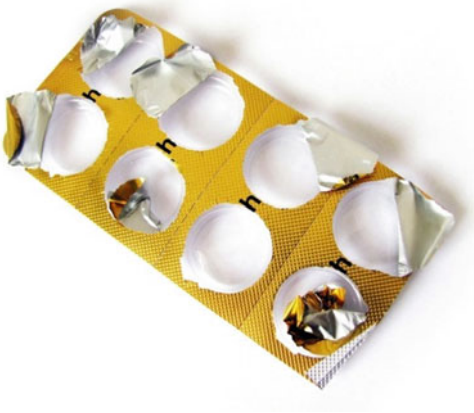

Fig. 17.2 Pain staking measures are taken by these traders of death to make the packaging as similar to the original product as possible. Only on close scrutiny and a discerning eye can detect the difference in appearance (Source: http://paktribune.com/news/PIC-deaths-London-lab-declares-Isotab-as-contaminated-medicine-247196.html)

Drug Courts, Tribunals and Drug Inspectors

Drug courts were established in Pakistan under the drug act 1976 to prosecute those violating the law concerning export, import, storage, distribution and sales of drugs. The Karachi (the largest city of Sindh province) drug court is still lodged in a temporary site since its inception.

The premises are inadequate and have poor security arrangements. It lacks storage facilities for confiscated counterfeit medicines. According to the drug laws, the quality control board members should hold at least one meeting in 60 days, but most of the times, they failed to hold meetings on time causing a delay in the approval of cases against counterfeit drugs for trial (http://www.dawn.com/news/743210/110-cases-pending-in-drugs-court). Even if the board members do meet up, if drug inspectors are not present on tribunal hearing day, the court has no jurisdiction to execute any prosecution orders.

The role of drug inspectors in controlling the counterfeit pharmaceutical products is highly questionable. These inspectors have failed to check the manufacturing of substandard medicines. In the past 2 years only 100 cases of malpractice were registered and those were only of minor violations. Many inspectors failed to register a single complaint between January 1st 2012 and March 2014. These statistics are released by Drug Courts Sind. In a city of Karachi with a population of 23.5 million only 38 cases were lodged. Looking at these figures, one is certain that other provinces will show similar trends.

Health Care Personnel and Access Issues for Pakistani Women

While we bemoan a lack of quantity, the lack of quality of health care personnel also needs serious addressing. As we have seen in the earlier sections of this chapter, a lack of trained work force (8.1 doctors/10,000 population and 5.6 nurses and midwives/10,000 population) has led to the vast majority of the population seeking health elsewhere. However, there are many (unregulated) traditional practitioners like hakims and Dais (local birth attendants with questionable or no formal credentials) to fill the gap.

This unfortunate scenario is especially true for female patients including women, adolescent women and girls. Like any other economic, social or cultural problem the end result is women being the major sufferers. They receive the poorest of poor health care services. Rural women are worse off. Poor access to regulated and trained health workers by women leads to their approaching untrained and fake practitioners. Poor access to fertility control or family planning centers due to social cultural and religious reasons leads to unwanted pregnancies and unsafe abortion causing high morbidity and mortality amongst women.

Abortion is illegal according to Pakistani laws unless the life of mother is in danger, hence women who seek termination of pregnancy resort to back door abortion clinics resulting in high morbidity. In a large nationwide study (http://www.guttmacher.org/pubs/IB_Abortion-in-Pakistan.pdf), 890,000 induced abortions took place in 2002, amounting to 29 abortions per 1,000 women of reproductive age. Of every 100 pregnancies, 14 ended in induced abortion. This study, conducted by Guttmacher Institute in collaboration with National Committee for Maternal and Neonate Health Pakistan, is one of the largest nationwide studies. The study highlighted, that the majority of women undergoing induced abortion (70 %) were less than 30 years old and were married. Since termination of pregnancy is allowed in limited conditions, women who seek it, subject themselves to clandestine and unsafe procedures.

Prescribing Habits of Doctors in the Developing World

Hand written prescriptions are a nightmare to read anywhere! Physicians in the developing world have the added burden of seeing large volumes of patients; hence the chances of errors are many fold.

Some interesting studies on the circumstances in which a doctor in a developing world writes a prescription have been published. Similarly, audits of prescriptions written by doctors here in Pakistan have revealed disturbing facts. An average doctor in his or her outpatient clinic in any public sector hospital has 70 plus patients to see in 4–5 h in any specialty. One can do the calculations to see how much time on average is spent per patient and this will reflect on quality of their care. This observation was ratified by a recent WHO study**.**

According to WHO's World Medicine Situation 2011 report (http://www.who.int/medicines/areas/policy/world_medicines_situation/WMS_ch6_wPricing_v6.pdf), on average doctors in developing countries spend less than 60 s prescribing medicines and explaining the regimen to their patients. As a result, only half of the patients receive any advice on how to take their medicines and one third of them don't know how to take their medicines immediately on leaving the facility. Though around 80 % of all prescribed medicines are dispensed, this is usually done by untrained personnel. As many as 20–50 % of medicines are not labeled and no Patient Information leaflet is provided to the patients.

According to the WHO report, "the dispensing process greatly influences how medicines are used. The WHO database shows that, on average, dispensing time is one minute. In such circumstances it is not surprising that patient adherence to medicines is poor."

A recent study conducted in Pakistan (2014) investigated prescribing habits of general practitioners in Pakistan (Raza et al. 2014). In a cross sectional survey of drug prescriptions in six teaching hospitals, 1,097 prescriptions were analysed to assess completeness, average number of drugs, prescription frequency of various drug classes and number of brands prescribed.

The results of this study reflect the general trends of poor training as well as accountability in public sector health care. Seventy-eight percent prescriptions failed to mention the indication or the diagnosis for treatment. The dosage, duration of use, signature of physicians and instructions for taking drugs were missing in 63.8 %, 55.4 %, 18.5 % and 10.9 % respectively. No prescription contained all essential component of a prescription (Siddiqi et al. 2002). The conclusions of this study are not dissimilar to the WHO study.

Pharmacovigilance and Adverse Drug Reporting

Lazarou and colleagues suggested that adverse drug reactions (ADRs) caused over 100 000 deaths in the United States in 1994 (Lazarou et al. 1998). Worldwide adverse drug reactions and events account for 0.2–20 % hospital admissions and are fatal in 3–7 % cases (Pirmohamed et al. 2004). Considering poor drug regulation and manufacturing systems with an ever increasing risk of spurious drugs, adverse drug reporting systems and pharmacovigilance face many challenges in developing countries.

Due to a lack of trained staff in pharmacovigilance, the WHO designated Poison and Toxicology wards in public sector hospital in Pakistan as Centers for Pharmacovigilance and adverse drug reaction reporting centers. The outcome of such delegation was there was very little adverse drug reaction reporting by these centers. These centers remained treatment wards for accidental or deliberate poisoning cases.

Only recently two separate Centers of Pharmacovigilance were inaugurated in Lahore and Karachi . Karachi center is located in a public sector tertiary care teaching hospital. Pharmacists are playing key role in these institutions, hence one may hope, some adverse drug reaction reporting will begin to be carried out (http://www.pharmanews.pk/pharmacovigilance-program-pakistan-pvpp/; http://www.pulsepakistan.com/index.php/main-news-july-1-13/381-pharmacovigilance-centre-established-at-duhs). These centers have begun their work only recently. It is difficult to forecast how effective they will be and whether they will be any focus on medicines for women.

Medicines Used in Women Health

After addressing the general situation in a developing country such as Pakistan, we will now address some of the individual types of drugs used in gynecology and obstetrics in low to middle income countries.

Contraceptives

A recent report on contraceptive use by the WHO highlights that contraceptive use has increased in many parts of the world, especially in Asia and Latin America, but continues to be low in sub-Saharan Africa. Globally, use of modern contraception has risen slightly, from 54 % in 1990 to 57 % in 2012. Regionally, the proportion of women aged 15–49 reporting use of a modern contraceptive method has risen minimally or plateaued between 2008 and 2012. In Africa it went from 23 % to 24 %, in Asia it has remained at 62 %, and in Latin America and the Caribbean it rose slightly from 64 % to 67 %. There is with significant variation among countries in these regions (Kaunitz et al. 2008).

Use of contraception by men makes up a relatively small subset of the above prevalence rates. The modern contraceptive methods for men are currently limited to male condoms and sterilization (vasectomy).

Oral Contraceptives

According to the WHO, an estimated 222 million women in developing countries would like to delay or stop child bearing, but are not using any method of contraception (http://www.who.int/mediacentre/news/releases/2014/guidance-contraceptive/en/). The report reinforces a key finding of the role of family planning in reducing the need for unsafe abortion. Moreover, the practice of family planning is in sync with the basic health rights of young women and men, to determine the number and spacing of their children which in turn improves maternal and child health. Countries where, contraceptive use is sub-optimal have higher fertility rates or vice versa (http://www.who.int/reproductivehealth/topics/family_planning/en/#story-03).

The total fertility rate in Pakistan like most developing countries is around 3.3/woman on average as compared to global average of 2.4/woman. On dissecting these statistics, birth rate is higher in women with poor literacy and socioeconomic status, as compared to educated and higher income class women. Population control is the key to human development and resource allocation. However, oral contraceptive use in Pakistan is around 27 % which is just above half of the regional figure of 45 % in Southeast Asia. The usage is primarily in urban areas. Contraceptive medicines and devices are available in family planning centers and in private pharmacies over the counter and without any prescription. Almost all the hormonal contraceptives oral as well as injectable products are available in this market, both marketed by multinationals as well as manufactured by local pharmaceutical companies.

In spite of the wide availability of contraceptives, we still see poor usage of contraceptive products in Pakistan. Visits to family planning centers in urban areas reveal large volumes of patients. Unfortunately the attending women have variable

literacy rates and the time spent with each patient is never enough to explain the usage, side effects and possible drug interactions with other medicines. Poor understanding and too little time spent per woman in these centers contribute to poor compliance of fertility drugs (Naqvi et al. 2011).

The Pakistan Reproductive Health and Family Planning survey (2000) found a wide gap between knowledge and use of contraceptives: 97 % of couples questioned knew about contraceptives but only 28 % of married women actually used them. Another study in a tertiary care hospital in Lahore asked over 200 women of reproductive age about their knowledge and use of contraceptive methods. The demographic revealed that educational status of the majority of women was below matriculation, with 88 % women being housewives. 68 % of these women were aware of the pill and 55 % had heard of intrauterine contraceptive devices (IUCD). Less than half of these women were actually using some sort of contraceptive. The most common method of contraceptive was a barrier method (15 %), followed by an IUCD (10 %) and the oral contraceptive pill (10 %). When asked about their attitude towards contraception, 85 % of these women and 74 % of men wanted family spacing and birth control (Khawaja et al. 2004).

In addition to usage of contraceptive medicines in the developing world, we also need to look at the safety aspect of hormonal contraceptives. Safety of oral contraceptives (OCs) has been a cause of concern worldwide especially with regard to the risk of venous thromboembolic with third generation progestogens, which is discussed in some detail in Chap. 6. The WHO conducted a large case-controlled study in 21 centers in Africa, Asia, Europe and Latin America (World Health Organization 1995). In both Europe and the developing countries, use of OCs was associated with 3–4 fold increase in venous thrombo-embolism. This risk was particularly high with third generation OCs. Desogestrel containing OCs had threefold higher risk than levonogesterol. Many observational studies conducted in different countries have confirmed these finding.

The reporting of drug-related adverse events is not optimal in the developed world (Edwards and Aronson 2000; Stephen 1998). Although ADRs are hardly reported in developing world, it cannot be assumed that these disorders rarely occur here. A case report of a 42 year woman attending the Aga Khan University Hospital Karachi, Pakistan (Sheerani et al. 2006) is summarized in Box 17.3 below.

The Aga Khan University Hospital is a private tertiary care teaching hospital. Her life was saved only because she was cared for in a private center. Unfortunately paucity of finances in the public sector would have led to fatal consequences in her case had she reported to public hospital.

The benefits of OCs are prevention of unplanned pregnancy with high degree of effectiveness, convenience and reversibility. However choice of right contraceptive and screening of a woman is therapeutically sound judgment call.

As highlighted above, issues of quality control and quality assurance in pharmaceutical products is marred by lack of political will and corruption leading to unfortunate outcome of counterfeit products is fertility failure and unsafe abortions.

Box 17.3
A 42 year old house wife was admitted to the stroke unit with sudden onset of left sided numbness and mild weakness. She was otherwise healthy with no history of any previous medical problems.

On examination her weight was 64 kg, blood pressure was 130/79 mmHg, pulse 80 per minute and she was afebrile. General examination was unremarkable. Cardiac and respiratory examination was also normal.

Neurological examination showed normal cranial nerves except for mild flattening of the left naso-labial fold. There was mild weakness on the left side which was graded as 4 on MRC scale. Left side also showed decreased sensation as compared to the right side.

Magnetic Resonance Imaging (MRI) of the brain showed small right parietal stroke. Magnetic Resonance Angiogram (MRA) was normal.

A workup for hypercoagulable state was performed including anti-phospholipid antibodies; protein C & S activity, antithrombin III, Factor V leiden deficiency and homocystein levels were within normal range.

As no definite cause of stroke was found, the history was re-assessed. Patient was asked several directed questions about medications. It was revealed by the husband that she had been on oral contraceptives for several days prior to this episode. She took oral contraceptives to cease her menstrual cycle temporarily as she was going for 'Hajj'. This information was not disclosed by the patient.

Magnetic Resonance Venogram (MRV) was performed after this information and a thrombus was seen in the right transverse sinus.

Patient was started on anticoagulation and she recovered completely.
Source: Sherani et al. (2006)

Injectable Contraceptives

Nearly 35 million women use injectable contraceptives worldwide, twice as many as last decade (Nair 1986). In the sub-Saharan region nearly one third of women of reproductive age rely on an injectable contraceptive to avoid pregnancy. This is more than for any other contraceptive used in developing countries. The depot form of medoxyprogesterone 150 mg administered every 3 months is a popular choice as failure to take a daily dose is not an issue. Injectable contraceptives are freely available in family planning centers as well as over the counter in Pakistan. Women can buy these injections over the counter and take them to nearest health clinic. If there is no such facility in their vicinity, they often end up in unregistered centers.

The World Health Organization has issued a list of indications and contra-indications to auxiliary workers about use of injectable contraceptives (http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf?ua=1). However, their safety is hardly discussed in family planning centers where consultation is carried out in a hurried attempt to accommodate more women.

While depot medoxyprogesterone acetate (DMPA) is a highly effective contraceptive used by millions of women, its use is associated with bone mineral density (BMD) loss, raising concerns about long-term risk of osteoporosis and/or fractures. Many studies have expressed concerns with injectable contraceptives and loss of BMD (Scholes et al. 2002; Cundy et al. 1991) citing its association with osteopenic effects leading to reduced BMD. Although reduced BMD is a concern and screening is too expensive for most developing countries, these effects on bone density are reversible and disappear (Kaunitz et al. 2008) within 24 weeks of their discontinuation.

Emergency Contraceptives

The emergency contraceptive (EC) pill (discussed in detail in Chap. 7) has been available for over three decades in Pakistan. However, a quantitative study carried out in a teaching hospital in Karachi in 2009, revealed that 88 % of women were not aware of EC. The vast majority of these women were housewives (83 %) and only 11.5 % had ever used EC to prevent pregnancy. Amongst these users, the correct timing of effectiveness of post-coital pill was known to 40 % only. None of these women were aware of use of IUCD insertion as an option for EC (http://www.who.int/mediacentre/factsheets/fs244/en/).

About half of the women in this study identified general practitioners or family medicine clinics as their main sources of knowledge about EC. Increased advertising was considered desirable by 72 % while 37 % considered over the counter availability of EC pill desirable. Interestingly, while 97 % of the population in Pakistan is Muslim, only 36 % of the women interviewed, were uncomfortable about using EC because of religious reasons. The authors of this study concluded that EC has the potential to offer Pakistani women an important option for fertility control. Lack of women's knowledge about EC use and availability may account in part for its limited use. There is a need to improve women's education about EC and primary health care providers can play a major role in informing their patients about this method of contraception (Irfan et al. 2009; Hamza et al. 2009; Khanum et al. 2010).

A similar study was conducted in women of reproductive age attending two randomly selected family health centers in Alexandria Egypt a predominantly Muslim country (El-Sabaa et al. 2013). This study interviewed 151 women about their knowledge and awareness of EC and the results showed that 75.5 % women were unaware of EC and 21.5 % had ever used EC. The majority of women in this study had a positive attitude towards using EC following unprotected intercourse or

failure of their regular method of contraception. This work is reflective of similar trends in developing Muslim societies, where EC is available, women have positive attitudes but women are often unaware of the availability of such options (El Hamri 2010).

Interestingly, not only are users unaware of such choices for post-coital contraception, a study conducted in community health workers revealed knowledge gaps in health workers. This study explored the explored the knowledge, attitudes and practices of the Lady Health Supervisors of the National Program for Family Planning Rawalpindi district, regarding emergency contraception pills (Mir and Malik 2010).

In this cross sectional anonymous questionnaire-based study, insufficient knowledge, a high level of misinformation and strongly negative attitudes were revealed. More than 50 % of health workers surveyed did not know that emergency contraceptive pills do not cause abortion. About 80 % believed that emergency contraceptive pills will lead to 'evil' practices in society. More than 80 % recognized that the clients of National Program for Family Planning need emergency contraceptive pills. The attitudes were significantly associated with knowledge and educational status (Khan 2005; Hossain et al. 2005; Raymond and Weaver 2008).

Fertility Rates

Social scientists take a divergent opinion on reduction of fertility rate in the developed world.

It is often assumed by western scholars that high fertility is a result of inadequate availability of contraceptives, while other evidence suggests that high fertility rate may be due to poverty (Saurabh et al. 2013). Rises in living standards and economic growth and better education may have played a more significant role in regulating fertility than contraceptive practices in the developed world. This view is supported by the fact that falls in fertility rates in the West preceded the licensing and marketing of oral contraceptive pills. It can be argued that the focus should be on girl education and improving living standards which will have fruitful results in human development.

Oxytocin

More than eight million women each year globally suffer from postpartum hemorrhage, accounting for 25 % of all maternal deaths due to pregnancy and labour related causes (http://www.everywomaneverychild.org/images/Key_Data_and_Findings_Maternal_Health_Medicines_FINAL_3_26_2012__COMPLETE_reduced.pdf). The WHO considers oxytocin as one of three life-saving essential

drugs along with ergometrine and misoprostol postpartum hemorrhage (Carroli et al. 2008). According to these reports PPH is disproportionately high in the developing countries. The most effective drugs in management of PPH are oxytocin and misoprostol (World Health Organization (WHO) 2007; http://www.rcog.org.uk/womens-health/clinical-guidance/prevention-and-management-postpartum-haemorrhage-green-top-52; Westhoff et al. 2013).

A synthetic form of oxytocin is used to induce labour, strengthen contractions during childbirth, and control bleeding after delivery or to induce an abortion (http://www.pdr.net/drug-summary/pitocin?druglabelid=1666). It is considered a relatively safe product when used by the trained health care professional and is approved for use in most major markets worldwide. Reported side effects include local irritation, nausea, vomiting, stomach cramps and anorexia but these are generally not severe and disappear after discontinuation.

While the safety of oxytocin is well established, misuse of oxytocin carries significant risks to a mother as well as fetus. It is first important to highlight obstetric emergencies here. More than 90 % pregnancies have a normal course and normal outcome but pregnancy events can turn for the worse at any time and often happen rapidly. It is the ability to recognize any abnormality during pregnancy or during labour which determines the skill of a birth attendant.

More than 50 % women in Pakistan are not attended by trained birth attendants as they live hours away from centers where trained staffs, essential supplies and resuscitation facilities are present. Increasing the number and availability of skilled obstetric and midwifery staff in developing countries is essential if maternal mortality reduction is our goal.

The old obstetric adage, 'prolonged or difficult labour can be due to abnormalities of the *Passage*, *Passenger*, *Powers* or a combination of all' still holds. If a birth attendant has failed to detect pelvic bone abnormalities or placental location (passage anomalies) and has mismanaged the labour by inappropriately incrementing oxytocins, the outcome is high feto-maternal morbidity or mortality.

Similarly, birth attendants must be able to detect malpositions of fetus, its lie (longitudinal, oblique or transverse) as well as malpresentations like Brow, Face, Occipito-Transverse or Occipito-Posterior presentation (all 'passenger' issues). In all these scenarios, labour management must be carried out in centers where facilities for maternal or fetal resuscitation are adequate.

In the author's own personal experience at Jinnah Post Graduate Medical Center in Karachi, Pakistan (a public sector tertiary care hospital) several laboring women attended by 'quacks' or mal-practioners were brought in, in a near-dead state. These 'quacks' failed to recognize any of the above situations and kept pumping in higher non pharmacological doses of oxytocin.

Hence, while oxytocin is a life-saving drug in post-partum hemorrhage, free, unregulated and over the- counter availability of oxytocin is dangerous and must be discouraged on all accounts. The culprit here is not the uterine stimulant itself but the unsafe use by someone not trained or qualified to do so. Lack of accountability, poor or insufficient midwife training as well as widespread corruption and lack of political will by decision makers has caused loss of many precious lives.

Obstetric Fistulae

A serious complication of mis-managed labour is that uterine rupture may occur during a prolonged labour complicated by mid-pelvic outlet obstruction, later resulting in vesico-vaginal or recto-vaginal fistulae due to pressure necrosis of soft tissues.

According to a recent report by the WHO (2010), each year between 50,000 and 100,000 women worldwide are affected by obstetric fistula caused by poorly managed obstructed labour (http://www.who.int/features/factfiles/obstetric_fistula/en/). The development of obstetric fistula is directly linked to one of the major causes of maternal mortality – obstructed labour. Women who experience obstetric fistula suffer constant incontinence, shame, social segregation and health problems. According to this report, more than two million young women live with untreated fistula in Asia and Sub-Saharan Africa (http://whqlibdoc.who.int/publications/2006/9241593679_eng.pdf?ua=1).

Hamlin Fistula Hospital, Addis Ababa, Ethiopia, has been providing care for women with obstetric fistulas since 1974, with success rates of 90 %. It is the only hospital of its kind, dedicated to obstetric fistulas, providing care for around 2,500 women per year. It has treated over 30,000 women so far (http://www.hamlinfistula.org/our-hospital.html). In Pakistan, it is estimated that 3,500 known cases of obstetric fistula occur in the rural and urban slums, according to data from UNFPA and the Pakistan National Forum on Women's Health (http://www.fistulafoundation.org/countries-we-help/pakistan/#sthash.YlqElQuS.dpuf).

Dinoprostone

Prostaglandin E2 is effective agent for cervical ripening and termination of pregnancy (http://www.pdr.net/drug-summary/prostin-e2?druglabelid=1882&id=1150). It is a safe drug with short half-life and is rapidly metabolized locally in the tissues. For cervical ripening, the patient has to be in a dorsal position and should remain in a supine position for 15–30 min after administration of cervical gel (after administration of vaginal suppository she should remain supine for 10 min). Following the administration of the vaginal prostaglandin, the patient should remain in a recumbent position for 2 h. Oxytocins should be administered 6 h after prostaglandin administration to induce uterine contractions.

When used by skilled and trained birth attendants, dinoprostone is a valuable agent both for induction of labour at term and management of a termination of pregnancy. However the problem arises when, due to unlicensed and over the counter availability of these agents, they fall into the hands of 'quacks'. Wrong storage conditions can lead to fall in efficacy of prostaglandin products. The suppository product should be stored at −4 F, inserts stored at −4 to −14 F and the gel should be stored in a refrigerator. In developing countries we are very well aware of power failures and electrical power fluctuations in under developed

localities which may affect the storage and therefore the efficacy of such products (http://www.drugs.com/ppa/dinoprostone-pge2-prostaglandin-e2.html).

Magnesium Sulphate for Hypertensive Conditions of Pregnancy

Magnesium Sulphate is a safe, effective and low cost drug for the treatment of preeclampsia and eclampsia. Clinical studies in women with severe preeclampsia show that seizures occurred in less than 1 % magnesium sulphate-treated women, compared to 2.8 % women treated with other antihypertensive agents (http://www.rcog.org.uk/womens-health/clinical-guidance/magnesium-sulphate-eclampsia-prophylaxis-query-bank).

One randomized, controlled clinical trial comparing magnesium sulphate with diazepam or phenytoin revealed that magnesium sulphate was able to control recurrent seizures substantively as compared to any other anticonvulsant. Recurrent seizures occurred in only 9 % of magnesium sulphate treated women as compared to 23 % treated with diazepam or phenytoin (http://apps.who.int/rhl/pregnancy_childbirth/medical/hypertension/kkcom2/en/).

According to the International Federation of Gynecology and Obstetrics (FIGO 2013), eclampsia is common in the developing world (http://www.figo.org/news/pakistan-criticised-over-eclampsia-drug-non-availability-0011594). In Pakistan the situation is quite grave. After PPH, the second most common cause of death is eclampsia and pre-eclampsia which accounts for about 14 % of total deaths in the Pakistan demographic health survey. It is estimated that 2,000 women die of eclampsia and 8–10 % women suffer from this condition during their pregnancies in Pakistan (Ahmed 2004; Bano et al. 2011).

Magnesium sulphate has been on the WHO Essential Medicines list since 1996. The White Ribbon Alliance Pakistan prepared comprehensive guidelines for health care professionals on treatment of severe pre-eclampsia and eclampsia in Pakistan (http://whiteribbonalliance.org/wp-content/uploads/2013/11/Clinical-guidelines-for-healthcare-professionals-on-use-of-magnesium-sulphate-in-Eclampsia.pdf). However, there was concern raised by senior obstetricians in Pakistan about the irregular and erratic availability of magnesium sulphate for the management of hypertensive conditions in pregnancy. Lack of central distribution and drug tracking policies have put women in remote areas at risk of high fetal and maternal morbidity and mortality.

Assisted Reproductive Technologies in the Developing World and Medical Tourism

More than five million babies have been born worldwide since the advent of assisted reproductive technologies i.e., in vitro fertilization, intracytoplasmic

sperm injection and gamete donation (http://www.eshre.eu/press-room/press-releases/press-releases-eshre-2012/5-million- babies.aspx). The technology is relatively safe where staff are well trained and the center is well equipped and well regulated. Even four decades since Louise Brown, the first IVF baby was born, the take home baby rate in best fertility centers in the world with IVF, ICSI, women above 40 years and frozen embryo transfer are 20 %, 30 %, <5 % each respectively (http://www.hfea.gov.uk/).

Fertility centers are heavily regulated in the UK by HFEA (Human Fertilization and Embryology Authority) Licensing body, in the USA by SART (Society for assisted reproductive technology), CDC, ABB and laboratory accreditation. Various transnational societies like *European society for human reproduction and embryology (ESHRE) and American Society for Reproductive Medicine (ASRM)* are active in implementation of some regulations like number of embryos transferred. Similar controls are observed in other developed countries (http://www.cdc.gov/art/; http://www.asrm.org/find_frm.html; http://www.hfea.gov.uk/108.html).

However, global survey of fertility treatment of more than 100 countries revealed wide variation in international laws regulating IVF leading to 'fertility tourism'. No other field of medicine is subject to a wide difference in clinical practice which is driven by social and religious attitudes rather than scientific evidence. Around 10,000 people go abroad for assisted reproduction. Spain and Czech Republic are popular destination for European patients. India is fast becoming a hot bed of medical tourism in particular for Surrogacy (Ferraretti et al. 2010; Connolly et al. 2010; Storrow 2010).

This had led to an announcing the code of practice on cross border care by European Society of Human Reproduction and Embryology (ESHRE) and the International Federation of Fertility Societies (IFFS) in 2010 (Jones et al. 2011; Nygren et al. 2013).

Several key questions were raised by Professor Ian Cooke, the education director at IFFS meeting 2011, (Jones et al. 2011), and quoted "What is considered acceptable varies from country to country. How carefully do they screen donors? How do they screen for multiple pregnancies? Does one want to come back with quadruplets?"

While it was generally agreed on giving patients the choice of going abroad, it was also important to have harmony in national standards to increase safety. The reasons for this surge in medical tourism are lax regulation abroad as compared to stringent home country regulation, shortage of egg and sperm donors and lower costs.

Since the arrival of assisted reproductive technologies, paradoxically we see mushrooming of fertility centers in high income areas of the developing world. There are 500 IVF clinics in India alone. These fertility centers are unregulated and strong ethical practices are left to the good will of fertility doctors.

Surat city in the Indian state of Gujrat is called the 'Surrogacy Capital' (http://www.siliconindia.com/news/general/Gujarat-Now-a-Hub-for-Surrogacy-nid-153487-cid-1.html; www.marieclare.com/world-reports/news/surrogate-mothers-india). It is an example of globalization gone mad. Poor women are exploited as home country legal red tapes are bypassed. India legalized surrogacy in 2002, notwithstanding various ethical and social issues raised by bioethicists.

In a study carried out by the Center for Social Research supported by the Indian Ministry of Women and Child Development (2011–2012), it was stated that though the Assisted Reproductive Technology ART Regulation Bill, 2010 has brought forward certain important points for the legal framework to be based on, it has left out many crucial issues relating to surrogacy arrangement (http://worldpulse.com/node/68762; http://www.wunrn.com/news/2013/07_13/07_15/071513_india2.htm; http://www.deccanherald.com/content/345338/surrogate-mothers-underpaid-uncared-for.html).

This study indicated that poverty and future of their children were two primary reasons for women to become a surrogate mother in large cities like Mumbai and New Delhi. Nearly three quarters of these women were approached by an agent for surrogacy.

Many ethical questions arise here about subjecting a woman to fertility drugs and subsequent pregnancy for financial reasons. Exploitation of these women by fertility clinics and their agents (but more so by the Western clients) is a cause of concern. Just like professional blood donors, these women may end up being professional 'rent-a-wombs'. Subjecting their bodies to repeated cycles of fertility drugs, the longer term side effects of which we may learn later on. Women in developing world are notoriously poorly nourished and anemic. Are the women undergoing repeated pregnancies for commercial reasons being properly screened? There are reports of these women not even being paid for their services. Who is looking after their interests (Fig. 17.3)?

Fig. 17.3 Indian Surrogate mothers in a fertility clinic in Surat India (Source: www.marieclare.com/world-reports/news/surrogate-mothers-india)

Social, Cultural and Religious Realities

Pakistan is a patriarchal society, where the major decisions of woman's life are not made by her. Before she is married, her fathers and brothers keep her restrained as someone inferior and incapable of making rational decisions about herself. The same role is overtaken by the husbands and, father in-laws after marriage.

In many religions practiced today, women are at the receiving end of the religious decree, be it childhood marriage, reproductive health, or inheritance rights. Women of lower socioeconomic status bear the brunt of these outcomes in particular.

Gender discrimination and feminization of poverty have made any progress in reproductive health a challenge. By feminization of poverty, the general understanding in economic terms is, women pay the ultimate price of rising poverty. Many societies have exploited religious beliefs in meeting reproductive choices and limiting family planning options to women. However we have seen a major shift in thinking when literacy rates are increased in a society.

"More education translates into better health outcomes in all societies," said Abulkalam Abdul Momen (Vice-President of the United Nations Economic and Social Council, 2011) while addressing a debate on the contribution of population and development issues for the Council's Annual Review (http://www.un.org/News/Press/docs/2011/pop994.doc.htm).

Some countries have involved community and religious leaders of progressive intellect to forward the public health agenda of government for women. This should be seen as a replicable model in other countries struggling to improve health literacy.

Whilst the literacy and education levels of girls reaches desired standards, involvement of community/religious leaders in reproductive and child health may be a way forward. Bangladesh has successfully involved religious groups to propagate family planning. Other countries with similar religious and cultural values can follow this example. Pakistan has successfully trained traditional birth attendants to improve antenatal care at a basic level. Most of the countries with high maternal mortality are war-torn with fragile health care systems. Expectations are bound to fail if local conditions are not taken into consideration.

Conclusions

Health systems in developing countries are weak and fractured. There is an endemic lack of accountability and poor legislative controls over health delivery. Health budgets are paltry with criminal negligence of health and education sectors since inception of many of these nations. There are misplaced priorities in resource allocation. Wars, regional conflicts manmade and natural disasters have pushed

these civilizations further back in time. Lack of cohesion in health infrastructures reflects a major failure by policy makers and managers.

Poor drug regulation and control is a natural fall-out of the above factors. Urban and rural divide in access to modern health facilities and essential medicines is notable in all interagency reports. State failure in delivering health and social care to her citizens has left a vacuum, only to be filled by the private sector with variable regulation.

Knowledge about the safety of medicines leaves a lot to be desired, compounded by the menace of counterfeit and spurious drugs. In this chapter I have highlighted some of the health system weaknesses in low to middle income countries as well as some individual drug stories.

Whilst women in the developed world have come a long way in getting their basic rights of health and education, their counterparts in socially and economically impoverished regions are still striving for respect and basic health rights. This includes the struggle to gain adequate access to medicines for women to control their fertility and improve their health and that of their children.

Millennium Development Goal no. 5 relating to reproductive health will not reach its targets unless drastic measures with public and private partnerships are taken. Responsibility lies with the governments, policy makers, health and other professionals: men and women must share this responsibility, unless they want to continue failing their girl and woman, or would prefer to make giant strides by focused, concerted and sincere efforts to improve women's and girls' access to health care. Problems with drug prescribing for women in the developing world are not stand alone, but part of a greater fault of lack of political will to improve a women's lives in these countries.

Take Home Messages

- We are still far from providing optimum care to half of the population in the developing world.
- Health indices provide dismal reading in many low to middle income countries.
- A vast majority of rural and urban-slum women have no access to skilled and qualified health workers.
- Drug marketing and sales are largely unregulated in developing world countries.
- Over the counter availability of drugs has dangerous consequences in poor countries.
- Problems of counterfeit drugs are rampant in many developing countries.
- Health inequality between a larger lower socioeconomic population and a smaller richer population subset brings out many ethical issues into debate.

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Chapter 18
Perspectives on Risk Communication and Gender Issues

Bruce Hugman

Introduction

The purpose of risk communication in clinical practice is to inform and protect; to support wise, balanced and rational decisions that match patients' wishes and needs.[1] Risk communication touches almost all aspects of our lives. The quality of the information on which risk communication is based is important, but much more influential for effectiveness is the quality of the communication through which the information is mediated and the way in which those who deliver it are perceived.

Such communication must be perfectly tailored to the reality of the audience and, in medicine, to the individual patient, delivered by a credible, trusted source. One critical variable in any audience profile is sex (commonly conflated with gender, the sociological concept). In this chapter we shall explore the radical impact for risk communication practice of having a female audience. We shall see how particular are the demands and challenges, how complex, how variable, and how very different from those of communications with men.

In this chapter we shall review the nature of the differences, the basics of risk communication theory and practice, and examine some of the powerful, influential variables that determine the nature of the risks women face and that must shape the risk communications they are offered.

[1] This is closely related to but goes much further than the WHO definition of the rational use of medicines which requires that, 'patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.' (WHO 2012)

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Part 1: The Basics of Risk Communication

A Woman Is Not Just Like a Man

Given the profound biological, physiological, cerebral, philosophical and psychological differences between the sexes, it is a small miracle that so many of us manage to muddle along together as well as we do. On the other hand, many, in all parts of the world, do not muddle along at all, but live in a state of repressed or open conflict between the sexes. The much debated causes of these differences and conflicts are not issues we shall explore in this chapter; we must accept that they exist and that we must deal with them.

Somewhat over-simplified, the theoretical position, on which the contents of this and the next chapter are based is this: sex- and gender-stereotypes and gender-preferences have a profound influence on the way the world is organised, the opportunities people have, the risks they face, the choices they make and the roles they adopt. They facilitate, maybe determine, certain kinds of behaviour by men and women, at the same time as they inhibit or exclude other types of choices and behaviour. Men and women display an immense variety of character and behaviour, with enormous variation across and within cultures.

The influence of gender-stereotypes is strong everywhere, most obviously in the tendency of men to hold social and economic power and to manage and lead, and the tendency of women to run the domestic infrastructure, rear children and provide the support services that allow men and children to flourish. While some might challenge the truth of this view in relation to Western countries, where some slight shifts have taken place, I believe they are largely mistaken and that progress has been patchy and intermittent, at best. This view is shared by critical observers (Singh et al. 2001) as well as contemporary feminist thinkers such as Naomi Wolf who writes, for example: "'Healthy' and 'diseased,' as Susan Sontag points out. . .are often subjective judgments that society makes for its own purposes. Women have long been defined as sick as a means of subjecting them to social control" (Wolf 2002).

Men and women are different; they have different needs and preferences; their relationships and communications with their own and the opposite sex have quite different characteristics; their physiology and their relationship with their own bodies are dramatically divergent.

In a world largely structured and managed by men, women are, in some important respects, disadvantaged, even when they are not trying to compete with males or to imitate or follow male patterns of behaviour, where the problems are only too well known and documented (Economist 2014). Nowhere is this disadvantage clearer than in certain aspects of healthcare: nurses, with intrinsic compassionate commitment to patient welfare, are increasingly being de-skilled in systems hostile to communication and relationship, with managerial and accounting priorities taking precedence over professional discretion and comprehensive nursing care (Allnurses 2012); drug information and risk communication focus on the male

preference for data and evidence and do not illuminate issues of concern to women such as the psychological, social, domestic, and spiritual aspects of safety and healthcare delivery, especially in pregnancy and post-natal care (Tabak and Ozmen 2008).

Women in many cultures prefer to be treated by a healthcare professional of their own sex, but this preference is rarely negotiated when it cannot be met, and its impact on welfare, trust and adherence rarely discussed. In many cultures, women value community, peer and family advice and support in health matters, but are often forced into isolating one-to-one relationships, frequently with male providers, when there is any affordable provision at all (Nicholls 1987; Chen 2010). Major aspects of women's life experience, notably pregnancy, menopause, and body-image have been increasingly medicalised and pathologised in ways that men's conditions have not; and menopause has remained, in some respects, a largely neglected area of research and development (Erhardt 2003).

Empathy, Sympathy, Altruism and Compassion

Empathy, that unique ability to grasp the reality of another person, to envisage accurately how they are thinking and feeling, to sense what it is like to be them, is at the very heart of all good relationships and communications. We can reach others only when they feel that we perceive and understand them in their own authentic terms. Without empathy, communications have only a superficial or transitory effect or miss the target completely.

The art of medicine embraces many qualities besides empathy: sympathy (the supportive expression of felt emotion about the lives of others); altruism (active concern for the welfare of others beyond self-interest); and compassion (a heartfelt concern for the comfort, welfare and inner peace of others). Some commentators, like Ralph Crawshaw, believe that these essential qualities are leaching from medical practice, that medical education 'leaves too many young people bereft of compassionate imagination and altruistic ideals' (Crawshaw 2002). There is probably no excess or deficit in essential compassion determined by sex, but its expression may be shaped by gender socialisation with women at greater liberty than men to be tender (Seppala 2013). Divergence in compassionate needs and delivery between the sexes may at times be problematic.

One Size Does Not Fit All

So much communication in healthcare, especially risk communication, has been a *one size fits all* transmission; so much healthcare delivery has been driven by the technical *body as object* framework (including biological essentialism; see, e.g. the debate at (javier44 2013)), mostly through male values and habits. Empathy for

audiences, collective and individual, especially for women, and sensitive adaptation of messages and behaviour, have been patchy or absent.

Package inserts (PIs) and patient information leaflets (PILs), those core elements of official risk communication practice, fail by the most basic of audience segmentation criteria: they are often difficult and off-putting for even for highly educated, literate, motivated patients (even physicians); for the illiterate, the partially-sighted, speakers of minority languages, those for whom the printed word is not the primary mode of learning, they are entirely useless. There are no PIs or PILs that exclusively address women as consumers of medicines. One size hardly meets the needs of anyone (Nink 2006).

There has been some progress. Women (as professionals and patients) have, in some places, taken a leading role in challenging out-of-date and disadvantageous practice. In the West, we can see evidence of improvement in society at large (more female surgeons and engineers, for example, in some places, (Gomez 2012) and changing attitudes to fatherhood), but we are, in some respects and in many places, still in the dark ages. In China, it is current state policy, and the subject of a major, official, sexist campaign, to roll back such progress as women have made towards independence, to make them fear being single and 'leftover'; to browbeat them into becoming wives and mothers (Lovell 2014; Fincher 2004). While the situation in most places is not as dark as this, women's rights and preferences and needs are substantially neglected, as this chapter will show.

Risk

Some general discussion of the meaning of risk is necessary before we approach the substance of this and the next chapter on health risks and risk communication for women.

While 'the chance or odds of something bad happening' is the starting point, it is very far from being the whole story. Paul Slovic is a researcher who has illuminated many aspects of risk. Among his insights is the characterisation of three kinds of risk: risk as *feelings*, risk as *analysis* and risk as *politics*. He explains it thus (Slovic 2010; Slovic et al. 2003):

> Risk in the modern world is confronted and dealt with in three fundamental ways. Risk as feelings refers to our fast, instinctive, and intuitive reactions to danger. Risk as analysis brings logic, reason, and scientific deliberation to bear on hazard management. When our ancient instincts and our modern scientific analyses clash, we become painfully aware of a third reality . . . risk as politics.

For the first, risk as feelings, which Slovic regards as the prime influence across all risk perception and assessment, there is strong experimental and real life evidence that even the most sophisticated, rational, statistical risk data is constructed and perceived with a greater or lesser degree of *affect*, that is covert, hidden or explicit feeling about the matter in hand.

Epstein, a polymath Professor of Family Medicine, observed:

> There is no dearth of evidence in everyday life that people apprehend reality in two fundamentally different ways, one variously labeled intuitive, automatic, natural, non-verbal, narrative, and experiential, and the other analytical, deliberative, verbal, and rational. (Epstein and Peters 2009)

Slovic's genius was to show the extent to which the latter (analysis) was often influenced, coloured or skewed by the former (automatic).

Nowhere are these issues more evident than in perceptions of risk and public reaction than in immunisation programmes, where risk *analysis* can drop out of the picture and be replaced entirely by risk as *feelings* and risk as *politics*. No amount of factual risk and safety data or information was initially going to change the minds of religious leaders in northern Nigeria about the acceptability of polio vaccination for their communities (Agbeyegbe 2007; Kaufmann and Feldbaum 2009); women in India were not assessing the risk of vaccination in relation to the health of their children or their communities when resisting interventions, but rather reacting to the fact that programme personnel were men from distant parts, strangers, and they wanted local, familiar women to vaccinate their children.

In the West, scares about MMR (Deer 2004) and pertussis vaccines (College of Physicians of Philadelphia 2014) have resisted almost all rational rebuttal, driven by powerful emotions and agendas with little sound science or fact (Gross 2012). Many individual and public health issues have been damaged or derailed by the failure of risk communication to take into account the potent non-scientific, social and psychological elements of human feeling, perception and reaction to risk, mothers' fears for their children being a prime example (Hugman 2010).

Another important concept comes from Peter Sandman, a distinguished thinker in the field of crisis management (Sandman 1993). He represents risk thus:

$$\text{Risk} = \text{hazard} + \text{outrage}$$

Sandman points out that the degree of outrage is not necessarily proportionate to the scale of the hazard: people can get very upset about even low, remote risks while, on the other hand, paying little attention to major and immediate hazards (drink-driving, obesity and climate change being examples). The occurrence of a single, rare, serious or fatal ADR, for example, maybe amplified in the media, may cause far more outrage and upset than more pervasive disadvantage or failure in healthcare.

The risk of not providing patients with good safety information about their medications or medical procedures, is not just the possible occurrence of unexpected and inconvenient events, it is also the *outrage*, the emotional response, that individuals or populations will feel when things about which they were not fully informed go wrong. The risk is not just the patient's possible experience of some temporary or chronic, even life-threatening disease or disability, but also the radical emotional and social implications – and a much higher risk of litigation (Renkema et al. 2014). Risk is not just a matter of scientific data and probabilities (Box 18.1).

Box 18.1: A Recent Non-medical Example: Outrage and Failure of Empathy

As I write this, I have just watched the Philippines Interior Minister, standing in the midst of the stinking débris of Tacloban City, respond to accusations that the Government's relief effort, 5 days after super-typhoon Haiyan, was slow and inadequate. His answer? A recital of (utterly unconvincing) claims about the number of trucks delivering aid and collecting corpses, the distribution of body-bags, the volume of food and medical supplies on the road, all in a defensive tone of barely-restrained indignation (CNN 2013). Apart from failing to acknowledge and address the fact that no-one in the area had seen any trucks or food or body-collection, there was not a hint of his understanding the *outrage*, the despair and disillusionment, being felt by tens of thousands of people. The risk to the Government is not just of being seen to fail in providing rapid and effective aid, but of being judged as distant and uncaring, utterly out of touch with the *feelings* of the people and their need for reassurance, for understanding, for *empathy* with their dangerous and tragic plight. Regulatory authorities and pharmaceutical companies sometimes have a tendency to behave in comparably alienating ways too.

People in power, and it is often men, frequently behave like this at times of crisis and it does untold damage to the reputation of governments, regulatory authorities, hospital managements, public health programmes, companies, to anyone in the public eye.

Differential Perception of Risk

Covello's work illuminates the extent to which our perception of risk is influenced by a multitude of issues, quite apart from the nature of the intrinsic hazard in question (Covello et al. 1989). Most people, for example, will take much greater risks in activities that are voluntary and self-determined, such as extreme sports, driving, and drinking, but will be less tolerant of much smaller risks when they are imposed on them, or are beyond their direct control, such as environmental hazards, food safety and medications. Unfamiliar threats, risks to children, hazards that might affect future generations, and other factors influence how we perceive risk, tolerate it and respond to harm in prospect or when it occurs. Patients will react to different risks differentially, not least based on the extent to which they trust the source of the risk information. The same information coming from different sources may be assessed in even conflicting ways, according to the recipient's perception of the source (a media anecdote as opposed to a regulatory declaration, for example).

In order to make satisfactory decisions about most things in our lives, including medicines, we need to have information about benefit and risk presented in ways that make sense to us and that meet our needs and preferences. We also need information about alternative choices, for example, the risks of the disease or

condition itself, the risks of no treatment, the benefits and risks of the treatment proposed by a health professional and the benefits and risks of other possible options. While the population probabilities may be well known, we still have to understand what the implications are for us individually (including genetic or other idiosyncrasies), and process them through our feelings, our preferences and our personal priorities. It is well known, for example, that patients with chronic or terminal diseases will accept greater risks for the potential benefit of short- or long-term relief; that mothers will be anxious about accepting any risk whatsoever to their fetus or children; that the more persuasive the benefits are the greater the risk that will be tolerated. Benefit-risk dilemmas of this kind are particularly associated with the use of anti-convulsants in pregnancy, contraceptives and HRT (see Chap. 19) and, for example, with prophylactic surgery in breast cancer.

As risk-perception is subject to great variability, so is benefit-perception. Effectiveness alone may not be adequate benefit in a patient's eyes if, for example, the medication has side effects that interfere in some way with perceived quality of life. On the other hand, for some, the reduction of pain may be a desired benefit, irrespective, for example, of its impact on mobility or clarity of mind. Benefit must be defined by patients in their own terms, often well beyond anything in the imagination of bureaucrats or that might appear in the Summary of Product Characteristics (SPC), the patient information leaflet or other regulatory information.

Tailoring Risk Information

Risk information must be presented in ways that make sense to us, emotionally, conceptually and factually. It must match our abilities, literacy, knowledge (or absence) of science and statistics, and a host of other variables, many of them discussed later in this chapter.

Probability is a concept not well understood by most people: for example, many people won't think that a natural disaster with a probability of occurrence of once in a 100 years could happen tomorrow. When an adverse reaction is described as 'rare,' many may not feel it is a threat to them personally, while '1 in 10,000' (customarily regarded as 'rare' by the authorities) may seem risky to some people. If a tossed coin lands heads-up three times in a row, many will bet on heads for the next toss, believing or feeling that the odds have changed from the ultimately implacable 50/50 for any such series (the gambler's illusion of a 'winning streak'). Many people suffer from the self-deceiving optimistic bias that reassures them that that they are less at risk than others, that, 'It won't happen to me' (a rationalisation employed by smokers, for example) (Klein).

So, if we say that an adverse reaction, or a negative outcome, or disease susceptibility has a probability of 1 in 10,000, or 0.0001 % or is 'rare,' we have first to ensure that our subject understands what we mean in absolute, balanced terms ('This happens to one person in 10,000; 9,999 are not affected'). If the

epidemiological population is large, then the numbers affected may also be large which may appear to make the risk larger. However small the risk, someone suffers the harm, so a small risk does not mean a 'safe' medicine or procedure which many people might instinctively seek. There is always a degree of uncertainty in risk statistics because unexpected events happen, and the past is not a certain guide to the future. This is very clear from post-marketing surveillance of drugs, when previously unknown adverse events, minor or serious, may take years to emerge. We can never assert more confidence than, 'The best current evidence available.'

Individuals differ markedly in their perception of risk, their preferences for the form in which risk information is given, and the ways in which they process such information. Research shows us that the effectiveness of risk communication varies enormously and by no means in ways one might anticipate. All these issues emerge in Part 2 of this chapter in the discussion of healthcare issues which primarily affect women, whose preferences and needs are, not surprisingly, often very different from those of men and whose risks and risk communication needs are very different too.

Risk Information: The Basics

Here I will briefly chart a course from the mathematics and the technicalities to the endpoints of good communication and decision-making for physicians and patients. Among the primary sources for this material are Cochrane Collaboration open learning material and Gigerenzer, who both represent the toughest, clearest and most intelligent approach to risk communication (Collaboration; Gigerenzer et al. 2007; Gigerenzer 2002).

How Is Risk Expressed?

Cochrane summarises the meaning of the major terms in risk research and statistics for studies with dichotomous outcomes (when one group is compared with another):

- The **risk** describes the number of participants having the event in a group divided by the total number of participants
- The **odds** describe the number of participants having the event divided by the number of participants not having the event
- The **risk ratio (relative risk)** describes the risk of the event in the intervention group divided by the risk of the event in the control group
- The **odds ratio** describes the odds of the event in the intervention group divided by the odds of the event in the control group
- The **risk difference** describes the absolute change in risk that is attributable to the experimental intervention

- The **number needed to treat** (NNT) gives the number of people you would have to treat with the experimental intervention (compared with the control) to prevent one event.

Physicians need to understand these terms and be able to evaluate the strength of research conclusions on their understanding of the data and the calculations. They need to assess the significance of results in relation to sample size; control and placebo group matching; the relative usefulness of surrogate outcomes (hypertension, for example); actual endpoint outcomes such as morbidity, survival rates (and their interpretative hazards) and mortality; a difference in risk and odds ratios; confidence intervals, p-values, and much more. Patients do not need to understand the mathematics of all this, but they do need to understand some basic concepts and be informed about the extent to which figures are reliable.

The question for us is how to build a bridge from this bewildering and complex field to expressions of risk that are useful in clinical practice and for patient decision-making.

Gigerenzer advises us:

> A major precondition for statistical literacy is transparent risk communication. We recommend using frequency statements instead of single-event probabilities, absolute risks instead of relative risks, mortality rates instead of survival rates, and natural frequencies instead of conditional probabilities.

Let's look at some of these in more detail:

Frequency Statements Instead of Single-Event Probabilities

Probability is a guess or a hypothesis, or, at best, an estimate of the likelihood of an event occurring. The probability of a fair coin landing heads up when tossed is 1 in 2, or 1/2 (0.5) or 50 %. The probability of drawing any particular card from a full pack (without jokers) is 1 in 52, or 1/52 (0.19) or 1.9 %. In the technical jargon, an impossibility has a value of 0 (0 %), a certainty, of 1.0 (100 %). A probability is not a prediction for the next event: you may toss a coin a dozen times and get only one heads; you may pick a card a hundred times from a pack and never draw the target card. Calculations of the probabilities of tossing coins or picking cards are relatively simple because there is a finite and defined range of possibilities (2 and 52 respectively), but you would still need an enormous number of tosses or draws to have evidence to support the hypothesis because chance (unpredictability) also affects every event. The longer the series or the larger the data-set, the more accurately a probability can be calculated: that is one of the reasons sample size and time-scales in trials are so important.

If an American woman's lifetime risk (probability) of breast cancer is in the region of 12.4 %, (a probability of 0.124) based on whole-population figures (Lifetime risk of breast cancer 2014; Institute 2012), then it is probably reasonably reliable. As a single event probability, however, what do those figures tell an

individual woman about her risk? Not a lot! The frequency statement of a risk of about 1 in 8 is much clearer and more helpful.

A Cochrane review of the benefits of statins in low-risk patients was summarised in Medscape as follows (Hughes 2011):

> . . .in the eight trials that reported on total mortality, none of the individual trials showed strong evidence of a reduction in total mortality, but when the data were pooled, a relative risk reduction of 17 % was observed with statin treatment. On combined fatal and nonfatal CHD events, nine trials reported on this end point, with four trials showing evidence of a reduction in this combined outcome, which was maintained in the pooled analysis, with a 28 % relative reduction. Seven trials reported on fatal and nonfatal stroke, and on pooled analysis, statin treatment was associated with a 22 % relative reduction.

That really doesn't tell us very much of interest to patients. It's all relative risk figures (see below for more on this) and needs frequency figures to make sense to most people.

The actual Cochrane review conclusions (Ebrahim et al. 2011) included this:

> Of 1000 people treated with a statin for five years, 18 would avoid a major CVD event which compares well with other treatments used for preventing cardiovascular disease. Taking statins did not increase the risk of serious adverse effects such as cancer.

This tells us plainly how many people benefit (without serious harm), and it states that statins are comparable in benefit to other treatments. But it's not the whole story.

Ebrahim commented (Ebrahim et al. 2011):

> If you look at the hard end points of all deaths and coronary deaths, the effects are consistent with both benefit and with the play of chance. But importantly, the absolute benefits are really rather small--1000 people have to be treated for one year to prevent one death.

(If we present the opposite ratio: of 1,000 people treated over 1 year, 999 will not die (i.e. no effect) – then we are speaking true to the data, but are implying a different value judgement of the data in choosing that *framing*.)

Here, we also have the introduction of Number Needed to Treat (NNT) that is another useful and important clarification of odds, chances, probabilities (all three terms commonly found in everyday language).

Absolute Risks Instead of Relative Risks

In Chap. 19, we look in detail at the communications issues at the heart of the 'pill scare' in the UK and Western Europe in 1995. Of interest to us here is that the official announcement was that women taking third generation combined oral contraceptives (OCs) *doubled their risk* of venous thrombosis; that is to say, women taking third generation OCs were at twice the risk of those who were not taking them, a relative risk of 2. Alarming? Apparently. But the absolute figures tell a very different story: *doubling* meant an increase from 15 in 100,000 to 30 in 100,000 (the figures have since been refined, but the risks are comparable).

The Cochrane open learning material summarises the issues in a vivid, non-medical example:

> Take the example of buying two lottery tickets instead of one. We could say you are doubling your chances of winning, or we could say your chances of winning have gone up by 1 in 400,000. Both versions give you incomplete information because neither tells us clearly what the chance of winning is in the first place. The statements are likely to be interpreted differently, because many people would think an increase of 1 in 400,000 sounds a lot less attractive than a doubling of the chance of winning.

This takes us to the thorny problem of *framing*, and the potentially manipulative use of data. The statins data, above, presented as 1 in 1,000 or 999 in 1,000 illustrates this: a proponent of statins may emphasise the one life saved, while a statins sceptic (or a financial manager) might emphasise the 999 people who take the pill with no benefit at all. The same alternative perspectives would apply equally if the 1 in 1,000 referred to the harm of a medicine, rather than a benefit: which way are we influencing or manipulating a patient with our choice of data presentation? (See Chap. 19, p. 585 for practical answers to this.)

Good, clear, simple figures can be hard to find. The FDA's fact sheet on statins for consumers, for example, doesn't give the relevant figures in any form (FDA 2013). And there are some fierce controversies raging among researchers too.

On the statins question, Baigent, responding to Ebrahim above, quoted in *heartwire* (Hughes 2011), says:

> I object to the conclusions they have drawn from their review. They say there is not good evidence of benefit, but their own data show significant reductions in deaths and cardiac events.

What is meant by 'significant' is a big issue and depends on whether you are a statistician, a physician or a patient: what is statistically significant ('the mathematical determination of an event, symptom, behavior, etc. not occurring merely by chance' (DeMaria 2011)), may or may not be clinically significant or seem important to a patient.

Other matters of individual judgement include: what you regard as a proportionate treatment effort to gain any particular benefit (a thousand patient years to prevent one death, for example); and what you regard as an acceptable risk of harm (1 in 10,000, for example). Such judgements take on a very different nature when they are made by officials drawing up public health policy. Their judgements, of course, may be strongly influenced by cost-benefit analysis which may or may not be relevant to a patient or physician deciding on individual therapy or indeed to good health.

Anyone reading popular, easily accessible material on the internet (like www.curezone.com) will find their minds being frazzled by the arguments and paradoxes raging in professional circles in relation to lipids, saturated fat, statins and much more. (In this and the next chapter I try to offer some tentative guidance about how patients can negotiate this hazardous maze.)

Understanding Terms Used to Define Frequency

'Common,' 'less common,' 'rare,' and all the rest, mean very different things to different people. If we are using such terms, we have to be very certain how the terms are being used in our source information, clear what we mean when we use them, and very sensitive to what they mean to patients.

The Council for International Organisations of Medical Sciences (CIOMS 1999) has suggested definitions for the quantification of risk (e.g. for adverse events) as follows:

Very rare	<0.01 %	<1 in 10,000
Rare	0.01–0.1 %	1–10 in 10,000
Uncommon	0.1–1 %	1–10 in 1,000
Common	1–10 %	1–10 in 100

A patient may not feel that '10 in 1,000' is 'uncommon' when she thinks of her city of half a million; a patient who is told that a side effect is 'rare' might ask, 'So how many people in [say] Accra?' Well, it's about 2.5 million. 'So, that's. . .' she says with a bit of quick mental arithmetic, 'that's 250 for the whole city at the low end, 2,500 at the high end. That's not rare.'

This may seem absurd, but it's not a foolish inference if it is not made absolutely clear that the figure applies only to the relatively few people like her taking the drug. And if we were looking at national figures for the number of prescriptions for (say) OCs, statins or HRT, the 'rare' numbers would look large too, whatever their statistical value.

The point is that these statistical thresholds are not based on popular consensus or usage, nor, certainly, on the unique mental set of the patient in front of us. If our perception of 'uncommon' does not match that of a patient, we risk offending her and losing credibility. The use of the word 'uncommon' from the doctor's routine vocabulary prejudices the discussion and may appear manipulative. The figures should come first, followed by an exploration of the patient's assessment of them, which may be very different from the doctor's.

Another problem is that the denominators are often different, so comparing risks and benefits might require some mental agility if they fall into different categories: how can a patient easily compare a chance of benefit of 1 in 100 for one medicine, with a risk of harm of 1 in 1,000 for another (or with the figures reversed?) Some may feel that a bigger denominator means a bigger risk. In this (very simple) case, it would probably be helpful to equalise the denominators, expressing benefit as 10 in 1,000, harm as 1 in 1,000 (or vice versa). Reducing the higher denominator wouldn't work, because the result would be one tenth of a person in 100 (nobody can make sense of 'one tenth of a person', or anything less than one whole person).

Reporting how often side effects may occur is often dealt with very unsatisfactorily: this from the Mayo Clinic (Clinic):

> Very rarely, statins can cause life-threatening muscle damage called rhabdomyolysis. The most common statin side effect is muscle pain

How rare is 'very rare?' How common is 'common' (1 in 2; 1 in 10; 1 in 100)? And if, as the Mayo guidance suggests, women are more at risk of statin side effects than men, we need to know how much more at risk and the actual risk figures on which that relative risk assessment is based. (Risks and benefits may be different for men and women (Sigurdsson 2013; Rosenberg 2012).)

WebMD, in its article headed, *Statin Risks Outweighed by Statin Benefits*, see also (Therapeutics Initiative (2014); Nissen 2012; Rutishauser 2011; Tonelli et al. 2011), mentions:

> A more common risk seen with statins is muscle tenderness, which occurs in some 5 % of patients. This can be extremely severe.

We do at least have a comprehensible figure here ('more common' seems to mean 1 in 20), but it does appear disingenuous in relation to the risk of rhabdomyolosis (1 in 10,000 according to about.com (Harper and Jacobson 2007), to say nothing of other serious stuff like diabetes, liver myopathy and peripheral neuropathy which aren't mentioned at all).

So what will you tell your healthy patients who have no previous history of CHD for whom you are proposing primary prevention?

You could say:

> There was a 12 % proportional reduction in all-cause mortality per mmol/l in LDL cholesterol. This reflected a 19 % reduction in coronary mortality' (Armitage 2007)

Hmm. Margaret McCartney points out (McCartney 2012) this is relative risk (and pretty much impenetrable). A bit more work is needed:

> Adding up all the 'major vascular events' there is a difference between the control group and the statin group of 17.7 % versus 14.1 % – a difference in absolute risk of 3.7 %. The difference between deaths related to cardiovascular disease is smaller: statins can reduce this, the study found, from 4.4 % to 3.4 %. That's a difference of 1 %. . . It's not good being told that your risk of death can fall by 12 % if you take the statin (the relative risk) when the figure is really on 1 % (absolute risk).

Mortality Rates Instead of Survival Rates

Wegwarth et al. (2012) vividly expose this issue in their study of physicians' responses to evidence about cancer screening.

> Primary care physicians were more enthusiastic about the screening test supported by irrelevant evidence (5-year survival increased from 68 % to 99 %) than about the test supported by relevant evidence (cancer mortality reduced from 2 to 1.6 in 1000 persons). When presented with irrelevant evidence, 69 % of physicians recommended the test, compared with 23 % when presented with relevant evidence ($P < 0.001$). When asked general knowledge questions about screening statistics, many physicians did not distinguish between irrelevant and relevant screening evidence; 76 % versus 81 %, respectively, stated that each of these statistics proves that screening saves lives ($P = 0.39$). About one half (47 %) of the physicians incorrectly said that finding more cases of cancer in screened as opposed to unscreened populations "proves that screening saves lives."

Their conclusion:

> Most primary care physicians mistakenly interpreted improved survival and increased detection with screening as evidence that screening saves lives. Few correctly recognized that only reduced mortality in a randomized trial constitutes evidence of the benefit of screening.

Some patients may be persuaded by the benefits of longer survival, even if, as is sometimes the case, it is mere weeks, but survival statistics are not the whole picture on which patients can make rational choices. For a more detailed treatment of the issue, see Gigerenzer and Wegwarth (2013).

Lead-time bias is an important element in survival rates. Screening may lead to earlier diagnosis, for example, but does a screened patient live longer than one who was not screened and not diagnosed as a result? The survival rate for early-diagnosed screened patients may be 5 years, but do the non-screened patients, whose diagnosis was known about for a shorter time, die at the same time anyway? Survival rates, or symptom-free survival periods can also be very misleading in relation to short-term surrogate endpoints (like hypertension or hyperlipidemia) as opposed to all-cause mortality over a long period.

Gigerenzer points out (WHO 2014) "... 5-year survival rates and mortality rates are uncorrelated ($r = 0.0$) across the 20 most common solid tumours".

And Gigerenzer also points out that there may be a further bias in cancer survival rates:

> ...*overdiagnosis*, the detection of non-progressive cancers – abnormalities that meet the pathological definition of cancer but will never progress to cause symptoms in the patient's lifetime. Non-progressive cancers inflate survival rates.

This serious error might affect interpretation of data relating to any medicine or procedure.

Causality

There is much popular confusion about causality. Events that have a close temporal association are often mistaken as having a causal link. It's too easy to leap to the conclusion that the vaccination or the drug must be the cause of an adverse event that follows shortly afterwards, but it may or may not be so. Coincidence is an experience to which we are all apt to attach too much significance, not least because we don't pay attention to the thousands of other occasions when there's no surprising association between similar kinds of events at all. At its simplest, it's obvious that out of a million children, there's a good chance that one or more of them will have a medical episode of some kind or other on the day of vaccination, whether they are vaccinated or not.

We may attach undue significance to chance events. Any random scattering of events is likely to show occasional clusters, which may or may not point to common causal factors (cancer and overhead power-lines, for example). Inference of

causality may also be driven by prejudice: 'I don't trust doctors so they must be to blame for this;' or: 'We've spent a lot of money developing this drug and the results look good.'

Establishing causality in assessment of adverse drug reactions based on an individual patient in clinical practice or on a single case report in pharmacovigilance (i.e. proving the adverse event was undoubtedly caused by the medicine) is, in most situations, difficult, if not impossible. Risk factors, other variables and confounders often prohibit confident conclusions and the result will usually be a qualified probability. In assessing a patient case report, de-challenge and re-challenge information are the most reliable indicators of causality. However, in the real life clinical situation, a patient will have to believe that there is an element of doubt about the reaction that has to be tested before they may agree to a rechallenge (defined as readministration of the medicine at the same dose). The Bradford Hill criteria are among the most trusted algorithms for assessing causality (Lucas and McMichael 2005). Even these, however, may result in an outcome where causality is far from certain and far from the certainty that patients and the public hanker for. Explanation of that to patients, related to the tentative and evolving nature of science, is, in itself, a complex challenge. Guidance on causality assessment can be found in many places (e.g. MHRA 2013a).

Large ADR databases, such as the WHO's VigiBase (Uppsala Monitoring Centre 2013), data-mining and rigorous signal detection may provide additional information about the likely strength of an association, but there is no real substitute for clinical observation and acumen and the collection of quality data. Clinical trials and pharmacovigilance can provide historic safety information of reasonable reliability and those sources are the basis of most of our risk information. Things do change over time, however, and old data are risky data.

Placebo (and nocebo) effect raises the question of causes being inaccurately attributed: did this patient get better because of the treatment or because they were cared for in ways that made them feel better? Did they fail to improve, or get worse, because of their suspicion, mistrust or lack of confidence in relation to the treatment or the provider?

So, patients may assert confidence about the causes of their troubles, while a doctor may be uncertain or even sceptical. Negotiating such differences requires some patience and skill in the performance of risk communication. This is particularly pertinent in highly-charged situations like vaccine and other medicines scares (see Chap. 19).

Trade-Offs (How We Assess Risks and Benefits)

As everyone perceives risk differently, so everyone calculates trade-offs differently. If I am in great pain, and if my personal tolerance of pain is low, I may want to trade-off the risk of harm of even potentially serious side effects from a medication that will give me the benefit of immediate relief, whatever my doctor

feels about the decision. If, on the other hand, I am healthy and have risk factors but no disease symptoms (hypertension, hyperlipidemia, smoking or being overweight, for example), my trade-off is between more or less distant or hypothetical risks, current inconvenience or discomfort, and possible benefits at some time in the future.

The professional risk of preventive treatment of healthy people is, as Margaret McCartney characterises it, of turning a person into a dependent patient (a truly radical transformation) or, in the case of a woman and hormone replacement therapy (HRT) of exposing her to the risks of the medicine and its consequences for limited or uncertain benefit. The all-mortality risks of smoking are clearly much more vivid than those, for example, of borderline hypertension, but there are still difficult decisions and trade-offs to be made.

These issues must be part of the risk communication initiated by doctors, on the understanding that ordinary people (pre-patients) or patients will not necessarily think or act in the ways that professionals would. The trade-offs that patients make will not be decided by absolute risk or frequencies alone.

Regulatory authorities and patient information customarily use terms with specific meaning, like 'serious,' (leading to death, hospitalisation, and so on (MHRA 2013b)) to categorise adverse effects. For patients, on the other hand, the subjective meaning of some technically 'non-serious' events may be quite different. Someone whose tropical holiday is ruined by the (officially non-serious) effects of the antimalarial Mefloquine they were prescribed may well regard such effects as 'serious' and a poor trade-off, though it was never a threat to their essential health. The dancer who finds her muscles deteriorating as she takes her statins may be in a terrible bind between anxiety about the risk of vascular events and distress about the loss of physical capacity. What trade-offs should she be making and should her doctor be helping her to make in relation to her quality of life? (McCartney 2012, p. 45). (There is also the technical distinction between 'serious' and 'severe' (see MHRA reference above) that may not be clear to patients.)

'How will this affect my quality of life?' is an essential risk information question patients will want to have answered. Doctors may not always be the best people to answer that question; other patients, in forums and internet communities, may be better qualified. Many patients do trust their doctors (Gallup 2011) (though there are mixed opinions on this (Riner 2014)) but even the best professional cannot provide the richness of understanding of any disease or medication that experienced patients can on the best forums such as HealthTalkOnline and PatientsLikeMe (Healthtalkonline; patientslikeme)

This is an elementary account of some of the main aspects of risk communication theory and practice. There are immense printed and electronic resources for those who want to learn more. John Paling's *Helping Patients Understand Risk* is among the most helpful and accessible and a good starting point (Paling 2006).

Part 2: Gender Specific Issues in Risk Communication for Women

Introduction

> *Around the world, the interplay of biology and culture, or nature and nurture, brings about differences in men's and women's health, which have been largely overlooked in clinical studies that [mainly] use only men as subjects. Although women live longer than men almost everywhere, they suffer from more illnesses and disabilities throughout their lives. Women's health disadvantages often arise from gender inequalities, which are pervasive particularly among the poor in the developing world.* (WHO 2000)

The purpose of this section is to examine a range of diseases, medicines, procedures, issues and questions that concern a wide spectrum of women uniquely or predominantly, especially the macro-context in which health is defined and treated; to develop some general and specific insights into the multiple risk factors and risk communication challenges for women. These, in turn, have radical implications for how female patients are perceived, how their diagnoses are made and how their risk decisions are negotiated. This material provides the broad context for a mature interpretation of everything in this book. Suggestions and methods for risk communication in practice, will be discussed in the following chapter.

Disease, diagnosis, prescribing, taking medicines and communication of all kinds take place in a socio-cultural-political context (see Chap. 16) and in relation to a host of individual variables. Among these multiple factors, many of them have particular impact on women as citizens and on women as patients. Healthcare as a whole must take account of these factors if women are to get equal and sufficient service. Health workers must take account of these factors when they manage relationships, prescribe medicines and communicate risk. While the material in this section applies to all aspects of healthcare, it is primarily focused on medicines and risk communication for women.

But for biological sex and its dependent variables such as longevity, the differences between the women of the world vary from minor to radical across many dimensions, just as they do between all men and between men and women. In taking 'women' as a category for discussion, there is always a risk of generalisation and oversimplification. In this part of the chapter we identify common themes and concerns where they are plausible (for example, women everywhere experience menopause and are at risk of physical and sexual violence). However, much of the research on which we are drawing and many of the observations we shall make are limited to specific populations with unique characteristics and risk factors (for example, Latinas in the US or elderly women in Japan). Some of these may raise issues that are useful for thinking and action in other contexts, but their utility can rarely be more than speculative without supporting research in different settings. We cannot expect to have specific, evidence-based material for every aspect of every patient's character and conditions, but we can draw on the widest range of accumulated knowledge, in this case about women and healthcare across the world,

that has any kind of bearing on the patient in front of us. Good practice requires understanding and wisdom far beyond clinical diagnostic skills, evidence-based therapy and grasp of basic demographic characteristics, as we shall see.

Women exist in every imaginable socio-economic and cultural milieu, from the most affluent, secure and independent to the most deprived, oppressive and dangerous; in circumstances where the very best of modern medical care is available, to those who have no access to resources beyond the wisdom of grandmothers and the local medicine man or fetish-priest. From this immense variety, we must try to find those areas where women have common interests and needs and those where conditions are unique.

The priorities and methods for risk communication differ immensely, therefore, across the world's population of women and within individual countries and regions. In Chap. 19, we shall look at principles and methods in more detail, but these can never be more than suggestive signposts on a very complex journey with many possible routes for each individual. In some countries, for example, the greatest risks to women's health are not adverse effects from medicines, but poverty or male indifference or hostility to women's symptoms and needs (Anonymous 2014; Watch 2009), or women's fears of stigma or rejection for being ill and their prioritising family and domestic responsibilities far above their own health.

Furthermore, access to good quality medical care is problematic for hundreds of millions of women even when they are motivated and free to seek it (see Chap. 17). In the West, and elsewhere, the male norm influences institutional and individual scientific and practice behaviour, biases diagnoses and treatments, and leads to neglect of research into the diseases and medicines that matter most to women. These are risks arising from fundamental socio-political and economic structures, values and practices that must be factored into the understanding of patients and their diseases and into their diagnoses, treatments and communications.

The Urgency and Complexity of Good Communication

Sound, trusting relationships with health professionals and tailored, appropriate information are essential for effective healthcare, for safety, for good outcomes and for patient satisfaction.

The evidence for the positive impact of good physician communication skills is now extensive. In their review of the literature, Wong and Lee conclude:

> Good doctor patient communication is important and has multiple impacts on various aspects of health outcomes. The impacts included better health outcomes, higher compliance to therapeutic regimens in patients, higher patient and clinician satisfaction and a decrease in malpractice risk. (Wong and Lee 2006)

To address the challenges of risk communication in women's health we have to take account of at least these issues:

- The immense variation between individuals within even apparently homogeneous groups
- The political, economic, religious and cultural context, particularly as it affects the dignity and autonomy of women
- The dominant norms, values and practices within healthcare

Scoping the Territory

In order to come to some useful conclusions about effective risk communication for women, we must review the relevant risk factors that affect women's lives and the social and cultural contexts in which they occur. These will all affect the nature of the risks faced, how they are perceived and, if they can be managed at all, how that is to be done. This overview includes many of the topics that are dealt with individually and in greater detail elsewhere in this book.

This chapter makes no attempt at comprehensive coverage of all major or lesser causes of risk nor of morbidity and mortality, but rather draws some tentative conclusions from a representative, but highly selective list.

Based on Buvinic et al. (1999), Table 18.1 presents one approach, directing attention to some of the broad categories for consideration that mark the priority territory of concerns for women.

Within all the groups in Table 18.1, the clinical picture of diseases and conditions as well as the socio-cultural-psychological dimensions will be either unique to women, or distinctly different from those presented by men. They will be different from those understood by men whose perceptions or practice are ill-informed, gender-biased in one way or another, or based on evidence from studies or trials that do not include women or women of the group being treated. Gender equity requires that conditions unique to women and drugs with unique effects on women should be researched with equal thoroughness to those conditions and drugs common to men and to men and women; that in research into common conditions and drugs, women should be equally represented with sex differences always disaggregated.

Table 18.1 An approach to differential grouping of women's conditions and diseases

Reproductive concerns
Cancer
Diseases associated with women's greater longevity
Diseases arising from the interaction of sex and gender with higher prevalence in women
Gender-based injuries
Diseases common to both sexes where characteristics and needs differ for women
Risks for women that may be inadequately diagnosed, understood, characterised and communicated

Table 18.2 WHO framework (WHO Gender Policy 2000)

Biological differences
(a) Anatomical/physiological
(b) Anatomical, physiological and genetic susceptibilities
(c) Anatomical, physiological and genetic resistances/immunities
Social differences
(a) Roles and responsibilities
(b) Access and control
(c) Cultural influences and expectations
(d) Subjective identity
Health situations, conditions and/or problems
(a) Sex specific
(b) Higher prevalence in one or other sex
(c) Different characteristics for men and women
(d) Generate different response by individuals/family/institutions depending on whether the person is male or female

The safety profile of drugs tested or used in male populations may be quite different when prescribed for women. Symptom presentation and treatment (in myocardial infarction, for example) may be quite different in men and women (Bankhead 2013). Then there are the multiple, non-clinical variables that will differ across age, ethnicity, socio-economic and geopolitical groups, and, of course between the sexes.

The WHO's radical Gender Policy (WHO 2000) proposed the framework shown in Table 18.2 for understanding gender profiles in health.

Themes from this list will recur in the following discussion.

Concomitant Risk Factors

Apart from important biological, genetic, metabolic and other intrinsic risk factors, which do not fall within the core ambit of this chapter, there are many other influential issues for consideration that the WHO framework begins to elucidate. All of these are relevant to men and women but have quite distinct weight and meaning in application to each of the sexes. Table 18.3 shows a much modified version of Warren et al's Predictors of Adherence to long-term statins (Warren James et al. 2013) which, though prepared for quite different purposes, provides a useful starting point and some synthesis of the issues raised so far. Each of the factors in the list may have a unique and specific effect on a patient's health and welfare, presentation of symptoms, perception of risk and risk communication needs.

Warren et al. alert us to some important influences on the risk factors associated with adherence to statins that may have significance well beyond the borders of

Table 18.3 Contextual risk factors in women's health

Age
Gender
Ethnicity
Religion
Highest educational qualification
Language spoken at home (i.e. the official national language or a minority language)
Partnership status
Sexual orientation
Domestic and caretaking responsibilities
Remoteness index (how far from city, town and health facilities)
Insurance status
Employment status
Annual income
Alcohol consumption
Current smoking status
Level of physical activity
Self-rated health
Functional limitation, disability
Psychological distress
Co-morbidity

Based on Warren James et al. (2013)

their Australian study. For example, and a high alert for risk communication, the strongest predictor of non-adherence in this study was when the language spoken at home was not English.

We can extrapolate major questions relevant to all patients even from this study:

- Risks may not be well managed even among populations we may assume to be mature and well-organised (employed or with higher education, for example)
- Lifestyle choices (smoking and drinking, for example) may be indicative of predispositions or tendencies that manifest themselves in other aspects of choice and behaviour
- Psychological distress may strongly influence perception, choice and behaviour
- Self-image with regard to health status (excellent to poor) may influence responses to symptoms, to risk, to diagnosis and to medication regimens
- The primary language (as spoken at home) may have a critical impact on adherence, safe medication use, and on the care of self and others

The interim message is this: the variables affecting patients' lives are multiple and interacting. If we now add sex and gender issues to our considerations, we must elaborate the risk factor list presented earlier as two distinct versions that would apply quite separately to women's and men's preferences and needs.

Gender Bias

Illustrative Evidence About Gender-Bias

As an illustration of the issues as they affect women, here's an illuminating summary of the influence of gender-bias in the treatment of women for heart disease at the beginning of the century. It's from the Beth Israel Deaconess Medical Centre (Ricciotti 2003).

> Gender bias in medicine usually happens in one of two ways: (1) a doctor assumes that women's and men's health situations and risks are similar, when in fact they are not; or (2) a doctor assumes there are differences where there are actually similarities. Despite the medical profession's best effort, gender bias may still play an insidious role in influencing physicians' decision-making. The following studies exemplify cases of gender bias in the care of women with heart disease:
>
> - In 1996, a national survey of physicians found that more than 65 % of respondents were unaware of gender differences in the symptoms, warning signs, and tests used to diagnose heart disease. Less than 40 % had received special training in the diagnosis of heart disease in female patients. Finally, a full 50 % of respondents did not know that heart disease is the number one health risk of women after menopause.
> - A 1997 article published in the Archives of Internal Medicine found that of 677 heart attack survivors over the age of 65, women underwent fewer tests and were less likely to be prescribed aspirin in the prevention of another heart attack.
> - A 1998 study published in the British Medical Journal found that of the almost 32,000 patients who received artificial pacemakers in 1992 and 1993, women were more likely to receive less sophisticated models. The authors believed that the patient's gender influenced the physicians' decision of which pacemaker to use.
> - A 1999 study published in the New England Journal of Medicine found that a patient's race and gender could significantly influence treatment recommendations. The study was conducted using actors as patients who reported the same symptoms and had the same lab test results. Yet black males and white females were 40 % less likely to be recommended for a potentially life-saving cardiac surgery than white males were. Black females were 60 % less likely to be recommended for the surgery.
> - A 2000 article published in the New England Journal of Medicine reported that of 10,000 people who reported to a hospital emergency room, a small number had heart problems but were mistakenly sent home instead of being hospitalized. These people were more likely to be women under the age of 55, minorities, and people whose electrocardiogram (EKG) was normal.
> - Another 2000 article published in the Journal of the American Medical Association suggested that hospitalized women with heart disease were less likely to have tests or procedures (e.g., catheter-based procedures) done while in the hospital.
> - A 2000 study published in the Archives of Internal Medicine found that men were more likely to be prescribed cholesterol-reducing drugs than women were, despite a 1999 report published in the Journal of the American Medical Association stating that men and women benefit equally from the drugs.

It seems that things have not significantly changed in the decade since then. In a large study in Sweden, Sederholm Lawesson (2012) concluded:

> In STEMI [ST elevated myocardial infarction], women had a higher risk of in-hospital mortality but the long-term risk of death was higher in men. More studies are needed in the

primary percutaneous coronary intervention (pPCI) era that are designed to determine why women fare worse than men after STEMI during the first phase when they are in hospital.

In a project the previous year, this was their research objective:

In ST elevation myocardial infarction women received less evidence-based medicine and had worse outcome during the fibrinolytic era. With the shift to primary percutaneous coronary intervention (pPCI) as preferred reperfusion strategy, the authors aimed to investigate whether these gender differences had diminished.

They found:

In spite of an intense gender debate, focus on guideline adherence and the change in reperfusion strategy, the last decade gender differences in use of reperfusion therapy and evidence-based therapy at discharge did not decline during the study period, rather the opposite. Moreover, higher mortality in women persisted.

In a study published in GlobalHeart (Sharma and Gulati 2013), the authors found:

. . . that women who go to the hospital with chest pain or other urgent heart symptoms are less likely to receive blood thinners and less likely to undergo cardiac catheterization. Women with heart symptoms were also less likely to be given early aspirin, beta-blockers, or timely treatment to restore blood flow through blocked arteries. . . Women with CAD tend to develop the disease about 10 years later in life than men do, but the consequences are worse. Women under 50 who have a heart attack are twice as likely to die, and women over 65 are more likely than men to die in the first year after having a heart attack.

Although they raise some doubts that these differences can be attributed solely to treatment failures, they conclude:

. . . much work remains to be done to raise the visibility of heart disease in women, expand treatment, and prevent unnecessary deaths.

Risk and Domicile

The extent of gender-bias, and, therefore, the risks of unequal treatment, are likely to be determined, to a large extent, by the country of domicile. The World Economic Forum's Global Gender Gap index (Forum 2013) gives us some indications of where women are likely to get a better deal and where they are disadvantaged across a wide range of variables. The index is based on an assessment of: Economic Participation and Opportunity; Educational Attainment; Health and Survival; Political Empowerment. The top 20 and bottom 10 countries in 2013 are shown in Table 18.4.

The Index Report's conclusion gives a picture of exactly what the rankings represent:

The four highest ranked countries—Iceland, Finland, Norway and Sweden—have closed between 81 % and 87 % of their gender gaps, while the lowest ranked country—Yemen—has closed a little over half of its gender gap.

Table 18.4 The World Economic Forum's global gender gap index (Forum 2013)

Countries are ranked according to how much of their gender gap they have closed, measured by a number of specific parameters for all countries			
Rank	**Country**	**Rank**	**Country**
1	Iceland	11	Belgium
2	Finland	12	Latvia
3	Norway	13	Netherlands
4	Sweden	14	Germany
5	Philippines	15	Cuba
6	Ireland	16	Lesotho
7	New Zealand	17	South Africa
8	Denmark	18	United Kingdom
9	Switzerland	19	Austria
10	Nicaragua	20	Canada
The bottom 10:			
Rank	**Country**		
127	Saudi Arabia		
128	Mali		
129	Morocco		
130	Iran, Islamic Rep		
131	Côte d'Ivoire		
132	Mauritania		
133	Syria		
134	Chad		
135	Pakistan		
136	Yemen		

While readers may well have questions about some of the rankings and about the validity of the processes that gave rise to them, the Index does provide an important perspective on the position of women across the world. It alerts us to the relative advantages and disadvantages, and therefore to the wide spectrum of risks and opportunities for women depending on where they live. Health workers in Yemen have very different issues to manage and very different risk communication challenges from those in Iceland. A national perspective does not, of course, represent the multiple gaps and divisions within a single country which may, for some, be as wide as those between the first and last in the international list.

Professional Values, Attitudes and Behaviour

Beyond technical competence, the quality of care a woman receives, her health and her safety, will, to a large extent, depend on the values and behaviour of the institutions and individuals who care for her. This is a huge area of medical philosophy and sociology that we can only allude to here. In the material that

follows, we shall see how the values and behaviour of medical professionals vary in decision-making style, in assumptions about women's symptoms and in the establishment of trust.

Every institution and individual health worker must have awareness of hidden values (for example, on the spectrum of patriarchy to democracy, in relation to notions of professional expertise and patient naivety, in relation to differential perception of the sexes), and understand how they affect their every thought and decision. No-one can be aware of everything at any one time, but alertness to mystery, complexity and hidden operators and pitfalls is essential to intelligent practice (training has an important part to play in this). This is not to suggest that there is a single, virtuous position to achieve in all situations (because women's preferences and needs differ so widely), but it is to assert that taken-for granted values and assumptions must be recognised and modified to the existential reality of each patient; if they are not, there has to be some understanding that the best quality of care cannot be delivered. Healthcare professionals themselves are one element in the matrix of risk that women face.

Women's Preferences and Needs

Across all healthcare provision, the meeting or explicit negotiating of patients' needs, expectations and preferences are likely to lead to greater satisfaction as well as better outcomes. They are likely to encourage patients to pay more attention to available information, including safety information, improve risk management, adherence and persistence. Dissatisfied, frustrated, unhappy or angry patients are very unlikely to enjoy optimal healthcare experiences and outcomes. The same negative prediction applies also to those patients who are neither explicitly satisfied nor dissatisfied with their healthcare but are, for one reason or another, disengaged or ill-informed about their disease and the benefits and harms of their medications.

The more we know about preferences and needs, the more we are likely to provide risk communications that have a positive effect, delivered in ways that sensitively take account of individual preferences and circumstances. It is impossible to predict what variables will be most influential in any given individual, but an understanding of the range and variability of individual preferences enables us to respond with greater sensitivity and accuracy. Generalisations do not answer the case, but a mental library of research and insight is an essential tool for good patient care.

First, a caveat about preference evidence provided by research. Montori et al remind us:

> Access to patients' preferences is complex. Individuals form their preferences when they have to make a decision, in a context replete with emotional and social influences. This context is often absent when volunteers, not facing a decision, report preferences. Hindsight bias, cognitive dissonance, and regret can reduce the validity of surveys of preferences in patients who are living with the consequences of a prior decision. (Montori et al. 2013)

The influence of local socio-ethnic-political-religious factors also affects preferences, so we must be cautious about generalizing from research in developed, predominantly Caucasian countries to the situation for women in developing countries living in utterly contrasting environments. (This caution also applies to the use of medicines tested in the West when they are provided for entirely different populations.)

We must be careful about believing we have unearthed the immutable truth when all we have done is to open the door to a complex and mutable landscape, especially when that landscape relates only to a specific culture or ethnic group in one country.

In an extensive review of the literature, published in 2004, Sampietro-Colom et al observed:

> The literature on preferences in women's health care is limited to a fairly homogeneous population (white women from the United States, United Kingdom, and Canada)... Women's preferences are not necessarily uniform even when asked similar questions using similar tools. Little information on women's preferences exists to inform policymakers about women's health care. (Sampietro-Colom et al. 2004)

Since then, there has been an accumulation of research across the world, but the primary populations studied remain predominantly the same. The following material illustrates some of the important insights that can be gained by asking women in many different places about their preferences and also casts light on a number of risk and risk communication issues across cultures, race, age and class.

Healthcare Provider Gender

Many women seem to have a preference for same-sex providers, female adolescents particularly, but that preference is also mediated by other factors, such as perception of the best available facility or doctor for the occasion (see Sacks, below). There is a stronger preference for female providers in breast screening, PAP smears, gynaecology, obstetrics and urology, but not exclusively so except in Muslim women (studied, for example, in Egypt (Zaghloul et al. 2005)). Female patients of the US Veterans' Administration (VA) showed a preference for all-female facilities for comprehensive medical care, views shaped by their perception of gender discrimination elsewhere (Mattocks et al. 2011).

In a small study of middle-Class African American women, with the intersecting variables of sex, class and race, there was evidence of a preference for female providers irrespective of race, and though respondents did express an affinity with black providers in some circumstances, this did not constitute a race preference. The researchers conclude:

> Although increasing racial diversity among the healthcare workforce is generally positive, the black middle-class women in this study suggest that alone will not ameliorate racial disparities in healthcare. The complexities of the healthcare encounter, including time pressure, clinical uncertainty and the patient's desire for expertise regardless of race or gender, all impinge on respondents' race preferences. Moreover, understanding the dual

> identities of minority women, i.e., black and female, highlight the importance of both race and gender preference for black women. Lastly, women noted that site-level factors may be conflated with the race of provider. That is, having a black provider does not necessarily lead to better care or protect women from discrimination or bias. As such, they do not necessarily prefer a black provider or rely solely on black providers to mitigate institutional-level bias. (Sacks 2013)

Here, amongst many interesting elements, we also see that the institutional context of healthcare, its values and behaviour, can have a marked effect on the confidence and trust of patients even when the provider-encounter seems satisfactory.

Henderson et al investigated the evidence from a 2002 evaluation of the National Centers of Excellence in Women's Health (CoE) suggesting that women receive higher-quality primary health care, as indicated by receipt of recommended preventive care and patient satisfaction, when they receive their care in comprehensive women's health centers (Henderson et al. 2004). Comparing CoE patients with others in the community, both receiving care primarily from female providers, they observed that there was a positive effect from institutional standards. Their conclusions are illuminating:

> The findings confirm a positive CoE effect for many of the quality of care indicators that were observed in the original evaluation. Women seen in CoEs are more likely to receive physical breast examinations and mammograms (ages $\geq$50). In addition, positive CoE findings for counseling on domestic violence, sexually transmitted diseases, family or relationship concerns, and sexual function or concerns were upheld. The CoE model of care delivers advantages to women that are not explained by the greater number of female physicians in these settings.

Racz et al found exactly what the title of their paper states: *Gender Preference for a Female Physician Diminishes as Women Have Increased Experience With Intimate Examinations* (Racz et al. 2008). This presupposes, of course, a sensitively calibrated first-encounter with a doctor of either sex.

Schmittdiel et al found that women who made a conscious choice of a female physician were the least satisfied among four groups of men and women who either chose the gender of their physician or were assigned a physician (Schmittdiel et al. 2000). Men, on the other hand, who chose the same female physicians were the *most* satisfied, suggesting influential differences in expectations between the sexes. While the reasons for these differences are not self-evident, the authors suggest that:

> One explanation for lower ratings may be that the female physicians in this study may not have achieved 'gender-based' care ideals such as better communication on social, lifestyle, prevention, and emotional concerns. Patients who had selected female physicians hoping for such qualities would therefore be disappointed.

What does all this mean for healthcare practice and for risk communication? Women's preferences for provider-sex vary across medical condition, age, class, race and religion, from strong and exclusive to negotiable on the basis of other influential variables, such as perceived quality of care and institutional discrimination. Individuals' preferences may change over time as they have reassuring

experience after initial caution and we could assume that change in a reverse direction may also be likely. Optimal healthcare provision and risk communication can take place only when such opinions, expectations and preferences are investigated and taken fully into account in a consultation. If they are underestimated or ignored in patients for whom they are a genuine concern, they will become obstacles to communication and their effects may be damaging to both treatment and safety. When preferences cannot be met, the divergence needs to be factored into the way relationships and communication are established. (A brief sample of how this might be done appears in Box 18.2).

In many countries where the number of health care workers per head of population is very low (as noted in Chap. 17), this issue, and the illustrative conversation, could be seen as a luxury or a first world problem. Nevertheless, it needs to be recognised and managed, in some way, everywhere.

Box 18.2: Managing Provider Gender Preference Problems

Scenario:	Male doctor in clinic; female patient enters and show signs of surprise as she notices the doctor
Doc:	Hello. Please come in and sit down. My name's Dr Sanjay. You're Fatima Shah, is that right?
Patient:	Er, yes. [Sits down looking anxious]
Doc:	You seem worried. Is something troubling you?
Patient:	Well, er, I hoped, I, well, wanted to see a woman doctor.
Doc:	Oh I'm sorry. There are none of our lady doctors available just now. Is it a physical examination you're worried about?
Patient:	Well, that yes. But I thought a woman would understand my problem better.
Doc:	OK. I won't ask you to let me examine you physically, but could we just talk about the problem first? You can judge if you think I can help – even though I'm a man! – and if you're not satisfied we'll make another appointment with a lady doctor. Many of my patients are women, so you may find I can help you. Is that OK?
Patient:	OK
Commentary:	This doctor is empathetic and responsive and engages in very skilled management of the encounter. He notices the patient's anxiety and quickly seeks its cause, inferring, correctly, the main issue (physical examination). He reassures her about that concern and asks permission to try the less risky path of verbal problem exploration. He leaves power of decision in the patient's hands; makes a

(continued)

Box 18.2 (continued)

light-hearted remark that engages with the patient's concern; reassures her by implying that other female patients find him a satisfactory provider, but that the patient may still decide to ask for a female doctor. It is only too obvious that failure to manage the patient's preferences and expectations would be likely to lead to a tense, incomplete and unsatisfactory consultation. This very short encounter demonstrates several of the fundamental skills of the best communication.

Decision-Making Participation

Lopéz et al investigated 'differences in treatment decision-making participation, satisfaction, and regret among Latinas and non-Latina whites with ductile carcinoma in situ (DCIS)' (López et al. 2014). In their group of 745 Latinas and whites, they found that Spanish-speaking Latinas,

> . . .had the highest mean preference for involvement in decision-making score and the lowest mean participatory decision-making score and were more likely to defer their final treatment decision to their physicians than English-speaking Latinas or whites. . . More participatory decision-making increased the odds of satisfaction and decreased the odds of treatment regret, independent of ethnicity-language.

Their conclusion also has a tragic thread to it:

> Language barriers impede the establishment of decision-making partnerships between Latinas and their physicians, and result in less satisfaction with the decision-making process and more treatment regret.

A particularly intriguing piece of research was carried out in Japan by Watanabe et al. (2008). Their paper, *Japanese cancer patient participation in and satisfaction with treatment-related decision-making: A qualitative study* provides some vivid signposts for our understanding of the impact of patient preferences on satisfaction with physician behaviour and has profound implications for the handling of treatment and risk information. In a historically paternalistic culture, the Japanese Medical Association has, for over a decade, been strongly promoting patient involvement in decision-making and the ideal of informed consent, in contrast to the traditional *Omakase* (entrusting) value of submission to experts.

The intensive interviews with cancer survivors (a small group with a slight majority of women), revealed two clear issues:

- Patient preferences varied considerably from individual to individual (this finding is unsurprising and common to other studies in the West)

Box 18.3: Japanese Cancer Patient Participation in and Satisfaction with Treatment-Related Decision-Making (Watanabe et al. 2008)

- Patient as the active decision maker, including rejecting physician advice
- Doctor selection (reviewing physician options and choosing a particular one to trust)
- Wilfully entrusting the physician
- Compelled decision-making
- Surrendering decision-making

- Satisfaction was determined by the extent to which physicians actively sought and engaged with a patient's *specific preferences*; failure to do so resulted in dissatisfied, resigned, angry, sometimes bitter patient reactions

The key findings in relation to the patient-doctor decision-making process in this Japanese study, with relevance and applicability across healthcare were five categories as shown in Box 18.3.

The authors point out:

> While the informants under the first 3 categories were fairly satisfied with the decision-making process, those under the latter 2 were extremely dissatisfied. Informants' views regarding their preferred role in the decision-making process varied substantially from complete physician control to complete patient control; *the key factor for their satisfaction was the relation between their preferred involvement in decision-making and their actual level of involvement, irrespective of who the decision maker was [our emphasis]*

The model missing from this research is that of true partnership and joint decision-making through genuine interactive discussion, the ideal that has been promoted in the West for some years now and is the underlying value of this chapter. That commitment does not imply, however, that it should be imposed on those who do not want it.

The range of preferences across all patients includes those who wish their doctors to make decisions for them either in the spirit of *Omakase* or at the end of a review of options. The conscientious pursuit of concordance and informed consent may, for some patients, be as oppressive as imposed decisions are for others. Unless we know what our patients prefer, we cannot make them comfortable nor rely on their paying attention to what we say. Their safety and health and their wellbeing are at stake in these matters. The risk information that patients want, its extent, detail, repetition and modes of access and delivery must be determined by them.

There is much useful wisdom in the conclusions of a small study by Wrede-Sach et al in Germany (Wrede-Sach et al. 2013). The authors sought to discover a typology for *Decision-Making of Older Patients in Context of the Doctor-Patient Relationship*. Good relationships with providers facilitated satisfying decision

making, and participants (half of whom were female) provided these useful insights into their feelings:

> Trust evolved as a response to a good doctor-patient relationship, and it helped patients to be more relaxed with decisions and led to better adherence. The patients often pointed out how doctors contribute to a good relationship: provide time, listen, pay attention and be open (patients 7 and 12), explain and give information (patients 14, 42, and 45), be truthful (patients 11, 14, and 32), be reassuring (patient 46), be a long-standing companion and share experiences (patients 13, 27, 28, and 45), know the patient through and through (patients 27, 28, 32, and 45), and be at eye level (Patient 33).

While the project found that older patients protected their autonomy to make decisions that affected their domestic and social life, they were inclined to rely quite heavily on their physicians for guidance and decision making in medical matters. Nevertheless, the range of preferences was broad, leading to the conclusions that:

> Owing to the varied patient decision-making types, it is not easy for doctors to anticipate the desired level of patient involvement. However, the decision matter and the self-determination of patients provide good starting points in preparing the ground for shared decision making. A good relationship with the doctor facilitates satisfying decision-making experiences.

(I cannot resist comment on one intriguing detail from that summary of patient hopes: that the physician should *be at eye level*. This and a number of other very basic behaviours and provisions may have much more impact on patient attention and satisfaction than might at first seem likely, and with differential effects for women and men. Computer screens invisible to the patient; the doctor sitting behind a desk piled with books and files; the patient sitting on a low or uncomfortable chair; the decoration, smell and temperature of the room; the doctor's mode of dealing with phone calls or interruptions; these and much more will have an impact, from minor to significant on a patient's mood, morale, attentiveness and trust. Do we pay enough attention to such mundane matters?)

An interesting footnote to the issues of good information is the question of situations in which information-sharing may not be helpful. An Ohio State University study (Epstein and Peters 2009) reported as follows:

> Being well-informed about their disease may lead to depression in women with heart failure who repress their anger and other emotions about their condition... The women's coping styles affected their levels of depression or anxiety... some of the women felt worse emotionally when they had more information about heart disease. For women who tend to deny their emotions, less knowledge about their disease may be better.

In his piece, *Identifying High Risk Abortion Patients*, Reardon remarks:

> Some pro-abortion researchers even argue that women should not be told of the psychological risks associated with abortion because such "demoralizing" information may make them even more prone to an adverse outcome. It is better, they would claim, to be ignorantly optimistic about the future than informed and worried. (Reardon 1993)

Reardon, like the author of this chapter, is sceptical about the ethics and humanity of such an approach in relation to abortion, or, indeed, any other procedure or condition.

Values, Beliefs and Personality

Montori et al. (2013) draw our attention to the major influence that patient preferences play in healthcare decisions and outcomes:

> Patient preferences refer to patient perspectives, beliefs, expectations, and goals for health and life, and to the processes that individuals use in considering the potential benefits, harms, costs, and inconveniences of the management options in relation to one another. Patients may have preferences when it comes to defining the problem, identifying the range of management options, selecting the outcomes used to compare these options, and ranking these outcomes by importance.

The authors are particularly concerned with the writing of over-assertive, evidence-based clinical guidelines that do not allow room for negotiating the patient's preferences. They remind clinicians that rigidly following guidelines may not be such good practice after all:

> Clinicians should remember that taking care of patients is supposed to be difficult. Although guidelines may simplify this task, when patient preferences and context matter, guidelines must not replace clinicians' compassionate and mindful engagement of the patient in making decisions together. This is the optimal practice of evidence-based medicine.

That is the challenge that has been implicit and explicit in much of this chapter and it takes us into the difficult territory of values, beliefs and personality.

This is a topic worthy of a book in its own right; here we can sketch only some of the issues most pertinent to risk communication. We need to consider, for example, a patient's disposition with regards to the future, their degree of optimism or fatalism: do they believe that a partnership for change and improvement is desirable and possible or, in fatalistic mode, that what will be will be and not much can be done about it? Is their view of the trade-offs between benefit and harm short- or long-term? Do they value quality of life above continuity and length of life? Are they risk-averse or adventurous? How far do rational, scientific considerations moderate their emotions and fears or are they driven by superstition? Do they trust officials and professionals or rely on family, community and informal networks? Are they (as we have discussed above) self-determining and autonomous, seeking to make their own decisions or disempowered, or trusting and dependent looking to others to shoulder responsibility? What is their response to pain?

These multiple variables impinge on every aspect of healthcare and certainly on every incident of risk communication. Many of them have been implicit in the discussion of specific aspects in this chapter. A health professional must make an accurate assessment of the entirety of the person in front of them and shape their relationships and communications to the specific, unique individual. They must, especially, moderate their own natural tendencies if they are to any extent divergent from the wishes and expectations of patients.

Satisfaction with Service Provision

Elliott et al found that women were less satisfied with their hospital experience than men, especially with regard to communication about medicines, discharge information, and cleanliness (Elliott et al. 2012). The gender gap increased with age and for patients with worse self-reported health status. The authors concluded:

> One of the more marked differences was the amount of information about medications or discharge plans that patients needed to feel sufficiently informed. Women generally wanted more information than they received, while men were satisfied with what they were told.

Stewart et al also found that women were far from satisfied with communications when recovering after an acute ischemic coronary event (ICE):

> Patients after ICE, especially women, reported receiving much less information than they wanted from all health professionals. Most patients wanted a shared or autonomous treatment decision-making role with their doctor, but only a minority experienced this. (Stewart et al. 2004)

Clinicians must do better, they say,

> . . .because meeting patients' information needs and respecting their decisional preferences are shown to be associated with better self-efficacy, satisfaction, and health-promoting behavior.

In the NHS (England) National Cancer Patient Experience Survey for 2013, covering over 66,000 patients, more than half of whom were women, levels of satisfaction for men were overall higher than for women, though there were variations across some of the 70 questions, and sex was a less significant factor in differences than other demographic variables such as age (Health 2013). While the comprehensive review of patient opinion and experience, and comparisons across years, does suggest many areas for improvement, it does not explicitly address the question of women's preferences, though the areas in which men expressed more satisfaction may be indicators of areas of concern to women who rated their experience of them less favourably. The main issues in this category were:

- Staff and staff working well together
- Privacy, being given respect and dignity, being told enough about their condition and treatment, and about being treated as a person rather than as a set of symptoms
- Discharge and post discharge arrangements
- Receipt of written information on types of cancer, and on free prescriptions

The questions are highly illuminating in terms of patient experience and also provide an agenda of good practice and topics for investigation for cancer (and most other) patients. For example:

> Q.17 Were the possible side effects of treatment(s) explained in a way you could understand?

The results:

> Of those patients saying they needed an explanation, 75 % said possible side effects of treatment were definitely explained to them in a way they could understand; a further 21 %

said the explanation was understandable to some extent. 4 % said side effects were not explained to them.

Q.18 Before you started your treatment, were you given written information about the side effects of treatment(s)?

The results:

82 % of patients said that they had received written information about the side effects of treatment and that it was easy to understand; a further 5 % were given written information but it was difficult to understand. 13 % of patients said they were not given written information about side effects.

Q.19 Before you started your treatment, were you also told about any side effects of the treatment that could affect you in the future rather than straight away?

The results:

55 % of those patients who needed to be told said they were definitely told about longer term side effects; 26 % said they were to some extent. 19 % said future side effects were not explained to them. 6 % said they did not need an explanation

These, and most of the results across the whole survey are, on the whole, pretty positive, but they are in considerable contrast with many of the results from the 2012 National Inpatient Survey in which issues such as involvement in decisions about treatment and getting understandable answers from doctors most of the time, were rated very much lower (Commission 2012).

Specific Preferences in Pregnancy

Hill et al looked into the preferences of women and health professional in relation to non-invasive prenatal diagnosis and current invasive tests for Down syndrome (Hill et al. 2012). Distinct preferences were very clear:

Safe tests, conducted early in pregnancy, with high accuracy and information about Down syndrome and other conditions were preferred. The key attribute affecting women's preferences for testing was no risk of miscarriage, whereas for health professionals it was accuracy.

Their conclusions have very clear implications for good risk communication through attention to women's preferences as opposed to professionals':

Women's strong preference for tests with no risk of miscarriage demonstrates that consideration for safety of the fetus is paramount in decision making. Effective pretest counseling is therefore essential to ensure women understand the possible implications of results.

This example represents one of the many decision-making and benefit-risk dilemmas in pregnancy in which women's preferences and priorities need careful discovery. (See also the section on anti-convulsants in Chap. 19.)

Preferences in Contraception

The effectiveness of medications, patient adherence and safety are influenced by many complex variables, as we have seen.

An ambitious, online study, by Hooper, across eight countries, with over 5,000 participants, discovered a wide range of variables in women's decision-making about contraception (Hooper 2010). This is an extract from his results:

> Many women did not plan on having children in the next 3 years (range 44 % in Russia to 77 % in the US and UK), but a quick return of fertility upon contraceptive discontinuation was desired by the majority of women in all countries (range 54 % in the US to 91 % in Russia). Rates of discontinuation or switching to a different hormonal contraceptive in the past year ranged from 30 % in Germany to 81 % in Brazil. Requests to switch because of side effects ranged from 24 % in Spain to 57 % in Brazil. Results from the Eight-Country Survey questionnaire indicated that 42 % of women would consider using one of the most effective contraceptive methods even if their menstrual cycle changed, 58 % would accept irregular bleeding initially if they had fewer periods over time, 53 % did not want/had concerns about foreign/additional estrogen in their body, 85 % would prefer a monthly option with a lower hormone dose over a daily pill, 80 % would consider switching contraceptives to minimize estrogen exposure and 74 % would prefer an estrogen-free/progestin (progesterone congener)-only pill to avoid potential side effects from foreign/extra estrogen.

This is just a glimpse of the complexity of women's critical thinking and needs in relation to their contraceptive use. Hooper concludes:

> [Our] findings demonstrate that a range of factors influence a woman's choice of contraceptive. This highlights the importance of individualized counselling during contraceptive selection to ensure that the option recommended is tailored to the personal preferences of each woman to improve compliance, continuance and prevention of an unwanted pregnancy.

(There is further discussion of contraceptive risks and issues in Chap. 19.)

An issue of enormous importance in patient safety is adherence and satisfaction right across healthcare: we may have the right patient and the right drug and the right dose, but do we have the right formulation? That is to say a formulation that suits the individual needs and preferences of the patient in front of us. Of all the hormonal-based contraceptive methods and others does a woman have enough information about their effectiveness and risks and how far they suit her body, her lifestyle and her capacity for adherence?

Beyond contraception, we know, for example, that multiple tablets or tablet-splitting and other complications are an obstacle to adherence and safety (Mishra et al. 2011) but, given that there are often alternatives, have we chosen the options, formulations and packaging that really have the best chance of being used reliably, safely and effectively? (This issue is further discussed in the material on oral contraception in Chap. 19, p. 600.)

Patient preferences themselves are not always rational or sound: in Africa and Thailand, for example, there is a strong popular preference for injections over oral formulations for all types of medicine (Leo 2013). This is not easily amenable to modification, whatever the risks and benefits (and costs) of either course may

be. The way in which such preferences are negotiated affects satisfaction, trust and adherence.

On the other hand, the mass roll-out of the injectible contraceptive Depo-Provera in developing countries brings its own ethical and professional concerns, noted as early as 1984 (Potts and Paxman 1984). Are women given adequate risk information about the drug, including the FDA black box warnings about menstrual and bone-density problems? Despite its cheapness and convenience, are the side effects and the continuing risk of STDs adequately explained and acceptable? Is informed consent sought and given?

Preferred Sources of Information

If risk communication is to be effective in protecting safety and facilitating patient decision-making, it must be available when and where it is needed, from a source that is trusted, and in a form that is acceptable.

Holton et al, in their systematic review, *The childbearing concerns and related information needs and preferences of women of reproductive age with a chronic, noncommunicable health condition*, reported (Holton et al. 2012):

> There are serious evidence gaps about the childbearing concerns and related information needs and preferences of women with chronic, noncommunicable health conditions. Research is required to address these gaps and to inform the development of appropriate tools to assist women in this situation with their childbearing decisions.

Their conclusion applies across many of women's major health concerns, but there are many studies that provide us with insights into specific contexts and needs. These studies also raise our gaze to much wider issues, particularly to the deep levels of empathy and ingenuity that are required to meet the communication needs of women across their immense variety. This sub-section offers a selection of those that will lead readers into contemplation of the broader challenges and, it is hoped, some pleasure at the revelation of many otherwise obscure issues.

Plutzer et al (Adelaide, Australia) investigated the *Effect of Motherhood on Women's Preferences for Sources of Health Information* (Plutzer and Keirse 2012). They concluded:

> Parents were listed most frequently as a preferred source of health information during pregnancy (67.8 %) followed by health care practitioners (48.8 %). By the time the child reached school age, 78 % listed health care practitioners as their preferred source compared with 15.5 % listing parents, 21.7 % friends and relatives, and 13 % the Internet. Data from the population-based comparison group of mothers with a first child of similar age mimicked those of mothers enrolled in the trial. Mothers put a lot more trust in information received from health care professionals than they did before their child was born.

In *Preferences for Perinatal Health Communication of Women in Rural Tibet,* Le et al found a very strong preference for close family, specifically, mother, as the most trusted source of information for perinatal women, with health workers and public health education initiatives very little favoured (Le et al. 2009). Their

conclusions demonstrate how finely targeted and calibrated communications must be if they are to reach an audience at risk, and how unreliable the uncritical use of common, default, obvious methods may be:

> Despite recent efforts in Tibet to use group teaching, television/radio programs, and health professionals visiting patients' homes as health communication modalities, participants preferred to learn pregnancy-related health messages from their close family, especially their mothers. Future health communication interventions in rural Tibet and similar communities should consider targeting close family members as well as pregnant women to maximize acceptability of advice on healthy pregnancy and delivery.

Raine et al examined women's experiences of communication in antenatal care (Raine et al. 2010). Their conclusions provide the elements of a basic communications course for health providers, with some very specific pointers about general and risk information provision:

> From the users' perspective, constructive communication on the part of health care providers was characterised by an empathic conversational style, openness to questions, allowing sufficient time to talk through any concerns, and pro-active contact by providers (e.g. text message appointment reminders). These features created reassurance, facilitated information exchange, improved appointment attendance and fostered tolerance in stressful situations. Salient features of poor communication were a lack of information provision, especially about the overall arrangement and the purpose of antenatal care, insufficient discussion about possible problems with the pregnancy and discourteous styles of interaction. Poor communication led some women to become assertive to address their needs; others became reluctant to actively engage with providers.

Vahabi focused on *Breast cancer and screening information needs and preferred communication medium among Iranian immigrant women in Toronto* (Vahabi 2011). Her work demonstrates the complexity of communications in such a minority group:

> This group is influenced by historical, sociopolitical, and cultural experiences pre- and post-immigration... Mere translation of breast cancer and screening information from generic materials, without considering and respecting women's unique historical, political, and cultural experiences, is insufficient.

Methods with the potential to reach such women require specific and sensitive tailoring:

> For instance, video presentations conducted by a trusted Iranian healthcare professional focusing on socioculturally relevant breast cancer risk factors, symptoms, and screening methods, as well as a list of available breast health resources, could improve Iranian women's knowledge and uptake of breast health practices.

On the question of health literacy, Ellis et al. looked into the information-seeking behaviour of patients with chronic arthritis and found, as might be expected, quite different levels of engagement depending on level of health literacy.

> Participants with low health literacy were less likely to be engaged with health information-seeking behaviour. Participants with intermediate health literacy were more likely to source arthritis-focused health information from newspapers, television, and within their informal social network. Those with high health literacy sourced information from the internet and

> specialist health sources and were providers of information within their informal social network. (Ellis et al. 2012)

The further, and vital aspect of this issue is that level of health literacy will have an impact on every aspect of attention, comprehension and retention of information given in any form and, particularly, by health providers. With maybe 50 % of even educated and literate populations having some level of difficulty with health information (especially risk statistics), the onus is on providers of information to ensure the content of their messages is exactly matched with the abilities and preferences of their patients. No assumptions can be made, however articulate and literate the individual may seem at first encounter.

The material above also reminds us that the most effective channels of communication may be intermediaries – mothers in Tibet, literate arthritis sufferers in their own community, for example. Patient forums and communities on the internet are popular and have a wide reach. Exclusive reliance on public health initiatives or direct contact with health workers may leave untapped the power of more influential voices.

Young People and Risk

The US annual *Youth Risk Behaviour Survey* (2012) provides comprehensive information about the lives of young people across the country, including diverse matters such as wearing a helmet when cycling, texting and emailing while driving, alcohol and tobacco use, patterns of sexual behaviour and contraceptive use, incidents of physical violence, patterns of diet and exercise, suicidal thoughts and suicide attempts (Eaton et al. 2012).

A glimpse of this – sometimes surprising and alarming – material is given here because it reveals dimensions of young people's lives that affect their health, welfare, safety and, of course, their relationships with healthcare professionals. Perception of risk in medicine and the kind of risk communication that will reach and influence them will be determined by their perception and management of risk in their own lives.

Although the 2011 data show some reduction in overall risky behaviour from previous surveys, some of the figures are quite stunning (7.8 % of the sample had attempted suicide, for example). In spite of some decrease, the report observes:

> . . .many high school students continue to engage in behaviors that place them at risk for the leading causes of morbidity and mortality. Variations were observed in many health-risk behaviors by sex, race/ethnicity, and grade. The prevalence of some health-risk behaviors varied substantially among states and large urban school districts.

Roughly half the sample was female. The overall results and trends are not disaggregated by sex, but the tables record male and female response (as well as age and ethnicity), so issues where females seem relatively more at risk can be extracted. Among those and other issues are:

- Electronic bullying
- Forced sex
- Feeling sad or hopeless
- Having serious thoughts about suicide or making a suicide plan
- Smoking, though overall less than men and more women than men try to quit, still large numbers
- Less drinking than men, but one fifth record binge drinking
- Cocaine and other illegal substances, less than men, but still considerable numbers
- One third of age group (females, Grades 9–12) sexually active
- Fifteen percent of females used no contraception
- Eighteen percent drank alcohol before sex
- Women exercised much less than men
- Around one third used computers or watched TV for three hours a day
- Percentage of males and females overweight roughly the same, but females trying harder to lose weight, including diet pills and fasting, with 6 % taking extreme measures like vomiting and laxatives
- Thirteen percent were currently suffering from asthma
- One fifth used indoor tanning equipment/services

Here's a couple of examples of analysed data that highlight the extent to which young females are exposed:

> **Made a suicide plan**
>
> During the 12 months before the survey, 12.8 % of students nationwide had made a plan about how they would attempt suicide (Table 23). Overall, the prevalence of having made a suicide plan was higher among female (15.0 %) than male (10.8 %) students; higher among white female (13.7 %), black female (13.9 %), and Hispanic female (17.6 %) than white male (10.6 %), black male (8.4 %), and Hispanic male (11.1 %) students, respectively; and higher among 9th-grade female (16.9 %), 10th-grade female (17.9 %), and 12th-grade female (12.0 %) than 9th-grade male (10.4 %), 10th-grade male (11.3 %), and 12th-grade male (9.5 %) students, respectively plan
>
> **Attempted suicide**
>
> Nationwide, 7.8 % of students had attempted suicide one or more times during the 12 months before the survey (Table 25). Overall, the prevalence of having attempted suicide was higher among female (9.8 %) than male (5.8 %) students; higher among white female (7.9 %) and Hispanic female (13.5 %) than white male (4.6 %) and Hispanic male (6.9 %) students, respectively
>
> **Did Not Use Any Method to Prevent Pregnancy**
>
> Among the 33.7 % of currently sexually active students nationwide, 12.9 % had not used any method to prevent pregnancy during last sexual intercourse (Table 71). Overall, the prevalence of not having used any method to prevent pregnancy was higher among female (15.1 %) than male (10.6 %) students; higher among white female (11.7 %), black female (17.5 %), and Hispanic female (22.6 %) than white male (8.3 %), black male (9.9 %), and Hispanic male (14.7 %) students, respectively

Do healthcare providers know what is going on in the lives of their young patients?

Hill et al. examined *Gaps between Adolescent Risk Behaviors and Disclosure during Outpatient Visits* (Hill et al. 2013) in a group of 221 young people aged

13–19 in a study on latent tuberculosis treatment; the majority (96 %) were identified as Hispanic, 45 % were foreign-born, and 46 % were male. The objective of the study was:

> . . .to determine the gaps between disclosed high-risk behaviors in low-income, mainly Hispanic youth and the identification of these risks by health care providers.

The gap turned out to be enormous, indeed shockingly so:

> A total of 399 risk behaviors were revealed to research staff by the participants; only 24 risk behaviors were revealed to [health] providers. . .The majority of risk behaviors based on the chart review were neither queried nor disclosed to the physicians. Physicians providing care to adolescents should consider strategies to improve disclosure as a necessary precursor to interventions.

The advice for practitioners is very clear:

> In order for teens to volunteer information about their own behavior, questions need to be asked in a nonjudgmental, confidential, and teen-friendly way. . . this study suggests a deficiency in provider-patient rapport. . .[and] revealed multiple barriers to the identification of risk factors by physicians of high-risk teens. Physicians should be aware that their adolescent patients are often engaging in high-risk behaviors and that adolescents limit their disclosure of this information.

What, then, are the implications for risk communication? The first, somewhat self-evident conclusion, is that a physician cannot help a patient manage a specific risk if the general risks in her life are not disclosed and shared. Second, diagnosis and treatment, and associated communication, cannot be complete and effective if the physician doesn't have a full picture of the patient's state of health and wellbeing and of the risk factors in her life. Third, the prognosis for a productive, trusting partnership between patient and provider is rather poor when major aspects of the patient's life are excluded from discussion, for one reason or another. Fourth, particularly with regard to risk communication about disease and medicine, it is unlikely that patients who have secrets, especially about risky feelings or behaviour, will put much faith in advice from providers who they know have little clue about their inner life or social reality.

(A vivid illustration of this are the health-related problems experienced by lesbians and gay men, for whom disclosure to a stranger physician, especially male, may be deeply problematic (Channel 2014) Yet sexual orientation may be at the root of psychological or physical problems, as well as having a significant impact on general health and conditions unrelated to sexual preference at all (Center 2010). The disadvantages and challenges for lesbians and bisexual women in healthcare deserve more extensive treatment than they are being given here; we note simply that it is another very important area for study and the remedying of prejudice, discrimination and disadvantage; it is a critical area of understanding for effective risk communication.)

Body Image

Women in every culture are under pressure to look good. Media images, advertising, models, film stars and male fantasies all form part of what might be regarded as the cultural conspiracy to promote ideal images and engender dissatisfaction. The icons are slim in the West, ample in Africa, pale in Asia. Cosmetics, clothes and shoes are amongst the tools of the trade. Dieting, forced feeding, cosmetic surgery, skin-whiteners, are amongst the risky remedial measures adopted. Eating disorders, depression, muscle and skeletal damage from high-heels, low self-esteem and premature death are amongst some of the effects.

These pressures in themselves put healthy women at risk, but they may also be important in women's perception of risk and the decisions they make with regard to medicines (or surgery). Compensation for 'loss of femininity' in menopause, for example, may be a powerful driving force in all kinds of decisions; mastectomy or hair-loss may be profound threats to self-image and quality of life. Decisions about medicines are not just about therapeutic effectiveness.

> In the United States, 20 million women and 10 million men suffer from a clinically significant eating disorder at some time in their life, including anorexia nervosa, bulimia nervosa, binge eating disorder, or an eating disorder not otherwise specified (EDNOS) (Wade, Keski-Rahkonen, & Hudson, 2011). (NEDA)

Vulnerability to concerns about body-image, to dieting and clinical eating disorders is not an exclusively Western phenomenon. Szabo and Allowood showed prevalence in a racially mixed, urban, sample of adolescent of females in South Africa to be close to that in the US and Western countries (Szabo and Allwood 2004). They mention studies in Nigeria and Egypt demonstrating that the problem is growing there too. A study of young, rural women in Tanzania showed the extent of negative impact of exposure to Western media on their self-image and eating habits, with a third of the sample being affected negatively in some way (IB Times 2011). Young women in Pakistan are also increasingly the victims of damaging body-image aspirations and eating disorders (Zain-Ul-Abideen et al. 2011).

In Africa, the traditional ideals are very different, as Yoknyam Dabale explains in her entertaining and informative blog (Dabale 2010):

> . . .most African men love, I mean *love*, Fat babes (When African men use the word fat, they mean curvy and voluminous – big breasts and ass – like the shape of a soft drink bottle or an hour glass). Growing up in rural Middle Belt Nigeria, I frequently witnessed the execution of this unwritten constitution. Every man and woman was aware of its power. A woman was considered beautiful if she carried extra weight around the chest, and most importantly, her ass. The complexion should be very dark, the hair needed to be braided at least once a week, and let us not forget it is a must for her to know how to husband her husband's home and those eight children she birthed from her ample hips.

This vivid ideal, driven by male preferences (and, to some extent, by female complicity and submission), has oppressive and risky aspects, not least the months a young bride-to-be might spend in a fattening farm. Pursuit of bulk cannot but be

contributing to the rapid increase in the burden of non-communicable disease in Africa, projected by WHO to exceed the combined deaths of communicable and nutritional diseases, and maternal and perinatal deaths' by 2030 (WHO 2011).

These preferences and practices bring an added dimension of complexity to risk communication and benefit-harm assessment for female patients. The discussion is no longer simply about the risks of disease and the benefits and risks of treatment, but also about the personal and social benefits and risks of a particular body-image. Weight loss or gain as goals for improved health or resisting disease may be in flat contradiction to a woman's image of her own attractiveness. Here the negotiation may be with powerful social ideals and norms that may be hostile to good health and drive some women to behaviour that is self-harming. These are matters that have to be sensitively negotiated in every element of risk communication.

The risks of skin-whitening preparations are well known among professionals (Choices 2012), but millions of women, especially young women, all over the world, are buying and using them every day. In Thailand, the Philippines and Indonesia recent years have seen multiple brands and products banned because of their toxic ingredients, but dangerous products are still easily available OTC and on the streets in many countries. Conversely (and perversely), of course, in the West, along with the pale, slim, effete models of the catwalk, there are those many who seek the real sun of the beaches or the artificial beams of the tanning salon, pursuing that exotic bronzed look – and taking the well known risk of skin cancer (75,000 cases annually in the UK and 1,800 deaths) (BBC 2014a).

These issues all raise the question of risk communication in regulatory activity, at the level of public health education and in relationships with individual patients. Risk communication with individuals takes place within the context of social perceptions of risk; an individual may be deaf to sound advice when it goes against the tide of social norms; women are especially vulnerable. Such issues, and especially public scares about medicines, vaccines or cosmetics, attack women where they are most vulnerable: in the daily routines of femininity and in their roles as mothers. This is the uncertain and confusing context in which decisions about all kinds of risks must be made; where scientific evidence may take a back seat to plausible scare-mongering; where precautionary values and habits may win the day. This has enormous implications for risk communication in healthcare, especially for practitioners' confidence and authority in providing good advice about such risks.

When the natural body is disfigured by disease, surgery or old age, then the risks and problems may multiply.

In summary: these matters have a profound impact on the lives of women and may give rise to intense emotions and anxieties. Risk communication about disease or medicine may have little or no effect if it is not rooted in a deeply empathetic understanding of the pressures and conflicts a woman may be suffering. Patients who are depressed or in mourning often cannot pay attention to communications that do not touch their immediate feelings; the same applies to women who are, for one reason or another, disturbed or depressed about their body image.

Women and Pain

Launching the Global Year Against Pain in Women (2007–2008) The International Association for the Study of Pain (IASP) made the case as follows:

> Every day millions of women around the world suffer from chronic pain but many remain untreated. Several reasons may explain why barriers to treatment still exist. Psychosocial factors, such as gender roles, pain coping strategies and mood may influence how pain is perceived and communicated. In addition, there may be a lack of acceptance or understanding of the biological differences between men and women that may impact how pain is perceived. These psychosocial and biological factors, coupled with the economic and political barriers that still exist in many countries, have left millions of women living in pain without proper treatment. (Pain)

The issues raised in this proposition will now be very familiar to readers of this chapter. The claims about women's suffering and about sex differences are well supported by research (see IASP website). The literature suggests that women report more pain than men, while Butte et al. found that women also report a greater intensity of pain across a large range of conditions:

> It's still not clear if women actually feel more pain than men do. . .But they're certainly reporting more pain than men do. We don't know why. But it's not just a few diseases here and there, it's a bunch of them—in fact, it may well turn out to be all of them. No matter what the disease, women appear to report more-intense levels of pain than men do. (Goldman 2012)

Old prejudices need to be cleared away:

> While pain has long been considered a troublesome female complaint rather than a legitimate symptom that something physically is wrong. . .the problem is not in a woman's head. (Kornblum 2014)

For women, pain, and its relief, may be important factors in their treatment and risk considerations and in ways that are quite different from the needs of men. (See Chap. 10 for a detailed discussion of chronic pelvic pain).

Physical Threats

In this sub-section we shall briefly look at four disparate, serious risks that women face: domestic violence, genital mutilation, 'honour killings' and so-called 'dowry fires' (estimated at around 100,000 per year in India, for example) (BBC 2014b). These are highly relevant to our concerns because they or their risk may, one way or another, deeply affect a woman's perception of risk, and her health, safety and engagement with healthcare.

Women are overwhelmingly the victims of domestic violence in all its forms (though it is not an exclusively female problem as is sometimes assumed). According to the Domestic Violence Statistics website:

- Every 9 seconds in the US a woman is assaulted or beaten.
- Around the world, at least one in every three women has been beaten, coerced into sex or otherwise abused during her lifetime. Most often, the abuser is a member of her own family.
- Domestic violence is the leading cause of injury to women—more than car accidents, muggings, and rapes combined. (Domestic Violence Statistics 2014)

In the work by Hill et al we saw how limited was the extent of voluntary disclosure of risky behaviour by teenagers to health providers. With regard to the victimisation of women, the extent of disclosure also appears to fall dramatically short of actual incidents. A global study of gender-based violence (GBV) reports as follows:

> Surveys from 24 countries, which revealed 93,656 women as survivors of GBV. They found that only 7 percent of women globally who are survivors of physical or sexual violence report GBV to formal sources, including legal, medical, or social support services. Additionally, disclosure of GBV to family, friends, or neighbors of the victims was low (37 percent). In 20 of the 24 countries studied, the majority of women told no one at all. (Medical 2013)

It suggests that the rates of underreporting are staggeringly high:

> ..estimates of gender-based violence (GBV) prevalence based on health systems data or on police reports may underestimate the actual total prevalence by 11- to 128-fold.

This is alarming enough, but it seems that even when presented with victims of domestic violence, health professionals may not always recognise it:

> While recent research has found that 40 % of patients in North American orthopedic trauma clinics reported having experienced intimate partner violence at some point, a survey has found 74 % of orthopedic surgeons substantially underestimate its prevalence among their patients [estimated at a rate of 5 %]. Additionally, only 23 % had training to recognize such injuries.

The recent research referred to (Della Rocca 2013) was published by The Lancet in 2013 and concluded:

> Orthopaedic surgeons should be confident in the assumption that one in six women have a history of physical abuse, and that one in 50 injured women will present to the clinic as a direct result of IPV [intimate personal violence]. Our findings warrant serious consideration for fracture clinics to improve identification of, respond to, and provide referral services for, victims of IPV.

A study in Australia found that:

> There is an overwhelming link between gender violence and key indicators of women's mental health, wellbeing and risk of suicide attempts. . . (Wales 2011)

If, as we now know, something between 15 % and 61 % of women in countries across the world are victims of violence of one sort or another, we are talking about truly enormous numbers. Of the patients who present themselves directly as a result of injury from violence, some of them will admit the cause, many will not; many of those seeking help for unrelated medical issues will have been abused at some time (median lifetime prevalence maybe around 30 %) and may or may not talk about it

and any possible association with their presenting condition; many may present with apparently unrelated conditions that have, in truth, an immediate, direct association or causal link with violence.

Professional awareness of these risks is critical to good healthcare. Risk communication about directly related matters or matters ostensibly distinct cannot afford to be ignorant of such realities and the profound impact they will have on every aspect of women's lives. Diagnosis, treatment, safety, adherence, may all fall short of optimal standards. Recognition in orthopedic and other clinics is an obvious example of good risk assessment, while, on the other hand, a looming threat to the safety of a fetus in pregnancy may easily be passed by (Hall et al. 2014).

Female genital mutilation, honour killings and dowry fires are radical risks for specific populations of women in developed and developing countries. Risk communication for women such as these must embrace the dramatic impact such experiences will have had on their perception of risk, their priorities in managing disease and medicines, and on their lives as a whole.

Summary

Risk communication is about the assessment and management of risk. For professionals, it is about understanding the risks that patients have faced or may face and making a full and empathetic judgement about what should be done, could be done and can be done in the light of the patient's experience, wishes and priorities. The general life-time risks that women face as well as the medical risks are complex and multifarious. Professional communications need to be proportionately insightful, knowledgeable and authoritative in their process and content.

A summary of some of the key questions raised and discussed in this chapter is presented in Box 18.4:

Box 18.4: A Summary of the Basis of Sound Risk Communication: Some Key Questions from This Chapter

1. What are this patient's levels of intelligence, literacy, numeracy and health literacy and numeracy?
2. How does this patient perceive risk and what are her attitudes to risk?
3. What are the sources and methods through which this patient prefers to receive risk information and can make sense of it?
4. How far does this patient understand probability, uncertainty, causality?
5. How far do this patient's view of such terms as *common, rare, serious, non-serious* match or diverge from the doctor's?

(continued)

Box 18.4 (continued)

6. What are the benefits this patient seeks and the harms she fears?
7. What specific mechanisms can the doctor adopt to establish a purposeful, comfortable, empathetic relationship with this patient (even in the briefest of time)?
8. Is the sex of the patient irrationally or negatively influencing the doctor's perception of the disease or the nature of the proposed treatment?
9. Are the available data and treatment guidelines reliable for application to women?
10. What are the unique personal, social, cultural characteristics of this woman that will influence her response and behaviour as a patient?
11. Are there high priority risk factors influencing this woman's life, e.g. poverty, stress, male oppression, striving for ideal beauty?
12. Does this patient have pressing needs or preferences that the doctor needs to know about, e.g. provider sex, privacy, decision-making participation mode?
13. Does this patient approach life optimistically or fatalistically; does she have a predominantly rational, scientific approach or a largely superstitious one?
14. Are there hidden risks in this patient's life (e.g. drug-taking, suicidal thoughts, depression, unprotected sex) that need to be accounted for?
15. What is this patient's attitude to pain and her levels of tolerance?
16. Has this patient suffered from violence or abuse or is she likely to do so?

Reality check: with a few minutes for each patient, no doctor can possibly work through a checklist of questions like this alongside the demanding process of making a good diagnosis and negotiating the best treatment. Just as a good diagnostician will often be able to come to rapid conclusions on complex questions, based on accumulated reading, wisdom, and experience, so a good communicator has these questions (and others too) integrated into the functioning of her perception, her behaviour and the questions she asks. Through training, practice, repetition, she instinctively and automatically feels, perceives or actively seeks evidence about the critical issues in her patient's life. This is not so much about length of time available, but about the intensity and quality of perception and interaction during whatever time is available.

Conclusions

This chapter has presented and discussed some of the basic concepts and tools of risk communication and suggested many of the best practice options.

It has also reviewed some of the multiple risks, issues and concerns that form the context in which healthcare is delivered to women and in which risk communication with women must take place. We have seen that reliable generalisations about women's priorities and preferences cannot be made, but that we can show very

clearly the areas in which their priorities and their preferences must be identified. For example, we must know about preferences with regard to provider sex and mode of decision making; we must know about perceptions of screening tests and the forms of medications; we must know who patients trust and how they want information delivered. We must know that some patients will withhold critical information about doubts, anxieties, assaults or risky behaviour. We must know about the social, cultural and idiosyncratic pressures and influences in each patient's life. And so the list goes on. For effective risk communication in healthcare, no less than for all communication between patients and their providers, we must anticipate the infinite variety of the people we care for and ensure that we make genuine, accurate, empathetic contact with every single individual.

Take Home Messages

- Women are different from men on a range of important dimensions, both hidden and apparent
- Women are (often) disadvantaged in a number of significant ways in life and in healthcare
- Empathy is the primary quality in all effective communication, risk communication included
- Risk and benefit are perceived and experienced very differently by different people
- Risk communication should always be based on absolute figures and natural frequencies
- Women have very specific preferences with regard to the extent and quality of their involvement in risk decisions and the amount of risk information they want
- Risk must be communicated to people in clear, simple ways that they can genuinely understand and use in their decision-making
- Subjective understanding of risk and benefit, including causality, trade-offs and quality of life issues, are critical to making good decisions, especially about medicines
- There are many conditions that are unique to women and women experience all other conditions in ways that are unique to their sex
- Women's experience of disease takes place within a complex social, cultural, political context and is influenced by the interaction of the multiple variables of their unique individuality with that context
- Some women will be preoccupied with the risks, pressures or dangers of their lives that will provide significant obstacles to risk communication about medicines
- Risk communication about medicines cannot reach or benefit women if it does not take account of the risks in their lives, their perception of risk and their individual assessment of the relative weight of benefits and harms

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Chapter 19
Risk Communication and Specific Medicines for Women

Bruce Hugman

Introduction

In this chapter we review the detailed issues, questions and skills in risk communication relevant to medicines for all patients and then focus on challenges of communication with regard to a small selection of medicines for women: anticonvulsant drugs in pregnancy, oral contraceptives, HPV vaccination and Hormone Replacement Therapy (HRT).

The Basics of Risk Communication

Chapter 18 opened with the statement: The purpose of risk communication in clinical practice is to inform and protect; to support wise, balanced and rational decisions that match patients' wishes and needs. At its heart is *risk assessment* from the best evidence available and *risk management* with the purpose of anticipating known or potential risks and taking measures to reduce or avoid them. In everyday life, we know that the risk of domestic fires is high; we manage those risks with smoke-detectors, sprinklers, fire-extinguishers, evacuation plans, escape routes and training and rehearsal. The principles of these activities and the communications associated with them apply to all aspects of life, from oil-rigs to natural disasters, from driving to rock-climbing (Hugman 2013a).

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In clinical practice, once a diagnosis has been agreed, the process of risk assessment and risk management begins as the options are discussed:

- What are the risks of the condition?
- What are the risks of no treatment?
- What options for treatment are available?
- What are the benefits and risks of the options available?
- What measures can be taken to avoid or reduce the risks?

Once a treatment has been proposed, its benefits and risks require further discussion before a final choice is agreed. Then further information is necessary about the specific therapy and managing its risks.

MedicineNet.com is an excellent source of intermediate advice for patients and the public, providing up-to-date, simple, well-structured information based on FDA guidance and package inserts. It is one resource among many for patients who want to research the options for themselves, but also provides a fine template for doctors to base their risk communication on.

Once a diagnosis has been made and agreed, all patients should have, and many will actively want to have, the following information about their treatment options:

- What is the drug used for?
- How should the drug be taken?
- What should you do if you miss a dose?
- What are the drug's side effects?
- What substances interact with the drug?
- What should you expect the drug to do?
- How should the drug be stored?
- Should you use a generic version of the drug?
- What laboratory tests or other observations should be done to monitor the effects of the drug? (Ogbru 2009)

This begins the active process of risk assessment (what are the risks?) and risk management (what action can be taken to reduce risks to the absolute minimum?) This is a stage at which physicians and pharmacists must remember that matters that are familiar and routine to them may not be understood by patients at all. Every element of communication needs to be checked, at least by using 'teach back,' that is by asking patients to repeat what they believe they've been told ('Can you just tell me how you're going to take this medicine?' 'What will you do if you have any symptoms of side effects?') Asking, 'Do you understand?' is risky, because many people, not wishing to appear foolish or inattentive, will answer, 'Yes' whether they understand or not. Those who are illiterate or semi-literate often have very sophisticated strategies for disguising their problems and may understand much less than they appear to.

To make the risk communication aspects of these question clear, here's an expanded and annotated version of the basic list from MedicineNet:

- **What underlies the disease or condition?**
  - While many conditions will be attributable to specific causes (infection, accident, for example), many others will have their roots in other risk factors and broader causes such as lifestyle issues (diet, exercise, smoking, and so on), working conditions, psychological state of mind, the demands, pressures and risks of women's lives, and many more. General health, prevention and healing may all be dependent on factors well beyond the presenting problem (injury from intimate partner violence or child abuse being amongst the most blatant), many of them discussed in the previous chapter. Diagnosis and risk communication need a very wide angle of view to embrace consideration of these broad issues and risks
- **What is the drug used for?**
  - Many patients leave their consultation without a clear grasp of their condition and its causes and what their medicine is for; one risk here is that they will simply treat the symptoms without understanding how they came about and what might be done to reduce the chances of recurrence. (Some studies suggest that, unknown to their prescribers, up to one third of patients may not fulfill their prescriptions at all (LaMendola 2012), implying strongly that communication with some patients has failed in all its purposes.) A simple example is common and troublesome vaginal candidiasis. Knowledge of the nature of the organism, possible reasons for its emergence as a problem, and what promotes or inhibits its growth is essential, alongside the rationale for topical treatment of symptoms and/or oral or topical anti-fungal treatment of the yeast itself.
- **How does the drug work?**
  - Not all patients will need or want such an explanation, but there are times when some understanding is essential. The most obvious example is that of antibiotics where the risks of inappropriate or incomplete use are considerable for individuals and populations who don't understand how they work. Women need to have some grasp of how OCs and other forms of contraception work in their bodies if they are to have optimum control of their fertility and avoid such risks as there are. Taking pills or using devices whose functions are not understood leads to risks of imperfect or non-compliant use.
- **How should the drug be taken?**
  - This not as simple as it sounds:

    'Three times a day after meals' may be unhelpful for people who do not have three meals a day, or for whom 'meal' means significant eating like an evening meal, or whose eating patterns are irregular or, for shift-workers, take place during the night (where pictograms are used, a rising sun usually marks the first dose of the day)

'After food' may not be helpful if the minimum amount of food is not specified (an apple, a snack, a glass of milk, a full meal?) and the reason for ensuring protective stomach contents is not explained

- Patients may not understand the rationale for the spacing of doses, that is, commonly, to ensure a reasonably constant level of the drug or drug-effect in the body. If that is explained, then some of the risks of ignorance and potential non-adherence are reduced. Cost-related non-adherence is a risk, especially for elderly or depressed patients (Briesacher et al. 2007)
- Whether tablets are to be chewed, swallowed whole or dissolved sub-lingually, how to use a nebuliser effectively are among issues that need careful attention; demonstration of devices is usually essential
- Information about route needs to be explicit and clear, especially with maybe unfamiliar forms such as pessaries where a degree of embarrassment may interfere with clear communication (patients have been known to swallow pessaries; mothers have put liquid oral antibiotics into their children's infected ears (Boodman 2011))
- There can be serious problems with regard to dosage forms: some patients have difficulty with large tablets; tablet-splitting can be troublesome and may result in inaccurate dosing. Common expressions such as 'teaspoonful' are liable to variable interpretation and are dangerous. Liquid medicines always need to be accompanied by a model spoon or a calibrated cup or syringe.

- **What should you do if you miss a dose?**
  - Very few patients are perfectly adherent and they need specific guidance as to what they should do when doses are missed. Adherence, especially in chronic diseases and with multiple medications, is a major issue (see below). Pill-boxes, electronic reminders, medication calendars, dated blister-packs, and other methods are important ways of reducing the risk of forgetfulness or confusion.
  - Very few doctors or pharmacists have any idea what happens to most patients once they have left the clinic or the shop, particularly with regard to adherence (see prescription fulfillment above). Best practice suggests some way of maintaining contact with patients through methods such as return visits, phone calls or electronic reminders and for providing opportunities for self-reporting (Royal College of General Practitioners 2009). (The evidence about patient adherence is shocking, especially in chronic conditions (WHO 2003; Brown and Bussell 2011); the wastage enormous, the risk to health substantial.)

- **What are the drug's side effects?**
  - Perhaps the single most challenging aspect of risk management and risk communication. This is discussed extensively in the previous chapter and in

relation to specific medicines below. Here we note only that information about known risks and their level of certainty will be crucial to a patient's decisions about therapy and that clear communication of these issues is one of the most difficult tasks for a doctor or pharmacist. Benefit-risk trade-offs for a patient will not always match those preferred by a professional. Early recognition of side effects and knowledge of what action to take is a further critical component of the communications process. Regulatory information about side effects in package inserts is often impenetrable and obscure and can never be a substitute for active professional interpretation and communication.

- **What substances interact with the drug?**
  - It's important that the discussion should cover all substances including food, alcohol, herbal and traditional remedies, supplements, oral and topical – as well as other prescribed and OTC medicines. For women, it's important to know that interactions with oral contraceptive (OC) medicines may reduce the efficacy of OCs and OCs may also affect the effectiveness of other medicine (see Chap. 5).
- **What behaviour is contraindicated?**
  - The starkest example here is the risk of fetal abnormality from teratogenic drugs such as isotretinoin and valproic acid. The management of this risk is extremely demanding, and none of even the most persistent warnings or elaborate protocols has succeeded in preventing some pregnancies and the delivery of some damaged babies (see also section "Anti-convulsants in Pregnancy" later in this chapter). The requirement for two reliable methods of contraception used concurrently is, for some patients, difficult to meet practically and psychologically and women do underestimate the risk of unintended pregnancy (see below, p. 600.) Some drugs may make driving or the operation of machinery hazardous; we must know if such issues are relevant for a patient.
- **What should you expect the drug to do?**
  - This sector of information relates to symptom relief, disease eradication and time scales. Patients need to have accurate and realistic expectations so that they are not disappointed or prematurely relieved, and do not abandon the medicine as soon as symptoms disappear. They need to recognise whether or not the drug has been effective and what to do if it has failed in some way. They need to know the degree of uncertainly in relation to effectiveness.
- **How should the drug be stored?**
  - Instructions on package inserts and patient information are not always explicit or comprehensive enough to cover the circumstances of all patients. How can you hope to store a medicine 'between 15 °C and 30 °C' and in a 'dry place' if

you live in the tropics? Can you store medicines in a refrigerator? What is the impact on medicines of temperatures above 30 °C in humid conditions? If there's no effect, then the storage instructions are irrelevant; if there is an effect, what is that doing for the health of millions whose pills are stored in hot places (including pharmacies without air-conditioning)? Thousands of children are poisoned by ingesting carelessly-stored pharmaceuticals intended for others (CDC 2012); specific warnings about this risk and (where available) the provision of child-proof containers are important risk management measures.

- **Should you use a generic version of the drug?**
  - In countries where regulation is adequate there is usually no problem with substitution. It's a different matter in countries where regulation and enforcement are lax and counterfeit or sub-standard drugs may be common. Patients need to understand the risks and make wise choices in the balance between cost and quality. Patients also need to know that the safety-profile of generics may not be identical to branded drugs, in relation, for example, to excipients.
- **What laboratory tests should be done to monitor the effects of the drug?**
  - This is essentially a clinical rather than a communications issue, but the necessity for tests and the meaning of results are challenges for communication, especially in the controversial field of screening. Thresholds for concern, in for example blood pressure and lipid levels, are matters of some debate as are the treatment choices based on them. When an option is the starting of life-time drug therapy in currently healthy people, patients need to have a very clear grasp of the true benefits and risks, the degree of uncertainty, and their personal view of them, which may be quite different from the prevailing marketing messages and general assumptions (statins are a good example, see Chap. 18, p. 540). There is evidence that doctors don't communicate bad test results to about 7 % of patients (Casalino et al. 2009), so patients need to be alert and active in seeking full information. Language is again important: patients may misunderstand a term such as 'positive,' for example, believing it means a good result.

In all aspects of risk communication, the language used must be tailored exactly to the literacy and abilities of the patient; technical forms should be avoided ('painkillers,' not 'analgesics,' for many patients, 'food,' not 'diet,' for example). Information needs to be prioritised with regard to the needs of the individual and critical aspects always repeated and checked through asking the patient what they have heard and understood. A fine example of good communication is provided in (Fig. 19.1). (For a comprehensive review of all the communications challenges in healthcare, see Healthcare Communication (Hugman 2013b)).

Name: Thomas

Information on your prescription for:

Amoxicillin
250MG/5ML

To treat an infection of the throat

7.5 mL (1½ teaspoons) by mouth 3 times a day for 14 days

Nombre: Thomas

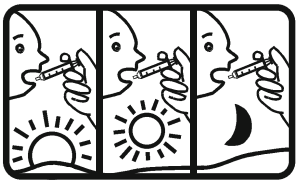
Información sobre su receta para:

Amoxicillin
250MG/5ML

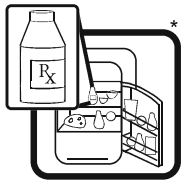
Para tratar una infección de la garganta

7.5 mL (1½ cucharaditas) por la boca 3 veces al día por 14 días

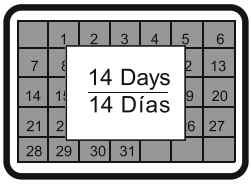
Shake well
Agite bien



Take **3 times a day** by mouth
Tome **3 veces al día** por la boca



Store in refrigerator
Guarde en la nevera



Give this medicine for 14 days,
even if your child is feeling better
Dé esta medicina por 14 días,
aunque su niño se sienta mejor

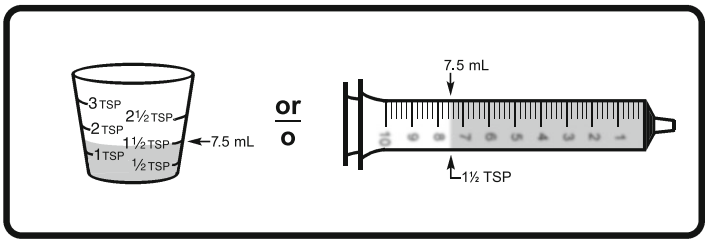
If you have questions call
(212) 562-5524 day or night
Si tiene preguntas llame
(212) 562-5524 día o noche

Read the instructions that come with your medicine. Lea las instrucciones que vienen con la medicina.

The H.E.L.P. Project Bellevue Hospital Pediatric Clinic (212) 562-5524

Fig. 19.1 (continued)

Keeping track of Thomas's Amoxicillin	Anotando las dosis de Thomas de Amoxicillin
7.5 mL (1½ teaspoons) by mouth 3 times a day for 14 days	**7.5 mL (1½ cucharaditas) por la boca 3 veces al día por 14 días**



✻ Date of first dose May 12, 2008	Fecha de la primera dosis Mayo 12, 2008
Parents: Please check (√) the correct box each time you give your child the medicine, 42 checks (√) total.	Padres: Por favor, marquen con (√) la casilla correcta cada vez que den la medicina a su niño, total de 42 marcas (√).

DAY / DIA			
Time/Hora:			
Monday / Lunes			
Tuesday / Martes			
Wednesday / Miércoles			
Thursday / Jueves			
Friday / Viernes			
Saturday / Sábado			
Sunday / Domingo			
Monday / Lunes			
Tuesday / Martes			
Wednesday / Miércoles			
Thursday / Jueves			
Friday / Viernes			
Saturday / Sábado			
Sunday / Domingo			
Monday / Lunes			

✻ Pediatrician: Please circle the starting dose and ending dose.

The H.E.L.P. Project Bellevue Hospital Pediatric Clinic (212) 562-5524

Fig. 19.1 This is an elegant, simple, perfectly tailored risk management tool: it is personalised, presented in English and the primary local minority language; it uses words and pictures; dosage quantity is visualised; there is a daily tick-off calendar and an enquiry line. Following a verbal explanation, the sheets require almost no interpretation through literacy skills, though they would be helpful to patients, literate or not. This is a very good example of communication at its best, reinforcing verbal explanation and translating complex verbal and technical information into easily accessible, self-evident images and activities

Specific Medicines for Women

In the previous chapter, I outlined a range of important variables that profoundly influence a woman's psychology, life-chances, health and safety. All aspects of the risk communication elements reviewed above are subject to those influences, crucially the extent to which a woman feels that her uniqueness and the specific particulars of her life are recognised, factored into the discussion and valued in each moment of the relationship and its communications.

If you now bring to mind all the risk and risk communication issues that we have covered so far, we can begin to apply them to particular medicines for women.

The writer of the material in this chapter is a communications expert with no professional medical background. While every effort has been made to ensure the currency of clinical evidence referred to, it is not offered here as direct guidance for practice but for illustrative purposes only. There is no attempt to provide reliable, comprehensive, up-to-date risk information about the medicines discussed. The focus here is on the knowledge, skills and processes relating to risk communication for women, illustrated by four high priority practice challenges and the medicines associated with them.

Anti-convulsants in Pregnancy

The term 'epilepsy' refers to a group of disorders and is commonly a symptom rather than a distinctive disease. It is one of the least understood of major syndromes (Global Campaign 2012). It varies considerably in incidence across the world, being highest in sub-Saharan Africa and Latin America (BMJ 2013). The risks of epilepsy in pregnancy, and of the medications used to treat it, to both fetus and mother are significant and pose a considerable challenge for benefit-risk communication and patient choice. (Anti-convulsant medicines in pregnancy are reviewed in more detail in Chap. 4.)

Failure to recognise and communicate the risk of anti-convulsant medication may have tragic consequences. On the UK website Epilepsy Action, a mother recounts the effects of lack of risk information when she became pregnant (EpilepsyAction 2014):

> No one was overly concerned that I was taking sodium valproate.

The outcome was serious for child and parents:

> At 10 days over [the] due date I was induced, and [he] was born 31 hours later. At birth he did not breathe straight away, was floppy, and needed help to start his life. . .For the next six months we felt that everything was fine. However, the doubts began to start and we knew that [he] was not developing as he should. . . After reading a news article about anti-epileptic drugs and pregnancy, things started to click into place. I saw my GP and told him of my fears. . .We were referred to a genetics consultant who diagnosed (when [he] was just 16 months old) fetal anti-convulsant syndrome (FACS). . .[he] has three types of epilepsy, medical problems and complex learning difficulties.

So what risk information do women with epilepsy need to have, and how should it be delivered, if they are thinking of becoming pregnant or if, too late for some information, they find themselves pregnant already?

They need to know, for example, that women being treated for epilepsy have a higher risk of pregnancy complications, fetal malformations with certain medicines and maternal death than the general population, though the absolute risks are very small (Tomson and Hiilesmaa 2007). They need to know this in order that they can first decide if they wish to take the risks of pregnancy and treatment at all; second, recognise side effects and signs of complications, the risks of non-adherence and the necessity for frequent monitoring of blood-serum levels. In prospect and as they occur, each of these aspects will have their own set of risk communications and benefit-risk assessments. The possible complications, according to the Mayo Clinic in its web-based information for patients, include (Mayo Clinic 2011):

- Severe morning sickness
- Anemia
- Vaginal bleeding during and after pregnancy
- Premature separation of the placenta from the uterus (placental abruption)
- High blood pressure and excess protein in the urine after 20 weeks of pregnancy (preeclampsia), with a higher risk if they are high-risk HPV exposed
- Premature birth
- A low birth weight baby
- Failure to progress during labor and delivery
- Babies with congenital abnomalies

This does not conform with best communication practice because no figures are given for the risks of these complications.

Borthen et al. investigated some of these risks in a large cohort study and do provide some figures (Borthen et al. 2009):

> RESULTS: We compared 2805 pregnancies in women with a current or past history of epilepsy (0.8 %) and 362 302 pregnancies in women without a history of epilepsy. Women with epilepsy had an increased risk of mild pre-eclampsia, [odds ratio 1.3: 95 % confidence interval (1.1-1.5)] and delivery before week 34 [1.2: (1.0-1.5)]. Antiepileptic drugs were used in 33.6 % (n=942) of the pregnant women with epilepsy. Compared to women without epilepsy, women with epilepsy and AED [anti-epileptic drug] use had an increased risk of mild pre-eclampsia [1.8: (1.3-2.4)], gestational hypertension [1.5: (1.0-2.2)], vaginal bleeding late in pregnancy [1.9: (1.1-3.2)], and delivery before 34 weeks of gestation [1.5: (1.1-2.0)]. No significant increase in the risk of these complications was observed in women with epilepsy not using AED. These results remained unchanged after exclusion of multiple pregnancies.
>
> CONCLUSION: Women with epilepsy have a low complication rate, but special attention should be paid to those using AED during pregnancy.

But what do the statistics mean? When we tell a patient that these risks are low, she may ask, "how low?" We need to be able to tell her in absolute terms (see Chap. 18 for more on this challenge).

Here is some of the current advice that a woman searching for information would find through the internet. The extent to which a patient can rely on such information is always open to question (see Box 19.2 on websites) and physicians clearly need to have the latest evidence at their finger-tips.

- All authorities agree that seizures pose a greater risk to mother and baby than well-managed medication
- A year or so before planning to become pregnant, anticonvulsant medication needs to be reviewed and changed if it would pose a high risk to a fetus (this would be the case with sodium valproate due to the risks of NTDs etc (see Chap. 4), for example)
- A regimen of daily folic acid is recommended (though the evidence for the benefits of this is not strong, see below) (American Academy of Neurology 2009)
- Women with epilepsy taking anti-seizure medication may wish to know that their risk of having a child with birth defects is around twice that of non-epileptic mothers (4–8 % compared with 2–3 %; or, to change the framing to its opposite: more than 90 % of women with epilepsy deliver normal, healthy babies). It appears that the risk is increased with particular drugs or when more than one anticonvulsant is used, particularly at high doses (WebMD 2014)
- Topamax (topiramate) taken during the first trimester doubles or trebles the rate of the risk of a child having a cleft palate and cleft lip compared with other anticonvulsants, to about 1.6 % (FDA 2011)
- Women should be prepared to discuss the possibility of the dose of their anticonvulsant being increased because of faster metabolism of anticonvulsants during pregnancy and as their blood volume increases throughout the pregnancy. Use of a drug such as Lamictal (lamotrigine), however, to protect against the possibility of breakthrough seizures, especially in the first trimester, poses a possible risk to the fetus (Drugs.com 2014b).

There are estimated to be ten million people with epilepsy in Africa (WHO 2004), maybe four fifths of whom receive no treatment at all. The disease is also associated with considerable social stigmatisation in many places, making access to care, or even help during seizures, problematic for large numbers of women.

The causes of epilepsy in Africa may differ from other parts of the world:

> In all developing countries, and particularly in the African region, a very large number of new onset seizures are a consequence of poor perinatal management, the high impact of infectious diseases, and head trauma. (Ngugi et al. 2013)

So there are these and many other additional risks to any otherwise healthy baby, delivered by a woman with epilepsy or not, besides the possibility of defects induced by anticonvulsant medications. The primary risk management action for women here, across the board, is to find expert pre-pregnancy care and a committed healthcare partnership throughout pregnancy, out of the question though it may currently be for millions of women.

Information for Women with Epilepsy

The Epilepsy Foundation/Epilepsy Therapy Group have a good website that, amongst much else, provides written risk information that is admirable in its clarity

and simplicity (Epilepsy Foundation 2011). Here I will quote two or three of the sections answering common questions and experiences as models for good practice.

This first illustrates the dilemma of a patient with a doctor who has not heard about respect for patients or the ethical imperative of joint decision-making and consent.

> My doctor told me that because I need to take antiepileptic medication, I should never get pregnant. Now that I am pregnant he recommends an abortion, but I want my baby. Am I wrong to think that my baby will be okay?

It's instructive that the doctor's paternalistic and unhelpful advice was ignored, though that fact doesn't seem to have taught him anything. Here we see, as discussed elsewhere, that healthcare providers are themselves, sometimes, among the risks that patients face.

Elsewhere from the Epilepsy Foundation:

> For women who have epilepsy, the risk of having a baby with a birth defect is double the risk for women in the general population. Any woman, whether she has epilepsy or not, has a two to three percent chance of having a baby with a birth defect. For women with epilepsy, the risk is four to eight percent. Even so, mothers with seizures have a better than 90 percent chance of having a normal, healthy baby.
>
> The actual cause of the increased risk of malformations has not been determined, but there are three strong possibilities:
>
> 1. The birth defects are genetically related to whatever causes the epilepsy.
> 2. The birth defects are related to antiepileptic medications needed to control seizures.
> 3. The birth defects occur because the baby may have a genetic susceptibility to possible harmful effects of medications.
>
> Whatever the cause of the malformations, they do not occur often enough to support avoiding or terminating a pregnancy. However, if an eight percent risk of having a child with a malformation is unacceptable to you, it is important that you make the decision that's best for you.
>
> Stillbirths or miscarriages are also more common for women who have epilepsy, occurring in 1.7 percent of pregnancies, which is about three times the amount in the general population.
>
> There is also a small increase in mortality rates during the first year of life for children of mothers with epilepsy. That risk is only about 0.6 percent, but is higher if the mother's seizures are not well controlled.

This is excellent risk communication. What do we notice?

- Relative and absolute risks are characterised in words and figures
- The framing is balanced (reference to both the scale of harm and the scale of not-harm)
- The uncertainty about causation is explained
- A judgement about the level of risk is offered, but quickly qualified by recognition that the patient may have her own views and feelings about it that should determine her decision
- Two other serious risks are mentioned, along with absolute figures (which could also be expressed, for example, as less than 2 women in 100 (1.7 %) or less than 1 in a 100 (0.6 % – but see comments on less than 1 whole person, Chap. 18), or

as less than 17 in a 1,000 and less than 6 in a 1,000, respectively. Does one or other of these make the risk seem less or greater? For some, the larger denominator may have that effect.)

Use of Contraceptive Medicines in Women with Epilepsy

We deal with oral contraceptives at greater length below, but here are the risk issues specific to women with epilepsy, again from the Epilepsy Foundation website.

How do I know which method is best for me?

You need to work with your gynecologist and your neurologist to choose the birth control method that is most appropriate for you. It is possible that your antiepileptic drug (AED) may make your hormonal birth control less reliable, resulting in an unwanted pregnancy. You and your physicians may consider different combinations of hormonal birth control and seizure medications to find the one that works best for you.

And details of the very specific issues that relate to particular pills and their risks:

How will my seizure medication affect my hormonal birth control?

There are complex interactions between the hormones (estrogen and progesterone) contained in birth control pills or devices, and some of the medications used to control seizures. Some of these medications increase the breakdown of contraceptive hormones in the body, making them less effective in preventing pregnancy. The seizure medications that have this effect are often called "liver enzyme-inducing" drugs because the liver is the organ that breaks down these hormones. They are carbamazepine (Tegretol, Carbatrol), oxcarbazepine (Trileptal), phenytoin (Dilantin), phenobarbital (Luminal), primidone (Mysoline), and topiramate (Topamax). Valproate (Depakote) and felbamate (Felbatol) do not increase breakdown of hormones, and may even increase hormonal levels, which may require an adjustment in the dose of your birth control. Gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), and tiagabine (Gabitril) have no effect on this system and do not interfere with the effectiveness of hormonal birth control.

This represents more detailed information than most women might wish, but the risks of hormonal pills or devices and the rationale for a particular suggestion or choice, contained in this text, are topics that will interest many women and help them make a final choice with confidence.

Finally, in this short selection of extracts from the Epilepsy Foundation website, here is an explanation of the risk of pregnancy while on the pill and anti-epileptic drugs:

Are there special concerns about "the pill" for women with epilepsy?

Yes, there are. The popular low-dose combined oral contraceptive pill has a relatively small amount of estrogen (less than 35 micrograms). That's not enough to protect women with epilepsy who take enzyme-inducing AEDs from becoming pregnant. You may need contraceptive pills with higher doses of estrogen, and even then, there is a risk of unexpected pregnancy. It is a good idea to use barrier methods (a diaphragm, spermicidal cream or a condom) in addition to the contraceptive pill, if you are taking one of the seizure medications that speed up the breakdown of the hormones in birth control pills.

The risk of unexpected/unintended pregnancy is not given a figure here, so that cannot be easily assessed by a woman faced with the possibility of using an additional barrier method; for some, any risk at all may be unacceptable; for others, trading a small risk for the simplicity of pill-only contraception may be preferable. The risks of unintended pregnancy are actually much higher than one might expect: around 50 % in the US, with higher than average incidence, '. . .among poor and low-income women, women aged 18–24, cohabiting women and minority women.' (Guttmacher Institute 2013). Risk communication in relation to this must negotiate the tricky diplomatic waters evident from the fact that some women may be less in control of their fertility than they naturally assume.

All websites I have reviewed state or assume the importance for women to be working in partnership with expert physicians or family planning advisers. However, the Epilepsy Foundation points out:

> Many physicians are not aware of this statistic [that more than 90 percent of pregnancies in women with epilepsy have a good outcome], nor are they up to date on the best medication choices for women with epilepsy considering pregnancy or already pregnant. (Epilepsy Foundation 2014)

Being reminded that they may not be entirely up-to-date in their knowledge is a challenge to the self-image of professionals, especially if the reminder comes from a patient. Active, well informed patients do reduce the risk of harm from less than optimal treatment, but there is never any substitute for professionals to know, or have quick access to, the latest data and evidence. A degree of humility in the face of complexity – and of patients – is a useful quality for doctors.

The American Academy of Neurology publishes a useful fact sheet on epilepsy, a summary of a much longer report. It has a similar question/answer section as the Epilepsy Foundation (above), but also a very good page on the evidence for the treatment of women with epilepsy (WWE). A selection of a couple of issues to illustrate the powerful value of such summaries for the planning of risk communication appears in Box 19.1 (American Academy of Neurology 2009). Note also the classification of the strength of evidence, an issue I have not discussed elsewhere but is vital to the enterprise of risk communication.

Box 19.1
Does preconceptional folic acid supplementation reduce the risk of birth defects in neonates of WWE taking AEDs?

Weak evidence Preconceptional folic acid supplementation in WWE may be considered to reduce the risk of major congenital malformations (MCMs) (**Level C**).

Clinical context Folic acid supplementation is generally recommended to reduce the risk of MCMs during pregnancy, and although the data are insufficient to show that it is effective in WWE, there is no evidence of harm and no reason to suspect that it would not be effective in this group. Therefore, all women of childbearing potential, with or without epilepsy,

(continued)

Box 19.1 (continued)

should be encouraged to take at least 0.4 mg of folic acid daily prior to conception and during pregnancy. There was insufficient published information to address the dosing of folic acid.

What is the risk of hemorrhagic disease in neonates born to WWE taking AEDs?

Insufficient evidence Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is insufficient evidence to support or refute an increased risk of hemorrhagic complications in the newborns of WWE taking AEDs (**Level U**).

They classify the strength of evidence according to this hierarchy:

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (American Academy of Neurology 2009)

The Dilemma for Women with Epilepsy

Epilepsy presents some of the most agonising of risk decisions, with the welfare of both mother and baby at stake. If we add the further anxieties and risks around pregnancy itself, we have a situation where a woman may feel distressingly confused or oppressed by the choices she faces. Only genuinely empathetic, patient, measured counseling can hope to provide a degree of clarity and open the door to voluntary, informed choice. If, as we saw in the anecdote above, the doctor's behaviour is patronising or prejudiced, or simply out of touch with a woman's feelings, advice will simply be ignored and a patient will be left angry and disillusioned – and she and her baby will be at greater risk.

While internet forums and patient communities are not all to be trusted (some are sponsored by or infiltrated by commercial, ideological and other interests), there are rich and reliable resources available to inform and support women with many different conditions. Doctors need the humility to refer patients to reliable

additional, alternative, resources that may provide a much broader spectrum of options and experiences than any professional can draw on. In the previous chapter we saw elsewhere how much some women favour and rely on the wisdom of their mothers and their female peers (in Tibet, Africa and elsewhere); interaction with such a virtual community of peers may lead to much more confident and positive risk perception and to choices that are more deeply acceptable, and to regrets that are fewer even when there's an unfavourable outcome.

On the other hand, informal social or anecdotal information, women's magazines, out-of-date websites or websites with an axe to grind, may be serious threats to authoritative understanding; patients' interpretative and authentication abilities vary enormously (Peterson et al. 2003).

Oral Contraception

The advent of the contraceptive pill in the 1960s was widely hailed, accurately, as ushering in a revolution for women: for the first time in history, they had simple, direct, permanent, largely reliable control over their fertility, without depending on much planning ahead, on more troublesome devices, on the whims and behaviour of men, or on other, less effective methods.

Nevertheless, all methods of contraception bring some risks (detailed in Chap. 5), not least of conception, resulting from non-adherence or imperfect or inconsistent use. A woman taking OCs runs the very small chance of becoming pregnant (less than 1 in 100 in study populations, though still slightly more than some other methods) (Trussell 2011). Oral contraception (OC) is the third most common method used by women, aged 15–49, who are married or in unions, with a worldwide prevalence of 9 %, after female sterilisation (19 %) and IUDs (14 %) (United Nations 2011). The UN reports unmet needs for contraception in more than 140 million women worldwide, the great majority of whom live in developing regions.

In spite of declining rates everywhere, Singh et al. estimated the number of unintended pregnancies worldwide and found that about 41 % of 208 million pregnancies in 2008 fell into that category (Singh et al. 2010).

The Guttmacher Institute's research (Guttmacher 2013) shows that in 2008, in the US, about half of all pregnancies (51 %; 3.4 m/6.6 m) were unintended (that is mistimed or unwanted), an increase of about 3 % on 2001, and, as noted above: "unintended pregnancy rates are highest among poor and low-income women, women aged 18–24, cohabiting women and minority women".

This finding reinforces the critical issues argued in Chap. 18: the risks a woman faces and her needs for risk communication are profoundly influenced by the characteristics of her life, her socio-economic status, her age and a multitude of other factors. 'Medicines for women' becomes a viable and safe concept in practice only when it is reformulated as 'a medicine for this unique woman.'

Unintended pregnancy is the principal reason for abortion, and though abortion rates declined overall in the US between 2001 and 2008, for poor women it increased 17.5 % from 44.4 per 1,000 births to 52 (Jones and Jerman 2014):

How can this apparent failure of contraception (and, therefore, of public health communication) be explained in the wealthiest nation on earth? In the Guttmacher study, nearly 11 % of women were using no contraception at all. A belief in their low risk of pregnancy, lack of forethought, distaste for contraceptive methods and male reservations were amongst their explanations. Dude gives us a further insight with her finding that 31 % of young women in the US, aged 15–24, had used withdrawal (coitus interruptus) at least once; that 7.5 % of them were likely to depend on emergency contraception and that 21 % of them had become pregnant (Dude et al. 2013). There is clearly a large space that public health education and risk communication need to fill.

The situation is very different in the developing world, where the overall prevalence of contraception is lowest and the unmet needs are greatest. In *Unintended Pregnancy and Induced Abortion in Uganda* The Guttmacher Institute reports (Guttmacher Institute 2006):

> An estimated 297,000 induced abortions are performed each year in Uganda, which translates to an annual abortion rate of 54 per 1,000 women aged 15–49. . . More than half of all abortions are believed to be carried out by medically trained providers (doctors, nurses, midwives). The remaining procedures are performed by nonprofessionals, including pharmacists, traditional providers and women themselves.

According to the UN, only about a third of Ugandan women of reproductive age use contraception of any sort and over a third of the remainder have an unmet need for contraception. In 2008–2010 there were 1.47 m births in Uganda (crude birth rate 42.1/1,000). Guttmacher reports:

> This means that 42 % of pregnancies in Uganda (the 16 % that resulted in abortions plus the 26 % that resulted in unintended births)—a minimum of 775,000 each year—can be classified as unintended. This analysis points to the fact that not all unintended pregnancies end in abortion: About 38 % [of 775,000] do, and the remainder lead to unintended births.

So, where does all this lead us in the context of risk communication? Some major issues that must influence medical practice and counseling:

- To a greater or lesser extent, depending on location, many women are not using contraception at all and many of those have unmet needs for contraception
- A major risk factor for low contraceptive use, unwanted pregnancies and abortions is poverty
- Among those not using contraception, whether or not with perceived unmet needs, there are a number of influential factors (many of which will vary according to the socio-political and religious environment in which women live):
  - Voluntary choice or forced decision, resulting from

    Perception of low risk
    Accidental or unexpected insemination

Male reservation (or refusal in many cases) about contraception in general or male contraception in particular
Pressure (usually male) in some societies to have a large family
Lack of access to contraception
Lack of resources, facilities and information
Poverty

- Some women (mainly in developing countries) are at physical risk from frequent births and from abortions, especially conducted by unlicensed practitioners
- Many women are almost certainly at risk for psychological damage or trauma as a result of the stresses of child-rearing because of unintended or unwanted births. They are also at risk of poverty and being unable to support their children financially

Good decision-making in this area for women requires an intimate knowledge of self in the patient (preferences, habits, intentions) and very good counseling and risk communication that takes into account many variables, including the risk of adverse effects, which we move onto now.

The Pill, Risks, Scares and the Media

Combined oral contraceptives (COCs) are associated with a risk of venous thromboembolism (VTE); this risk is discussed in detail in Chap. 6. Here I will focus on issues which arose from the 1990s onwards when government agencies in Europe badly handled the risk communication for health professionals and women, with a number of negative outcomes.

Making Sense of Health Statistics and Deciding What to Do

In October 1995, the UK Committee on the Safety of Medicines (CSM) issued a nationwide warning to 190,000 professional recipients about the increased risks of third generation combined hormonal contraceptives compared with older types. The advice was that:

> . . .these pills should only be used by women who were intolerant of other combined oral contraceptives and were prepared to accept an increased risk of thromboembolism. (Barnett and Breakwell 2003)

Their public announcement (which was made before the key studies had been published in peer reviewed journals) stated that the risk of venous thrombosis was ‘doubled’ for women taking these pills, containing the synthetic hormones gestodene and desogestrel. The absolute figures (an increase from 1 to 2 in 7,000 or 15 to 30 in 100,000) were not highlighted. A substantial number of health

professionals did not receive their notifications until after the story had broken in the media. The author of one of the unpublished papers that the CSM had reviewed flew from Canada to the UK to assert that his findings had been misrepresented. It was a communications mess that became a crisis.

Large numbers of women besieged their doctors or called helplines; many stopped taking their pills immediately and numbers of prescriptions dropped dramatically for a long time afterwards (de Jong-van den Berg L et al. 2003). There was evidence of an increase of 13,000 abortions in the following year, especially among young women (de Jong-van den Berg et al. 2003). It was all pretty chaotic and alarmed a lot of women.

The following year, the European medicines regulation body, The Committee for Proprietary Medicinal Products (CPMP), cast doubt on the CSM's advice for women to change to older types of OCs:

> [The CPMP] acknowledged the data indicates that the blood-clot risk of desogestrel or gestodene-containing Pills is higher than other brands but said the impact of "biases and confounders [in the studies] on the differences could not be fully evaluated. . .[and they had] failed to establish any scientific reason to change advice to women taking these Pills in the EU, or recommend a change in the drug-licensing requirements." (Health Editor 1996)

In 1999, the MHRA changed its advice:

> . . .provided women are fully informed of these very small risks and do not have medical contraindications, it should be a matter of clinical judgement and personal choice which type of oral contraceptive should be prescribed. (MHRA 1999)

When questioned about the quality of the 1995 advice, Dr Jeremy Metters, Deputy Chief Medical Officer in the UK, is reported as saying:

> We would have been criticised if we had sat on the data. Contraception is a very personal thing and women have a right to all the information that is available. (Lattimer)

Here, we see a national institution taking a precautionary stance, and, in their original advice, a probably over-cautious view of the risks, expressed through unsatisfactory risk communication practices that did not anticipate its likely effects at all.

This so-called 'U-turn' irritated a lot of people and led them to reflect on the damage they felt had been caused:

> The advice given by the CSM in 1995 that these pills should not be prescribed was unnecessary and alarmist. The pill scare that followed was a disaster that should never have happened. It caused a massive increase in the rates of unintended pregnancies and undermined general confidence in the safety of the pill. It reversed a downward trend in the number and rate of abortion. (Lattimer)

Since then, indeed since 1995, the science and risk of third generation OCs has hardly changed, with most authorities in agreement that they are equally effective as second generation pills, but carry a higher risk of VTE (probably about twofold) and that they should not be prescribed as first-line medication. Nevertheless, the potential for scares in the media does not seem to have reduced at all. After the

European Medicines Agency (EMA) completed a review of target combined hormonal contraceptives (CHCs) in 2013, the agency concluded:

> . . .that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks, and that the well-known risk of venous thromboembolism (VTE) with all CHCs is small. (EMA 2013)

These very moderate conclusions, including somewhat reduced estimates of the risks, more or less confirmed what had been known for over a decade, yet the UK tabloid, The Mail on Sunday, in a headline occupying one third of its front page, and the full width, declared:

"DEADLY RISK OF PILL USED BY 1m WOMEN"

and reported: "..doctors in the UK have been ordered to alert women to the deadly dangers" (Daily Mail Online 2014).

Even the broadsheet Times of London was alarmist in its headlining (Dixon 2014):

GPs warn 1m women of deadly blood clot risk

There is, indeed, a potentially 'deadly blood clot risk' that may kill healthy, young women. We know the risk is actually very small and that it is not one million women who are all equally and immediately at risk as the headlines imply. The newspaper headlines are not untrue, but in their unqualified starkness, they are misleading and alarmist.

Fortunately, the risk information provided by the EMA in 2013 is a fine example of how the job should be done by authorities and doctors, hardly justifying the dramatic headlines, characterising the small risks of venous thrombosis clearly and simply, and in absolute figures as detailed in Table 19.1 below:

And the textual information from the EMA is also simple and clear and provides a good model for face-to-face counseling:

> Advice for women:
>
> - If you have been taking CHCs [combined hormonal contraceptives] without any problem, there is **no reason for you to stop taking them** on the basis of this review.

Table 19.1 Absolute risks of VTE in women taking the combined pill

Women **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a CHC containing levonorgestrel, norethisterone or norgestimate	About 5–7 out of 10,000 women
Women using a CHC containing **etonogestrel** or **norelgestromin**	About 6–12 out of 10,000 women
Women using a CHC containing drospirenone, gestodene or desogestrel	About 9–12 out of 10,000 women
Women using a CHC containing chlormadinone, dienogest or nomegestrol	Not yet known

Source: EMA (2013)

But it is important that you are **aware of the risk of blood clots** associated with these medicines, even though it is very low.

- The risk of blood clots in the veins varies between CHCs, depending on the type of **progestogen** (a hormone) they contain, and ranges from 5 to 12 cases of blood clots per 10,000 women who use them for a year (see table [above]). This compares with 2 cases of blood clots in the veins each year per 10,000 women who are not using CHCs.
- You should also be aware of the factors that increase your risk of a clot and be aware of how these may change over time. **Risk factors** include, among others, being very overweight, increasing age, having a member of your family who has had a blood clot at a relatively young age (e.g. below 50), having migraine or being immobilised for a long time (e.g. because of an illness or injury). Your risk of a blood clot is higher in the first year of using a CHC.
- You should discuss with your doctor or nurse what is the **most appropriate type of contraception for you**.
- When taking CHCs, you should be **alert for the signs and symptoms of blood clots**, which may include severe pain or swelling in the legs, sudden unexplained breathlessness, rapid breathing or cough, chest pain, and weakness or numbness of the face, arm or leg. If you develop any of these signs and symptoms you should seek medical advice immediately.
- If you have any questions or concerns, speak with your doctor, pharmacist or nurse.

In this chapter, we cannot review all the risks of contraception (most are covered in other chapters in Part II of this book). Of interest is the information about relative risks of different methods. One example from a Danish study of incidents of venous thrombosis reported in the BMJ:

> Compared with non-users of the same age, women who used a skin patch had an eight times increased risk (9.7 events per 10,000 exposure years), while women who used a vaginal ring had a 6.5 times increased risk (7.8 events per 10,000 exposure years).
>
> Use of a progestogen-only subcutaneous implant carried a slightly increased risk, while use of a progestogen-only intrauterine device did not confer any risk, and may even have a protective effect, say the authors. Unlike combined pills, no reduction in risk was seen with long-term use of a patch or a vaginal ring.
>
> Based on these findings, the authors calculated that 2,000 women using a vaginal ring and 1,250 women using a skin patch should shift to a combined pill containing levonorgestrel to prevent one event of venous thrombosis in one year. (Conley 2012; Lidegaard et al. 2012)

How, then, can women make judgements about the relative risks of contraceptive methods and the risk of the method they might prefer? They should not, it seems, rely on the product information accompanying their medications; according to the Royal College of Obstetricians and Gynaecologists, in their politely restrained observation:

> Summaries of product characteristics and patient information leaflets produced by the manufacturers of contraceptives are often at odds with evidence and with national guidance and can cause confusion. (RCOG 2013)

They might, on the other hand, turn to a website like Womenshealth.gov, where they would find many common questions answered, and a table (Women'shealth.gov 2012):

Contraceptive methods and their risks of pregnancy per 100 users in 1 year

Method	Failure rate (the number of pregnancies expected per 100 women)
Sterilization surgery for women	Less than 1 pregnancy
Sterilization implant for women (Essure)	Less than 1 pregnancy
Sterilization surgery for men	Less than 1 pregnancy
Implantable rod (Implanon)	Less than 1 pregnancy Might not work as well for women who are overweight or obese.
Intrauterine device (ParaGard, Mirena)	Less than 1 pregnancy
Shot/injection (Depo-Provera)	Less than 1 pregnancy
Oral contraceptives (combination pill, or "the pill")	5 pregnancies Being overweight may increase the chance of getting pregnant while using the pill.
Oral contraceptives (continuous/extended use, or "no-period pill")	5 pregnancies Being overweight may increase the chance of getting pregnant while using the pill.
Oral contraceptives (progestin-only pill, or "mini-pill")	5 pregnancies Being overweight may increase the chance of getting pregnant while using the pill.
Skin patch (Ortho Evra)	5 pregnancies May not work as well in women weighing more than 198 pounds.
Vaginal ring (NuvaRing)	5 pregnancies
Male condom	11–16 pregnancies
Diaphragm with spermicide	15 pregnancies
Sponge with spermicide (Today Sponge)	16–32 pregnancies
Cervical cap with spermicide	17–23 pregnancies
Female condom	20 pregnancies
Natural family planning (rhythm method)	25 pregnancies
Spermicide alone	30 pregnancies It works best if used along with a barrier method, such as a condom.
Emergency contraception ("morning-after pill," "Plan B One-Step," "Next Choice")	1 pregnancy It must be used within 72 h of having unprotected sex. Should not be used as regular birth control; only in emergencies.

CDC also has an excellent page on these issues. Some of the CDC risk statistics vary from those in this table, but the primary message – that there are risks with every method – remains the same (CDC 2013)

This is the kind of simple data that provides information that many women will not know and permits informed choice, albeit in discussion with a physician. Readers need to know that I deleted the side effects column from this table, which appears on the website alongside the two columns above. This is because there were doubts about the evidence-base for some of the material (weight-gain from OCs for example) and the authority of the list was, therefore brought into

question. It required a physician to point out to me that there might be weak or inaccurate information, and it raises the unnerving question, as to how patients can judge the reliability of information they discover on their own. The answer is – they probably can't and must consult with their health professionals. Women do need accurate and quantified risk data for their contraceptive choices, and only a review of a variety of resources and discussion with their doctors will allow them to make the best decisions (see Box 19.2 on website reliability).

Box 19.2 Reflection on the Reliability of Websites
Our research for this book has confronted us with a huge range of websites, covering the entire spectrum from wacky and dangerous to professional and authoritative. Even at the positive end of the spectrum, however, it is very difficult to judge how reliable and up-to-date the information is, even when the 'updated' event is recent (some 'updating' is no more than token). The National Institutes of Health and WHO have some useful guidance for assessing websites (NIH 2011; WHO 1999). There are schemes, such as the HONCode (HONCode), run by an NGO, which offer certification of websites on a number of demanding criteria, but it is unclear how rigorous the certification process is and whether or not the approval and logo might remain on a website past its currency. The gold standard of evidence has to be in professional publications, largely inaccessible to the public, such as BMJ Clinical Evidence and Cochrane Reviews. How quickly best evidence from these sources appears on publicly-accessible sites is far from certain. Patients will come with information and opinions based on unreliable sources and doctors need to be alert to the risks and have the current knowledge to manage them. All official guidance suggests that information from the internet should be mediated through consultation with a professional. Gigerenzer in his remarkable book, Risk Savvy, proposes that free access to the Cochrane Library, to journal articles and to medical records are amongst the reforms necessary to support literate patients in their pursuit of the best possible information and decisions (Gigerenzer 2014).

Summary of Risk Communication Issues with Contraceptive Medicines

- Even nationally responsible agencies may come to premature conclusions and provide guidance that will not survive professional scrutiny or stand the test of even a quite short period of time
- Their methods of communicating risk, particularly in relation to ensuring that health professionals have information before stories break in the media, are not always timely or reliable

- The use of relative risk statistics without reference to the absolute figures has the potential to mislead, confuse and alarm
- The media have a tendency to amplify risk and to generate public reactions that are distressing and disproportionate
- Poor risk communication in the public domain can lead to very serious public and individual health consequences
- Women (and men) must be helped to understand that no contraceptive method is without risk; that although population risks may be known, each individual's risks are unique to them; that, in all things, there is a measure of uncertainty
- Product information, provided by manufacturers, may not be a reliable guide to effectiveness or risk (nor may information on the internet)
- There are reliable, up-to-date data about risks and benefits of contraceptive medicines available: women themselves, and their physicians, need to know where to find them and how to judge what is reliable.

HPV Vaccination

This is now established as an effective and safe vaccine which is significantly reducing morbidity and mortality from cervical cancer and other diseases (see Chap. 9). It's a good news story for women (Australian 2014), but it has not been universally accepted and, in some places, has been mired in controversy that has led to low-uptake. I must remark on the use of the word 'safe' in this context. To the public, 'safe' means without risk. We know that no medicine is 100 % safe for all people in all circumstances, so any claim that a vaccine or drug is 'safe' must be made with great circumspection. The professional definition of 'safe' – i.e. may cause minor ('non-serious') adverse effects and rare serious effects; has benefits that significantly outweigh harms – does not match public expectation of the concept. Any parent whose child has even a mildly unpleasant reaction to a vaccine that they have been assured is 'safe' may be disappointed, angry or lose faith in the source of the information; temporal association with a serious adverse event or a death will have even more radical impact. Over-blown claims or unqualified assertions, especially about safety and the degree of certainty about evidence, even with the best intentions, are, without exception, intolerable and unethical practice in risk communication.

In 2008 the Government of Romania – a country with the highest incidence of cervical cancer in the European Union – initiated an HPV vaccination programme for 11–12 year-old girls. Very rapidly there was a national storm of controversy with apparently overwhelming opposition to the programme among parents, doctors and the media. The project was abandoned. What underlies this kind of public hostility to vaccination in general and the HPV vaccine in particular?

Craciun and Banan interviewed mothers in Romania after the crisis and concluded:

> . . .[the] main reasons for not vaccinating their daughters perceiving the vaccine as risky, the belief that the vaccine represents an experiment that uses their daughters as guinea pigs, the belief that the vaccine embodies a conspiracy theory that aims to reduce the world's population and general mistrust in the ineffective health system. Mothers stated they would need clear, factual information about the HPV vaccine and its link to cervical cancer in order to motivate them to accept it for their daughters. (Craciun and Baban 2012)

Field-testing of Gardasil®, and subsequently all HPV vaccination, was suspended by the Indian Government in 2010 after alleged protocol violations and concerns about unexplained deaths and serious adverse events. The depth of anger and suspicion about the programme is evident in one commentator's remarks at the time:

> Unfortunately, the rest of the world does not seem to care as much for their citizens as does India. Similar concerns about HPV vaccine efficacy, benefits versus risks, questionable marketing campaigns, political 'deals', and the risk of serious adverse events, including death have been raised by at least 12 other countries around the world, with virtually no response. (Seumasach 2010)

A more recent study in Sweden investigated parental attitudes to vaccination and low take-up rates:

> Some parents say no to allowing their daughters to be vaccinated against . . . HPV. The reasons include insufficient information, the child's age and distrust of authorities. . . (Gran Dahl 2014)

The US National Coalition of Organised Women is implacably opposed to HPV vaccination. They have produced a powerful, emotive video in which pediatricians, parents and allegedly injured girls plead, often passionately and tearfully for the removal of HPV vaccines from the market (National Coalition of Organized Women 2012).

On 8 June 2005, the US FDA approved Gardasil® for the prevention of cervical cancer and other HPV-related diseases. Very quickly, and well before the controversy about adverse side effects erupted, conservative groups and politicians raised the objection that the vaccine would encourage promiscuity, on the grounds that young women would have irresponsible, unprotected sex because they were safe from (some strains) of HPV. There is now some evidence that this is not the case (Bednarczyk et al. 2012; Choices 2012), but the prejudice and the myth linger on, contributing, alongside other factors, to relatively low take-up in the US and other countries.

Managing Concerns About Vaccination Programmes

How can public health officials and physicians respond effectively to widespread and emotive issues that fly in the face of all the scientific evidence? (HPV is not the first, by the way: there was the pertussis row in the US some years ago which continues to damage public health (California Department of Public Health 2014);

the polio disasters in northern Nigeria and Pakistan; the MMR fiasco, amongst many others; vaccination programmes are particularly vulnerable to this kind of disruption. These, and some others, are discussed and analysed in *Expecting the Worst*, Chap. 9 (Hugman 2013a))

The first line of useful response is probably not simply coming up with the evidence. Although the Romanian mothers (quoted above) said they wanted clear information, that alone would almost certainly not deal with their perceptions and emotions (*risk as feelings* and *as politics*, Chap. 18, p. 534). Parents will be deaf to scientific evidence while they are under the influence of compelling beliefs about unexpected death or injuries, however flimsily based; about political, neo-colonial, religious or commercial conspiracies; or about associated moral issues. Distrust of public authorities and Western influence is a common and damaging perception in many parts of the world and it requires radical changes in official behaviour and intensive, enlightened communication interventions, aimed at education and reconciliation, far beyond the ambit of specific campaigns (and well beyond the scope of this chapter).

(One fact in the genesis of such distrust cannot be passed over: some public authorities and pharmaceutical companies have been guilty of selective communication, misrepresentation, culpable error, dishonesty, arrogant dismissal of public concerns, lack of transparency and blatant fraud, especially with regard to the risks of medications. As long as such things happen, and linger in the public memory, a response of scepticism or distrust is not in the least unreasonable. In such a climate, a doctor's response to a patient's question, 'Can I trust this information?' has to be: 'I understand your worries, but I've looked into this very carefully, and to the best of my knowledge this is my conclusion....' But no doctor should pretend that there's only one view of any risk, nor imply a degree of certainty that the data do not support.)

At the individual level, professional empathy must engage with the depth and passion of these feelings as the essential starting point. If a conversation with a sceptical or hostile parent does not start with 'Tell me about your feelings and beliefs,' followed by a period of very intense, respectful listening, there's little hope of progress. Parents are, after all, defending what they believe are the health and best interests of their children; they will fight against all comers if they believe they are being harassed or manipulated into a decision they do not agree with. Furthermore, their trust in medicine and doctors across the board will be badly damaged.

There will be some particular risk communication issues and problems that may emerge once the encounter has moved on to a phase of discussion and debate:

- The confusion between temporal association and causality: 'She had the vaccine and never walked again' (See section "Causality", Chap. 18, p. 544)
- The power of anecdotes in the media and in social interaction, those vivid, compelling stories without science: 'We buried my daughter today'
- The influence of 'experts' in the public eye, in the media and on the internet who promote compelling, ostensibly science-based arguments challenging the status quo

- The influence of politicians who have broader agendas (and little knowledge of science) in which scientific issues get swept up into political and moral crusades
- The influence of religious leaders, the impact of some of whose principles may have the effect of damaging health and the public interest
- Reluctance to put a healthy child at even a very small risk of adverse effects
- The issue of small immediate risk as trade-off for large, future risk reduction
- The interaction of individual choice and community health, herd-immunity, in particular

Here, you can see the complex mix of issues and problems that may be influencing a parent, only some of which are amenable to rational argument and scientific evidence. Nevertheless, the facts and the evidence, such as they are, do need to be presented at some point and, as far as possible, in ways that are as compelling as the arguments used by the opposition.

Finding Facts About HPV

Where do we go to find the facts and good information about benefit-risk? The US CDC website is a good place to start.

> Approximately 79 million Americans are infected with human papillomavirus (HPV), and approximately 14 million people will become newly infected each year. Some HPV types can cause cervical, vaginal, and vulvar cancer among women, penile cancer among men, and anal and some oropharyngeal cancers among both men and women. Other HPV types can cause genital warts among both sexes. Each year in the United States an estimated 26,000 new cancers attributable to HPV occur, 18,000 among females (of which 11,500 are cervical cancer) and 8,000 among males (of which 5,900 are oropharyngeal cancers). (CDC 2014)

Gardasil® and Cervarix® are the vaccines that protect against the types of HPV infection that cause most cervical cancers and their safety record appears to be good, according to the US Vaccine Adverse Event Reporting System (VAERS):

> From June 2006-March 2013, approximately 57 million doses of HPV vaccines were distributed and VAERS received approximately 22,000 adverse event reports occurring in girls and women who received HPV vaccines; 92 % were classified as "non-serious." Reports received by VAERS peaked in 2008 and decreased each year after that; the proportion of female HPV reports classified as "serious" (reports are classified as "serious" if they contain information that the event resulted in hospitalization, prolongation of an existing hospitalization, permanent disability, life-threatening illness, or death) peaked in 2009 at 12.8 % and decreased after that to 7.4 % in 2013. (CDC 2014)

These figures provide the starting point for further exploration and discussion of the data and the risks. Parents will want to know exactly what is meant by 'non-serious,' and 'serious' and just how frequent such events are; they may want to hear about the alleged deaths from vaccination about which CDC and EMEA are unequivocal:

- There is no diagnosis at death that would suggest that the Gardasil® vaccine caused the death (CDC)
- No causal relationship has been established between the deaths of the young women and the administration of Gardasil (EMEA 2009).

Can these official assertions stand up beside the claims of an active anti-vaccination campaigning group like Judicial Watch (Judicial Watch 2007):

> The FDA adverse event reports on the HPV vaccine read like a catalog of horrors," stated Judicial Watch President Tom Fitton. "Any state or local government now beset by Merck's lobbying campaigns to mandate this HPV vaccine for young girls ought to take a look at these adverse health reports. It looks as if an unproven vaccine with dangerous side effects is being pushed as a miracle drug.

These battles are country-dependent. The picture is very different in Australia where the national HPV vaccination programme began in 2007 and has achieved a first-dose coverage of over 80 % (compared with 30 % in the US) with very little controversy or evidence of exceptional serious adverse effects (six million doses; anaphylaxis at a rate of 2.6 per million, for example, comparable with other vaccines in international studies, and 'no deaths.') (TGA). A study of the Australian programme in BMJ (2013) reported:

- In women, with 83 % first dose vaccine coverage, a 93 % decline in diagnosis of genital warts was seen by the fifth year of the national quadrivalent HPV vaccination programme in Australia
- Despite men not being vaccinated, an 82 % decline in genital warts occurred in heterosexual men, attributable to herd immunity
- No women who reported that they had been vaccinated were diagnosed as having genital warts in the final year of the study (Ali et al. 2013)

This study, published in a high ranking peer reviewed journal indicates positive outcomes from the HPV programme, even though there is active anti-vaccination campaigning in the country.

Navigating our way through all this is bewildering: 'facts' presented by opposing parties will appear to contradict each other. To balance the heart-wrenching stories of those who believe they have been injured we can find no comparably weighty advocacy in favour of the vaccine in the scientific and regulatory literature, nor in most public health campaigns; the facts are promoted, but they do not have the drama and colour of stories about alleged injury to children. It's no wonder parents are confused and hesitant.

What Can We Tell Parents?

We cannot anticipate what every young girl's parents will want to know, but we can speculate that these are some of the primary questions and issues they may seek information about and want to resolve:

- What are the risks and consequences of (a) HPV infection, (b) genital warts, and (c) cervical cancer and are those risks individually and collectively larger or smaller than the risks of HPV vaccination?
- What causes other than HPV are linked to cervical cancer? How far are those risks reduced by vaccination? How likely is my child to get cervical cancer even if she has the vaccination?
- If my child is vaccinated will she still need to be tested for cervical cancer in the future?
- If my child has an adverse reaction, will she recover from it?
- Are there any serious reactions she might not recover from?
- How strong is evidence for the safety of the vaccine?
- How can you explain the stories in the media about children being made sick or dying after vaccination?
- Has anyone died from the vaccine?
- How can I explain the vaccine to a young girl?
- Won't the vaccine encourage young women to have more unsafe sex?
- Can't she wait until she's a bit older and can understand the vaccine?

Many of these questions you'll be able to answer now you've read this chapter. Few physicians in the world will have time to work through such extensive material with their patients and this highlights the profound need for supplementary reliable risk communication resources, including leaflets, videos, websites, and so on. Chapter 9 of this book (HPV vaccines) includes a useful and concise 'frequently asked questions' primarily aimed at physicians (see p. 283).

As with all vaccination programmes, as noted above, it is critical that the antecedent conditions in the community are accurately understood (especially any kind of well articulated opposition), that such conditions are assessed as risks to the programme, and are thoroughly managed long in advance of the first dose being offered.

I wrote earlier about the complex emotional, psychological and, for some, moral and spiritual aspects associated with the HPV vaccine (and other vaccines too). Those, along with the specific issues just listed, encapsulate many of the biggest challenges in risk communication. They demonstrate just how empathetic, skilled and knowledgeable programme managers, physicians and health workers need to be in every aspect of medical, scientific, social and psychological wisdom in order to help lay people make good decisions that they will not regret. Those decisions cannot always be based simply on data: intuition or 'gut feeling' may also be an important element, not to be dismissed as inevitably unreliable, especially under conditions of uncertainty, as Gigerenzer points out:

> A gut feeling is neither caprice nor a sixth sense, nor is it clairvoyance or God's voice. It is a form of unconscious intelligence. (Gigerenzer 2014)

He calls for a 'heuristic revolution' that requires 'learning how to deal with uncertain worlds with the help of smart rules of thumb.' While a doctor needs 'statistical thinking to understand the results of medical research,' he also needs 'good intuitions to understand the patient' (p. 32).

Hormone Replacement Therapy (HRT) and Menopause

Transition or Tragedy? Deficiency or Opportunity?

There are several contrasting narratives of menopause. We have to understand these in order to arrive at an authentic view for ourselves and to understand the differing feelings, values and beliefs of women who may seek advice or treatment. Appropriate risk communication will be shaped by how women view themselves and their time of life, as well as the nature and intensity of their symptoms.

First, a brief historical excursion to illuminate some of the roots of modern attitudes to female sexuality and reproduction. The myths of history: women's organs, the uterus in particular, have, since ancient Greece, been thought to be the source of many diseases and afflictions, both physical and psychological. Hippocrates thought a 'wandering womb' might explain a range of symptoms. In the English-speaking world the Greek word for womb, 'hystera,' led to coining of the term 'hysteria' used as a label for all kinds of women's problems, later, in the nineteenth century, especially applied to sexual dysfunction. Such was the negative and ill-informed view of women's sexual anatomy, largely a male-construct, out of which modern attitudes to menstruation, pre-menstrual tension and menopause arose.

Many of the 'witches' executed at Salem in 1686 were menopausal women (Sarudy 2013). In the West, menopausal women were, in most respects, stigmatised as being past the useful (child-bearing) stages of their lives and, when they spoke up were seen as wilfully disruptive, and probably making a fuss about very little. In some cultures, menopause marked the transition to freedom, serenity and social respect, especially in the East (Southin 2014a). Worldwide, menstruation has been associated with all kinds of myths and superstitions covering the whole spectrum from being a sign of women's superior powers to being evidence of a pact with the Devil (Southin 2014a). Menopause was first used as a technical term, almost certainly by de Gardanne in 1821. In the 1920s, hormones and the part they played in women's biology began to be understood, and the modern era began, though many of the old prejudices and myths lingered on. (A fascinating historical timeline at (seahare.com); *An Interdisciplinary Analysis of the Hormone Replacement Therapy Saga* at (Ashton and Alvarez-Dardet 2005).)

Major Narratives

This section of the chapter is a socio-cultural exploration of menopause and its meaning, intended to help practitioners clarity their own position on the issue, and to illuminate the widely differing views that women will hold. Apart from an understanding of the risks and benefits of HRT, women will have quite different views on medication in general and on specific symptoms (for example, hot flushes,

sleeplessness or mood-swings), depending on many variables, including their mental concept of menopause itself, their self-image and their levels of tolerance for discomfort. Risk communication and all aspects of the consultation must take account of these. If a physician is working from a different mental model, and does not recognise the discrepancy she may not offer or facilitate a solution that sensitively matches the patient's preferences and needs.

1. **Menopause as disease/deficiency:** Dr Robert A Wilson's 1966 book, *Feminine Forever* (Wilson 1968), set the tone for decades of the increasing medicalisation of menopause and the view of it as pathology with a predominant focus on its negative aspects, boosted by aggressive marketing of products by pharmaceutical companies and makers of 'natural' remedies. Wilson's language is emotive and uncompromising

   > [He] claimed that menopause caused a precipitous decline in women's overall health, sexuality and mental state and that estrogen was the only cure. A woman is not "complete" unless she takes hormone replacement pills. She will be "condemned to witness the death of her own womanhood." She cannot be "forever feminine" unless she takes hormone-replacement therapy." ... Wilson's descriptions of menopausal women suffering from "living decay" and being in a "vapid, cow-like state" certainly offended some women, but many more absorbed the message that menopause must be treated.

   This view of menopause and the self-evident, healing virtues of HRT more or less held sway, in spite of ideological objections and well argued serious doubts, until the results of the Women's Health initiative were first published in 2002 when big questions were raised about risks and benefits (Women's Health Initiative 2002). Even among contemporary researchers and practitioners who espouse this model of menopause, and are enthusiastic advocates for HRT, there is a great deal more moderation and qualification in their views than there was a few years ago. This model is, nevertheless, an example of the partial politicisation of health and risk (that is to say the manifestation of conflicting vested interests rather than science and best practice), as mentioned in the opening section of this chapter. Vigorous promotion of commercial products adds another powerful and distorting dimension in the propagation of the virtues of HRT.

2. **Menopause as transition/opportunity:** this radical non-medicalised view of menopause has been promoted especially by crusaders like Marie Stopes (1936) and feminist writers such as Alice Wolfson, Barbara Seaman (2003), Naomi Wolf (2002) and Germaine Greer (1991). They talk of menopause as one of life's natural transitions, comparable to the menarche and to child-bearing, none of which, they assert, are intrinsically medical conditions or diseases. Women may need expert intervention for dealing with symptoms or problems, but they should not be turned into needy patients simply because they are experiencing the essential changes of women's bodies. Marie Stopes thought that nearly every case of menopausal difficulty she saw admitted to hospital was 'induced by the ghastly things women had read and been told about what was going to happen.' She believed most of the problems were caused by doctors.

Barbara Seaman's book, *The Greatest Experiment Ever Performed on Women: Exploding the Estrogen Myth* (Seaman 2003), is one of the most powerful expositions of this position. *The Change: Women, Aging and the Menopause*, by Germaine Greer (1991) promotes the view that menopause allows women to be liberated from all the duties, demands and expectations of the earlier, fertile years, and to explore life's new opportunities. She scathingly refers to the 'Masters of Menopause' who write and, as she sees it, pontificate about matters they barely understand with, what's more, subversive male motives for their interest.

The natural childbirth movement is an analogous phenomenon, in which women assert their wish to avoid incorporation by the medical hegemony and to retain greater control over their bodies and reproductive functions.

3. **Socio-cultural diversity:** menopause is a developmental stage, not a disease or an identifiable syndrome. While its central feature, cessation of ovulation and menses, is universal, its symptoms and manifestations are multiple and dependent on a host of variables, at least: individual psychology, biology, socio-economic status, diet, ethnicity, country of domicile. For example, in Japan menopause has not been pathologised as it has in the West. Japanese women report quite different experiences, far fewer vasomotor symptoms, for example, than do women in North America:

> Differences are demonstrated in postmenopausal experiences and symptom reporting in Japan as compared with Canada and the United States. Reporting of hot flashes and nights sweats is significantly lower in Japan. These findings, together with the well established figures about greater longevity and lower incidence of heart disease, breast cancer, and osteoporosis in Japan, compared with North America, indicate that cultural and biological variables act in concert to produce this variation. (Lock 1998)

(There are signs that the differential will close, however, as changes in diet and lifestyle begin to make their mark in younger generations (Southin 2014b)).

In a study of women from five racial/ethnic groups in the US, one study found:

> Caucasian women reported significantly more psychosomatic symptoms than other racial/ethnic groups. African-American women reported significantly more vasomotor symptoms. Perimenopausal women, hormone users, and women who had a surgical menopause reported significantly more vasomotor symptoms. (Avisa et al. 2001)

Differing views of menopause and its meaning may have profound psychological effects:

> . . .studies on Mayan and Greek rural women [referenced in the document referenced here] have reflected that they enjoy their sex life more after attaining menopause because they do not have the fear of becoming pregnant again. . .This could be a plausible explanation why Greek and Mayan women have fewer psychosomatic and psychological problems during midlife. (Dasgupta and Ray 2009)

Ignorance may, in some respects, be a kind of benefit:

> Generally, women from developing countries, including those of the present study, tend to view menopause and its symptoms as a natural process that does not require medical care, so they are less aware about the health-related issues of menopause.

This is not to say that some women in developing countries don't need help or support – even medication – to cope with menopause, but it does highlight the possibility that shining a spotlight on the problematic aspects of a condition may upset an otherwise balanced and tolerant view of it.

4. **The body beautiful and everlasting life:** images of the young and the beautiful, and the pre-eminence of sexual attractiveness in women press upon us from a million directions (Wolf 2002). Natural and pharmaceutical remedies to sustain youthful beauty and sexual performance are aggressively marketed; plastic surgery to remedy sagging breasts, remove wrinkles and rejuvenate ageing features is promoted as the 'natural' response to natural decline. Film stars and chat-show hostesses boast of their remaking and the happiness it has brought them. This may poison any possibility of philosophical acceptance of ageing cheerfully and optimistically; it firmly identifies menopause as the culprit and the enemy to be attacked with every weapon available, largely, of course, by the affluent. (See also section "Body Image", Chap. 18, p. 571).

This superficial sketch, then, indicates the complex and variable influences and context in which women experience menopause and in which they may (or may not) want health professionals to intervene. Risk communication, as noted earlier, must take account of all these variables, not least because of the damage that may be caused by women being treated by doctors whose views are not in line with their own or by their uncritically accepting marketing messages or solutions driven by male prejudice.

What Advice Can We Offer?

Women's particular beliefs and values, fed from many sources, will influence how they experience menopause, what they want to do about the effects it has on their lives and how they view the remaining years of their lives. Physicians need to be very sensitive about their patients' beliefs and values and highly aware of their own assumptions and prejudices (for example, do women have to be rescued from the pathology of menopause or supported through a normal phase of life?). Women who regard menopause as an intolerable plague in their lives, anxious to take any path that will relieve them of symptoms, need to be very carefully cautioned about the risks of excessive medication, of ostensible 'bioidenticals' and of unregulated, untested 'natural' remedies. Other women, however, maybe on very strong principle, will be looking for helpful advice about ways of managing symptoms (hot flushes or night sweats, for example) that do not involve medication. Reaching for the prescription pad will not please them.

Hormone Replacement Therapy

At the point a woman wishes to consider the possibility of HRT, she must have good risk information. Chapter 11 (Menopausal Hormone Therapy) summarises the best current knowledge and I shall not repeat the substance of that here.

If HRT is a suitable and acceptable method, then there is some good, high level risk information that appears to be agreed by most authorities:

> The evidence suggests that HRT may be associated with an increased risk of: coronary heart disease; stroke; venous thromboembolism . . .; breast cancer; ovarian cancer; or endometrial cancer. These risks depend on how long HRT has been taken for, [type of HRT—ie, oestrogen-only or oestrogen plus progestogen], the woman's age and underlying health, and are lower in healthy younger women.
>
> The balance of risks and benefits differs between individual women according to her need for treatment. For all women, the lowest effective dose should be used for the shortest possible time, and treatment should be reviewed yearly.
>
> No single recommendation for optimum duration of treatment or safe upper-age limit for use of HRT is therefore possible (MHRA 2007)

A number of sources of information for patients are available on the internet, but searchers are, as always, faced with the problem of knowing which are reliable and up-to-date. The Australian Menopause Society (AMS) is one such impressive-seeming source, but there are elements of that website that are not in line with the MHRA report (see reference above) which is regarded by many as the most authoritative current statement of evidence and knowledge.

The question of evidence aside, AMS has some useful material. There's a short list of questions a woman might like to ask herself (or her doctor might ask her) as she weighs benefits and risks:

- How much do my symptoms impact on my quality of daily life?
- What could happen if I did nothing at all?
- What are my treatment choices?
- What are their risks and benefits? How reliable is the evidence for these risks and benefits? Are the findings of these studies relevant to me and my treatment?
- Have I now got enough information to make a decision?

Specifying the Risks

The MHRA report presents tables of attributable risk for oestrogen-only and combined HRT for women of various age groups, with and without a uterus, for treatment periods of 5 or 10 years. These provide the absolute figures, against background incidence, and overcome the sometimes alarming impact of relative risk figures. Here's one of those tables, showing aggregation of all HRT risks, to illustrate the point (Table 19.2):

Table 19.2 Comparison of overall balance of benefits and risks associated with oestrogen-only and combined HRT in different prescribing scenarios (Table 6 (ii) from MHRA report) 5 years' use of HRT in women aged 60–69 years

Type of HRT	Baseline risk per 1,000 women	Absolute risk in 1,000 HRT users	Attributable risk in 1,000 HRT users
Oestrogen-only (women with uterus)	82	88 (82–97)	6 (0–15)
Oestrogen-only (women with uterus)	85	97 (90–108)	12 (5–23)
Combined HRT	70	92 (86–101)	22 (16–31)

Overall, this presentation of risk information is clear and simple for those with some level of numeracy, but it will not suit everyone.

Presentation as charts or on one of Paling's palettes (Paling) as illustrated in Fig. 19.2 would offer further methods that might be more attractive or meaningful for some women.

In the booklet, produced by AMS, *Menopause, Presenting a positive outlook* (MacLennan and MacLennan 2012), there are some very elegant, well designed, well framed charts, like those shown in Fig. 19.3.

However, there are potential problems for some women. It may not be possible for many women to make sense of so much information on their own. Even these elegant and lucid materials will be quite beyond the reach of those with poor literacy and/or poor health literacy. Even literate women will wish to turn to their medical adviser for some kind of verbal exposition, overview and guidance about how the evidence applies to them. In any case, doctors and health workers need to have on hand first, the evidence and knowledge, and, second, a wide range of alternative methods of presenting it.

Decision Aids

The evidence and risk information, of course, relates to populations, not to individuals. The risks are different for every individual, dependent on many variables. One very effective way for a woman to better understand her own risk, or for a physician to help her do so, is to use a decision aid. The University of Sydney School of Public Health provides one such useful tool in its HRT risk calculator (Sydney). This is for a specific population of Australian women, around 50 years of age, suffering serious hot flushes and contemplating starting a regimen of combined HRT. It produces an individual risk profile derived from the population data. The calculations would be different for women in different parts of the world and specific decision aids would be necessary for them.

Because of the known risks of hormonal medication in menopause, there is pressure for the development of non-hormonal treatments. The FDA approved the

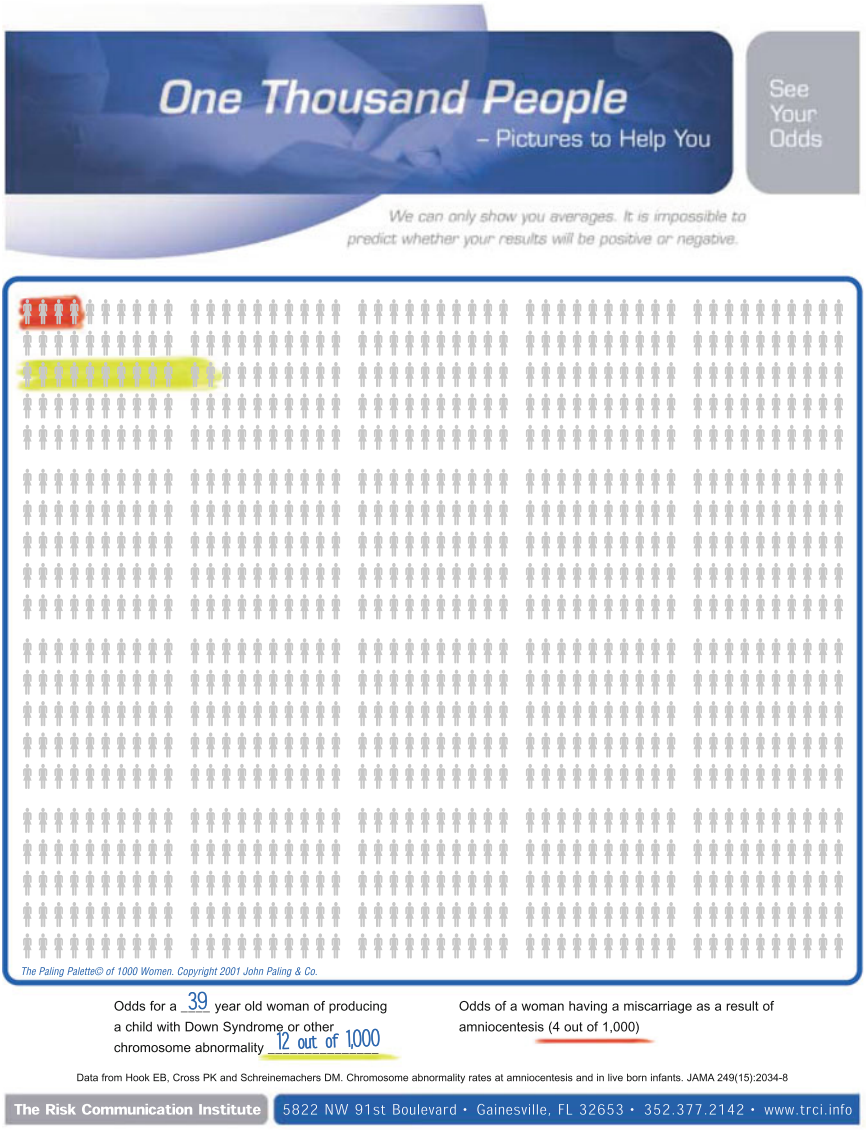
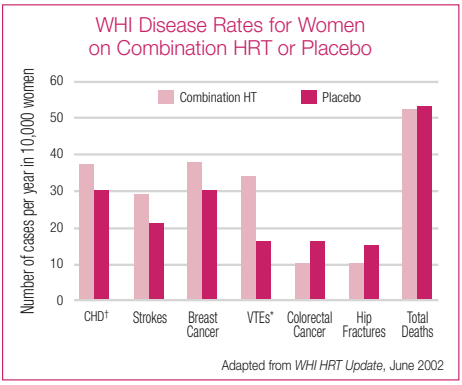


Fig. 19.2 John Paling's work in risk communication is an invaluable resource. One of the principal tools he has developed is the *palette*, which allows absolute risk figures to be displayed visually for different populations (women, men, families) and different denominators (particularly 100 and 1,000). This one shows the odds of a woman aged 39 having a child with Down syndrome or other chromosomal abnormality (12/1,000) and the odds of a miscarriage as a result of amniocentesis. The great benefit of this approach is the display of harm and not-harm with absolute equity; the *framing* does not skew the data in either direction. For some patients this approach will be welcome, helpful and reassuring. (Paling) Gigerenzer also offers a range of imaginative and useful methods of graphic presentation of data, including excellent materials from the Harding Centre for Risk Literacy of which he is Director (Gigerenzer 2014)

Figure 1



† CHD = coronary heart disease (heart disease caused by thickening of blood vessels, including angina, heart attack and heart failure)

* VTE = venous thromboembolism (clotting)

Figure 2 (all ages)

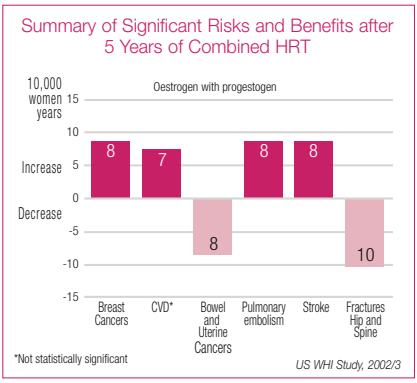


Figure 3 (all ages)

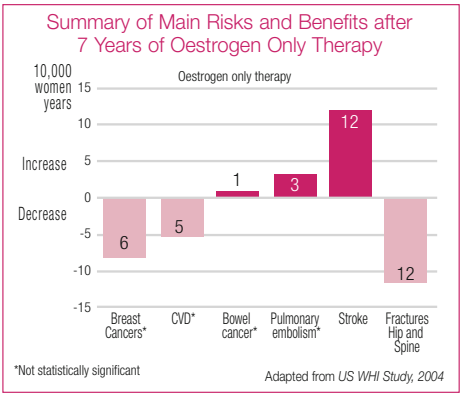


Fig. 19.3 Elegant and lucid presentation of complex information from the Australian Menopause Society (MacLennan and MacLennan 2012)

first such medication in 2013 but rapid and heated controversy immediately arose about its safety (see Box 19.3).

Box 19.3 Controversial Non-hormonal Treatment for Moderate to Severe Vasomotor Symptoms

In June 2013, against the recommendation of its advisory committee, the FDA approved the first non-hormonal treatment for vasomotor symptoms, Brisdelle (paroxetine) which is a lower dose version of the antidepressant Paxil. The advisory committee voted 10 to 4 against there being any clinically significant benefit at 12 weeks in the company-sponsored trial. There was evidence of multiple harms, including dizziness, nausea, fatigue, mood swings and suicidality, side effects well recognised in patients taking higher dose SSRIs. The list of side effects for Brisdelle, from 'rare,' through 'incidence unknown,' to 'more common' has more than 100 items. It is in Worstpills.org's stringent 'Do not use' category. It is marketed in a comfortingly mauve pack as the 'first and only' approved non-hormonal treatment for women who cannot or do not wish to use HRT.

Women and their physicians must make their own judgement about the benefit-harm profile of this drug, the comparative risks of HRT and the effects of no treatment. For the writer of this chapter, the question is how such a drug was ever approved (Drugs.com 2014a).

Risk Communication, Timing and the Media

HRT was the subject of a major public health scare in Australia in 2002 after the results of the Women's Health Initiative (WHI) study were released. Although the absolute risk figures were included in the small print of the press releases, it was the relative risk figures that caught the attention of journalists and hit the headlines.

The front-page story in Australia's largest circulation newspaper, the Sydney Daily Telegraph, was headlined as follows:

> **Medical warning**
> A study of sixteen thousand women shows links between long-term HRT and breast cancer. Don't panic but **Call your GP**

A further dimension of the problem was that neither the Therapeutic Goods Administration (TGA) nor doctors had had prior information about the story and could not provide immediate information to the 600,000 women taking HRT, many of whom thought they now had a 26 % risk of breast cancer. The TGA handled the crisis with exemplary speed and decisiveness (critical for crisis management and resolution) by assembling its expert drug evaluation committee and issuing a definitive statement within 30 hours of the crisis breaking. Within 2 days, the issue had largely subsided and everyone began more or less calmly reassessing

their view of the risks of long-term HRT (Case study in *Expecting the Worst*, Appendix 1A (Hugman 2013a)).

The simple lesson: relative risk figures are dangerous for everyone: any claim for risks or benefits, put forward by any party at all, that does not include absolute figures must be treated with critical scepticism, if not grave suspicion, even supposing the trials or figures on which they are alleged to be based are to be taken seriously which, from time to time, they are not. We must ask: a percentage or factor of *what* in terms of absolute numbers and class of event.

Conclusions About HRT

HRT has a complex mix of benefits and harms across a range of symptoms, organs and diseases. Some non-hormonal and non-medical treatments are available for some women for mild, even serious symptoms, one of which, referred to above, may be very risky indeed. Those who feel drawn to HRT as their favoured choice, maybe because of severely distressing symptoms, need to have a very clear idea of the benefits and risks as they apply to them individually. Doctors need a very considerable knowledge-bank of good evidence about HRT itself; about other methods of symptom management; and a creative, tailored range of methods for presenting and discussing it with each individual.

Conclusions

The challenging process of risk communication with individual patients has been presented in all its demanding detail. Apart from the pharmaceutical risks of medicines themselves, there are further substantial risks to safety, adherence and effectiveness, inherent in the disposition and character of the patient, that must be specifically addressed by prescribers or dispensers. Risk communication must take account of multiple variables intrinsic within patients and in the total context of their lives; it must also take account of the fact that many patients and many health professionals are seriously deficient in risk literacy.

In reviewing the risk communication elements of a small group of women's conditions and medicines, it was clear that there was mostly good evidence about the benefits and harms of most of the medicines. However, as with all reproductive concerns, especially issues touching directly on motherhood and gender identity, there are other potent influences that will exercise women in their decision-making. 'Clinical significance' and perceived quality of life issues may not always be in step. Women, in all their immense and remarkable variety, need a synthesis of risk information that matches the profile of their individual needs, presented in ways that leave them free to make a decision that is best for them.

Take Home Messages

- Risk assessment is multi-factoral and requires painstaking, empathetic review and discussion for every patient
- Women will have profoundly different views of their sexuality and reproductive concerns depending on their personal philosophy, socio-economic status, country of domicile and many other factors
- Benefit-risk communications must be based on credible evidence and be shaped by the perceptions and priorities of the patient, including their response to uncertainty
- Risk communication about a specific medicine requires detailed and thorough attention if the patient is to avoid a number of common and unexpected risks and pitfalls and to gain maximum benefit from therapy
- Women's health embraces a wide range of crucial issues beyond disease symptoms and the traditional concerns of medicine
- Some women's medicines and conditions are subject to strong social, cultural and religious influences which must be taken account of in risk counseling
- Risk information for women is vulnerable to many distortions and misrepresentations, including male prejudices, social scares and commercial pressure, that require careful interpretation and management
- Risk communication demands the exercise of intense empathy if all individual, psycho-social and cultural obstacles and pitfalls are to be avoided and if the safety of patients is to be protected as far as is humanly possible

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