Introduction

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Over the past decade, attention to clinical therapeutics has grown substantially from many different directions, including the important influences of gender differences and pregnancy [1–3]. Despite these advances there is increasing concern that discovery and development of new drugs for these important populations is lagging [4–9]. At the same time, recognition has grown that select populations are excluded from the drug development process, especially women and children [5, 10–12]. One consequence of this failure to specifically develop drugs for maternal and child health is to dissociate therapeutic opportunities for women and children from the drugs and treatments currently available. This distancing of women and children from drug development and therapeutic knowledge produces a host of clinical challenges for the concerned practitioner. In the absence of sufficient therapeutic knowledge, appropriate dosing is not known [13–17]. Without understanding of appropriate dosing, the clinician does not know if the dose recommended on the product label will produce the desired drug concentration at the site of action – or if the concentration produced will be above or below the needed concentration, producing toxicity or inadequate response, respectively. Similarly, without thoughtful therapeutic development in women and children it is not known if differences in pharmacodynamics will produce different treatment goals and needs for monitoring effectiveness and safety [14, 18–21].

A consequence of the failure to develop drugs for use in pregnancy is that most drugs are not tested for use during pregnancy [4, 22]; consequently, labeling, which may include extensive information about fetal safety [10, 23], includes nothing about dosing, appropriate treatment, efficacy, or maternal safety [3–5, 10, 11, 22, 23]. Yet these are concerns of health care providers considering treatment during pregnancy. Therefore, the practitioner treats the pregnant woman with the same dose recommended for use in

adults (typically men) or may decide not to treat the disease at all. However, is the choice of not treating a woman during pregnancy better than dealing with the challenges which accompany treatment? Clearly treatment of depression poses risks for both mother and fetus, as does stopping treatment [24–26]. This is also the case with respect to influenza during pregnancy [13, 27, 28]. All combined, the state of therapeutics during pregnancy underscores the continued tension that exists between maternal–placental–fetal health and maternal quality of life during pregnancy and the lack of critical study of "gestational therapeutics". This book hopes to address many of these imbalances.

Medical and health care providers caring for women during pregnancy have many excellent resources describing the safety of medications for the fetus [10, 23]. However, none of these references provide information on appropriate dosing as well as the efficacy of the various medications used during pregnancy for maternal/placental therapeutics. We are all familiar with the potential/actual costs, financial and psychosocial, of having treatments which produce developmental toxicity – however, how many of us ever think critically about the costs of having inadequate therapeutic options to treat the major diseases of pregnancy; growth restriction, pregnancy loss, preeclampsia/eclampsia. Where we have effective treatments for maternal disease – infection, depression, diabetes, hypertension – we are recognizing that continuation of treatment during pregnancy carries benefit for mother, placenta, and baby. In the end what is important for the mother, baby, and family is the appropriate balancing of benefit and risk – as indeed is the important balancing for all clinical therapeutics [11, 12]. This book provides medical and health professionals involved in the care of pregnant women with contemporary information on clinical pharmacology for pregnancy. It covers an overview of the impact of pregnancy on drug disposition, summarizing current research about the changes of pharmacokinetics and pharmacodynamics during pregnancy. This is followed by specific sections on the treatment, dosing and clinical effectiveness of medications during pregnancy, providing health care providers with an essential reference on how to appropriately treat women with medications during pregnancy. At one level the question is simple – how to treat, how to monitor for benefit and risk, how to know if treatment is successful? This book was developed to explore that question for women during pregnancy. The book is meant to be a guide to clinicians who care for women during pregnancy – we hope the busy clinician and student of obstetrics will find this a useful guide.

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Physiologic Changes During Pregnancy

2

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2.1 Physiologic changes during pregnancy

Human pregnancy is characterized by profound anatomic and physiologic changes that affect virtually all systems and organs in the body. Many of these changes begin in early gestation. Understanding of pregnancy adaptations is vital to the clinician and the pharmacologist as many of these alterations will have a significant impact on pharmacokinetics and pharmacodynamics of different therapeutic agents. A typical example of the latter involves the increase in glomerular filtration rate leading to increased clearance of heparins requiring the use of higher doses during pregnancy. The present chapter discusses the most relevant physiologic changes that occur during human gestation.

2.2 Cardiovascular system

Profound changes in the cardiovascular system characterize human pregnancy and are likely to affect the pharmacokinetics of different pharmaceutical agents. Table 2.1 summarizes the main cardiovascular changes during pregnancy. Cardiac output (CO) increases by 30–50% during pregnancy secondary to an increase in both heart rate and stroke volume [1]. Most of the increase occurs early in pregnancy, such that by the end of the first trimester 75% of such increment has already occurred. CO plateaus at 28–32 weeks and afterwards remains relatively stable until the delivery period [2]. As CO increases, pregnant women experience a significant decrease in both systemic and pulmonary vascular resistances [1]. Systemic vascular resistance decreases in early pregnancy, reaching a nadir at 14–24 weeks. Subsequently, vascular resistance starts rising, progressively approaching the pre-pregnancy value at term [1]. Blood pressure tends to fall toward the end of the first trimester and then rises again in the third trimester to pre-pregnancy levels [3]. Physiologic hypotension may be present between weeks 14 and 24 and likely this is due to the decrease in the systemic vascular resistance described previously.

Maternal blood volume increases in pregnancy by 40–50%, reaching maximum values at 32 weeks [4]. Despite the increase in blood volume, central filling pressures like the central venous

Table 2.1 Summary of cardiovascular changes during pregnancy

Variable	Change
Mean arterial pressure	No significant change
Central venous pressure	No change
Pulmonary arterial occlusion pressure	No change
Systemic vascular resistance	Decreased by 21% (nadir at 14–24 weeks)
Pulmonary vascular resistance	Decreased by 34%
Heart rate	Increased (approaches 90 beats/minute at rest during the third trimester)
Stroke volume	Increases to a maximum of 85 mL at 20 weeks of gestation
Colloid osmotic pressure	Decreased by 14% (associated with a decrease in serum osmolarity noticed as early as the first trimester of pregnancy)
Hemoglobin concentration	Decreased (maximum hemodilution is achieved at 30–32 weeks)

and pulmonary occlusion pressures remain unchanged secondary to an increase in compliance of the right and left ventricles [5].

The precise etiology of the increase in blood volume is not clearly understood; however, increased mineralocorticoid activity with water and sodium retention does occur [6]. Production of arginine vasopressin (resulting in increased water absorption in the distal nephron) is also increased during pregnancy and thought to contribute to hypervolemia. Secondary hemodilutional anemia and a decrease in serum colloid osmotic pressure (due to a drop in albumin levels) ensue.

The latter physiological changes could have theoretical implications on pharmacokinetics. The increase in blood volume, increased capillary hydrostatic pressure, and decrease in albumin concentrations would be expected to increase significantly the volume of distribution of hydrophilic substances. Highly protein bound compounds may display higher free levels due to decreased protein binding availability.

2.3 Respiratory system

The respiratory system undergoes both mechanical and functional changes during pregnancy. Table 2.2 summarizes these changes.

The sharp increase in estrogen concentrations during pregnancy leads to hypervascularity and edema of the upper respiratory mucosa [7]. These changes result in an increased prevalence of rhinitis and epistaxis in pregnant individuals. Theoretically, inhaled medications such as steroids used in the treatment of asthma could be more readily absorbed in the pregnant patient. Despite this theoretical concern, there is no evidence of increased toxicity with the use of these agents during pregnancy. Mainly driven by progesterone, minute ventilation increases by 30–50% secondary to an increase in tidal volume. Respiratory rate remains unchanged during pregnancy [8]. The increase in ventilation results in an increase in the arterial partial pressure of oxygen (PaO_2) to 101–105 mmHg and a diminished arterial partial pressure of carbon dioxide ($PaCO_2$), with normal values of $PaCO_2$ during pregnancy of 28–31 mmHg. This decrement allows for a gradient to exist between the $PaCO_2$ of the fetus and the mother so that carbon dioxide can diffuse freely from the fetus into the mother through the placenta and then be eliminated through the maternal lungs.

The normal maternal arterial blood pH in pregnancy is between 7.4 and 7.45, consistent with a mild respiratory alkalosis. The latter is partially corrected by an increased renal excretion of bicarbonate,

Table 2.2 Summary of respiratory changes during pregnancy

Variable	Change
Tidal volume	Increased by 30–50% (increase starts as early as the first trimester)
Respiratory rate	No change
Minute ventilation	Increased by 30–50% (increase starts as early as the first trimester)
Partial pressure of oxygen	Increased (increase starts as early as the first trimester)
Partial pressure of carbon dioxide	Decreased (decrease starts as early as the first trimester)
Arterial pH	Slightly increased (increase starts as early as the first trimester)
Vital capacity	No change
Functional residual capacity	Decreased by 10–20% (predisposes pregnant patients to hypoxemia during induction of general anesthesia)
Total lung capacity	Decreased by 4–5% (maximum diaphragmatic elevation happens during the third trimester of pregnancy)

rendering the normal serum bicarbonate between 18 and 21 meq/L during gestation [9]. As pregnancy progresses, the increased intra-abdominal pressure (likely secondary to uterine enlargement, bowel dilation, and third-spacing of fluids to the peritoneal cavity secondary to decreased colloid-osmotic pressure) displaces the diaphragm upward by 4–5 cm leading to alveolar collapse in the bases of the lungs. Bibasilar atelectasis results in a 10–20% decrease in the functional residual capacity and increased right to left vascular shunt [10, 11]. The decrease in expiratory reserve volume is coupled with an increase in inspiratory reserve volume; as a result no change is seen in the vital capacity [10].

Changes in respiratory physiology may impact pharmacokinetics of certain drugs. Topical drugs administered into the nasopharynx and upper airway could be more readily available to the circulation as local vascularity and permeability are increased. As discussed earlier, the latter assumption is theoretical and no evidence of increased toxicity from inhaled agents during pregnancy has been demonstrated.

2.4 Renal system

Numerous physiologic changes occur in the renal system during pregnancy. These changes are summarized in Table 2.3.

Table 2.3 Summary of renal changes during pregnancy

Variable	Change
Renal blood flow	Increased by 50%. Increase noticed as early as 14 weeks of gestation
Glomerular filtration rate	Increased by 50%. Increase noticed as early as 14 weeks of gestation
Serum creatinine	Decreased (normal value is 0.5–0.8 mg/dL during pregnancy)
Renin–angiotensin–aldosterone system	Increased function leading to sodium and water retention noticed from early in the first trimester of pregnancy
Total body water	Increased by up to 8 liters. Six liters gained in the extracellular space and 2 liters in the intracellular space
Ureter–bladder muscle tone	Decreased secondary to increases in progesterone. Smooth muscle relaxation leads to urine stasis with increased risk for urinary tract infections
Urinary protein excretion	Increased secondary to elevated filtration rate. Values up to 260 mg of protein in 24 hours are considered normal in pregnancy
Serum bicarbonate	Decreased by 4–5 meq/L. Normal value in pregnancy is 18–22 meq/L (24 meq/L in non-pregnant individuals)

The relaxing effect of progesterone on smooth muscle leads to dilation of the urinary tract with consequent urinary stasis, predisposing pregnant women to infectious complications.

The 50% increase in renal blood flow during early pregnancy leads to a parallel increase in the glomerular filtration rate (GFR) of approximately 50%. This massive elevation in GFR is present as early as 14 weeks of pregnancy [12]. As a direct consequence, serum values of creatinine and blood urea nitrogen will decrease. A serum creatinine above 0.8 mg/dL may be indicative of underlying renal dysfunction during pregnancy.

Besides detoxification, one of the most important functions of the kidney is to regulate sodium and water metabolism. Progesterone favors natriuresis while estrogen favors sodium retention [13]. The increase in GFR leads to more sodium wasting; however, the latter is counterbalanced by an elevated level of aldosterone which reabsorbs sodium in the distal nephron [13]. The net balance during pregnancy is one of avid water and sodium retention leading to a significant increase in total body water with up to 6 liters of fluid gained in the extracellular space and 2 liters in the intracellular space. This "dilutional effect" leads to a mild decrease in both serum sodium (concentration of 135–138 meq/L) and serum osmolarity (normal value in pregnancy ~280 mOsm/L) [14]. In the non-pregnant state, normal serum osmolarity is 286–289 mOsm/L with a concomitant normal serum sodium concentration of

135–145 meq/L. Changes in renal physiology have profound repercussions on drug pharmacokinetics. Agents cleared renally are expected to have shorter half-lives and fluid retention is expected to increase the volume of distribution of hydrophilic agents. A typical example involves lithium. Lithium is mainly cleared by the kidney and during the third trimester of pregnancy clearance is doubled compared to the non-pregnant state [15]. Not all renally cleared medications undergo such dramatic increases in excretion rates (digoxin clearance is only increased by 30% during the third trimester of pregnancy).

2.5 Gastrointestinal system

The gastrointestinal tract is significantly affected during pregnancy secondary to progesterone-mediated inhibition of smooth muscle motility [16]. Table 2.4 summarizes these changes.

Gastric emptying and small bowel transit time are considerably prolonged. The increase in intra-gastric pressure (secondary to delayed emptying and external compression from the gravid uterus) together with a decrease in resting muscle tone of the lower esophageal sphincter favors gastroesophageal regurgitation. Of note, recent studies have shown that gastric acid secretion is not affected during pregnancy [17].

Table 2.4 Summary of gastrointestinal changes during pregnancy

Variable	Change
Gastric emptying time	Prolonged, increasing the risk of aspiration in pregnant women. Intra-gastric pressure is also increased
Gastric acid secretion	Unchanged
Liver blood flow	Unchanged in the hepatic artery; however, more venous return in the portal vein has been documented with ultrasound Doppler studies
Liver function tests	No change during pregnancy except for alkaline phosphatase (increases in pregnancy secondary to placental contribution)
Bowel/gallbladder motility	Decreased, likely secondary to smooth muscle relaxation induced by progesterone
Pancreatic function enzymes (amylase, lipase)	Unchanged

Conflicting data exist regarding liver blood flow during pregnancy. Recently, with the use of Doppler ultrasonography, investigators found that blood flow in the hepatic artery does not change during pregnancy but portal venous return to the liver was increased [18]. Most of the liver function tests are not altered. Specifically, serum transaminases, billirubin, lactate dehydrogenase, and gamma-glutamyl transferase are all unaffected by pregnancy. Serum alkaline phosphatase is elevated secondary to production from the placenta and levels two to four times higher than that of non-pregnant individuals may be seen [19]. Other liver products that are normally elevated include serum cholesterol, fibrinogen, and most of the clotting factors, ceruloplasmin, thyroid binding globulin, and cortisol binding globulin. The increase in all these proteins is likely estrogen mediated [19]. Also mediated by progesterone, gallbladder motility is decreased, rendering the pregnant woman at increased risk for cholelitiasis. The latter changes will clearly affect pharmacokinetics of orally administered agents, with delayed absorption and onset of action as a result. Antimalarial agents undergo significant changes at the gastrointestinal level during pregnancy that could decrease their therapeutic efficacy [20].

2.6 Hematologic and coagulation systems

Pregnancy is associated with increased white cell count and red cell mass. The rise in white cell count is thought to be related to increased bone marrow granulopoeisis and may make a diagnosis of infection difficult sometimes; however, it is usually not associated with significant elevations in immature forms like bands. On the other hand, the 30% increase in red cell mass is thought to be secondary to increase in renal erythropoietin production, and may be induced by placental hormones. This occurs simultaneously with a much higher (around 45%) increase in plasma volume leading to what is referred to as "physiologic anemia" of pregnancy which peaks early in the third trimester (30–32 weeks) [21, 22]. This hemodilution is thought to confer maternal and fetal survival advantage as the patient will lose a more dilute blood during delivery, and the decreased blood viscosity improves uterine perfusion, while the increase in red cell mass serves to optimize oxygen transport to the fetus. To that account, patients with preeclampsia, despite having fluid retention, suffer from reduced intravascular volume (secondary to diffuse endothelial injury with resultant third-spacing) which makes them less tolerant to peripartum blood loss [23, 24].

Table 2.5 Hemoglobin values during pregnancy

Gestational age	Mean hemoglobin value (g/dL)
12 weeks	12.2
28 weeks	11.8
40 weeks	12.9

Pregnancy is associated with changes in the coagulation and fibrinolytic pathways that favor a hypercoagulable state. Plasma levels of fibrinogen, clotting factors (VII, VIII, IX, X, XII), and von Willebrand factor increase during pregnancy leading to a hypercoagulable state. Factor XI decreases and levels of prothrombin and factor V remain the same. Protein C is usually unchanged but protein S is decreased in pregnancy. There is no change in the levels of anti-thrombin III. The fibrinolytic system is suppressed during pregnancy as a result of increased levels of plasminogen activator inhibitor (PAI-1) and reduced plasminogen activator levels. Platelet function remains normal in pregnancy. Routine coagulation screen panel will show values around normal. This hypercoagulable state predisposes the pregnant patient to higher risk of thromboembolism; however, it is also thought to offer survival advantage in minimizing blood loss after delivery [25]. Tables 2.5 and 2.6 summarize some of the most relevant changes discussed previously.

2.7 Endocrine system

Pregnancy is defined as a "diabetogenic" state. Increased insulin resistance is due to elevated levels of human placental lactogen, progesterone, estrogen, and cortisol. Carbohydrate intolerance that occurs only during pregnancy is known as gestational diabetes. Most gestational diabetes patients are managed solely with a modified diet. Approximately 10% of patients will require pharmacological treatment, mainly in the form of insulin, glyburide, or even metformin. Available literature suggests that glyburide and metformin may be as effective as insulin for the treatment of gestational diabetes.

Pregnancy is associated with higher glucose levels following a carbohydrate load. By contrast, maternal fasting is characterized by accelerated starvation, increased lipolysis, and faster depletion of liver glycogen storage [26]. This is thought to be related to the

Table 2.6 Summary of hematological changes during pregnancy

Variable	Change
Fibrinogen level	Increased (elevation starts in the first trimester of pregnancy and peaks during the third trimester)
Factors VII, VIII, IX, X	Increased
Von Willebrand factor	Increased
Factors II and V	No change
Clotting times (prothrombin and activated partial thromboplastin times)	No change
Protein C, anti-thrombin III	No change
Protein S	Decreased. Free antigen levels above 30% in the second trimester and 24% in the third trimester are considered normal during pregnancy
Plasminogen activator inhibitor	Levels increase 2–3 times leading to a decrease in fibrinolytic activity
White blood cell count	Elevated. This increase results in a "left shift" with granulocytosis. Increase peaks at 30 weeks of gestation. During labor may see values of 20,000–30,000/mm^3
Platelet count	No change

increased insulin resistance state of pregnancy induced by placental hormones such as human placental lactogen. Pancreatic β-cells undergo hyperplasia during pregnancy resulting in increased insulin production leading to fasting hypoglycemia and postprandial hyperglycemia. All of these changes facilitate placental glucose transfer, as the fetus is primarily dependent on maternal glucose for its fuel requirements [27].

Leptin is a hormone primarily secreted by adipose tissues. Maternal serum levels of leptin increase during pregnancy and peak during the second trimester. Leptin in pregnancy is also produced by the placenta.

On the other hand, the thyroid gland faces a particular challenge during pregnancy. Due to the hyperestrogenic milieu, thyroid binding globulin (the major thyroid hormone binding protein in serum) increases by almost 150% from a pre-pregnancy concentration of 15–16 mg/L to 30–40 mg/L in mid-gestation. This forces the thyroid gland to increase its production of thyroid hormones to keep their free fraction in the serum constant [28, 29]. The increase in thyroid hormones production occurs mostly in the first half of gestation and plateaus around 20 weeks until term. Other

Table 2.7 Summary of endocrine changes during pregnancy

Variable	Change
Free T4 and T3 levels	Unchanged
Total T4 and T3 levels	Increased secondary to increased levels of thyroid binding globulin (TBG) induced by estrogen. This elevation begins as early as 6 weeks and plateaus at 18 weeks of pregnancy
Thyroid stimulating hormone (TSH)	Decreases in the first half of pregnancy and returns to normal in the second half of gestation. During the first 20 weeks of pregnancy, a normal value is between 0.5 and 2.5 mIU/L
Total cortisol levels	Increased, mainly driven by increased liver synthesis of cortisol binding globulin (CBG)
Free serum cortisol	Increased by 30% in pregnancy

factors that influence thyroid hormones (TH) status in pregnancy include minor thyrotropic action of human chorionic gonadotropin hormone (hCG), higher maternal metabolic rate as pregnancy progresses, in addition to increase in transplacental transport of TH to the fetus early in pregnancy, inactivity of placental type III monodeionidase (which converts T4 to reverse T3), and in maternal renal iodine excretion. Although the free fraction of T4 and T3 concentrations declines somewhat during pregnancy (but remains within normal values), these patients remain clinically euthyroid [28, 29]. Thyroid stimulating hormone (TSH) decreases during the first half of pregnancy secondary to a negative feedback from peripheral thyroid hormones secondary to thyroid gland stimulation by hCG. During the first half of pregnancy, the upper limit of normal value of TSH is 2.5 mIU/L (as compared to 5 mIU/L in the non-pregnant state).

Serum cortisol levels are increased during pregnancy. Most of this elevation is secondary to increased synthesis of cortisol binding globulin (CBG) by the liver. Free cortisol levels are also increased by 30% during gestation. The endocrine changes during pregnancy are summarized in Table 2.7.

2.8 Summary

Pregnancy is associated with profound changes in human physiology. Virtually every organ in the body is affected and the clinical consequences of these changes are significant. Unfortunately, our knowledge of how these changes affect the pharmacokinetics and

pharmacodynamics of therapeutic agents is still very limited. Future research involving pharmacokinetics of specific agents during pregnancy is desperately needed.

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Impact of Pregnancy on Maternal Pharmacokinetics of Medications

3

Mary F. Hebert

3.1 Introduction

Variability in drug efficacy and safety is multi-factorial. Both the pharmacokinetics (how the body handles the drug) and the pharmacodynamics (how the body responds to the drug) play significant roles in drug efficacy and safety. This chapter will discuss the effects of pregnancy on medication pharmacokinetics.

The physiologic changes that occur during pregnancy result in marked changes in the pharmacokinetics for some medications. Whether or not the physiologic changes will result in clinically significant pharmacokinetic changes for an individual medication depends on many factors. The discussion of these factors will be the focus of this chapter. Generally speaking, pharmacokinetic changes are most important clinically for medications with narrow therapeutic ranges. The therapeutic range includes all the concentrations above the minimum effective concentration, but less than the maximum tolerated concentration (Figure 3.1A and B). Medications such as cyclosporine, tacrolimus, lithium, lamotrigine, gabapentin, levetiracetam, phenytoin, digoxin, vancomycin, and the aminoglycosides are examples of narrow therapeutic range drugs. These are medications for which the concentrations needed for therapeutic benefit are very close to those that result in toxicity.

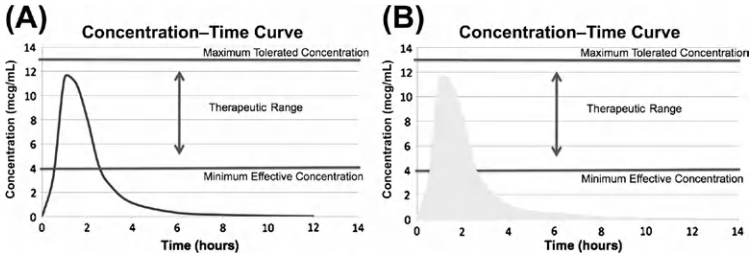

Figure 3.1 **A:** Stereotypic oral concentration–time curve. The upper horizontal solid line represents the maximum tolerated concentration and the lower horizontal solid line represents the minimum effective concentration. The therapeutic range for this drug, represented by the vertical double-sided arrow, includes all the concentrations between the minimum effective concentration and the maximum tolerated concentration. **B:** Stereotypic oral concentration–time curve with the shaded area depicting the area under the concentration–time curve, which is a measure of total drug exposure.

For these agents, small changes in drug concentrations can lead to inefficacy if the concentrations decrease or intolerable toxicity if the concentrations increase. Typically, when drug interactions, disease states or conditions alter the concentration–time profile for a medication, if no changes have occurred in the pharmacodynamics, the patient's dosage is adjusted to keep the concentrations similar to those prior to the altered state or similar to those for the population in which the drug has been approved. This dosage adjustment is done to maintain concentrations within the therapeutic range. For narrow therapeutic range medications, even a 25% change in drug concentration can be considered clinically significant. In contrast, for most medications, which have wide therapeutic ranges, small changes in pharmacokinetics have little to no clinical effect. However, given the magnitude of some of the pharmacokinetic changes that occur during pregnancy in which there can be two- to six-fold changes in drug exposure (Figure 3.2A), even medications that have wide therapeutic ranges can be clinically affected.

3.2 Effects of pregnancy on pharmacokinetic parameters

A change in pharmacokinetics for a medication can result in the need to change dosage. As described above, altered concentrations during pregnancy can result in the need for higher (Figure 3.2A)

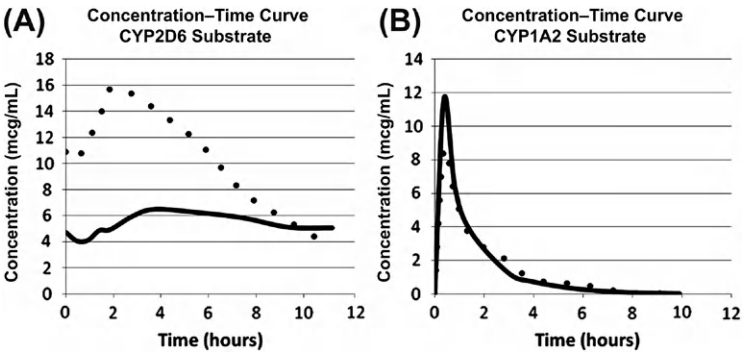

Figure 3.2 **A:** Concentration–time curves for a CYP2D6 substrate during pregnancy represented by the solid line and in the same subject 3 months postpartum represented by the dotted line. The increase in metabolism that occurs during pregnancy results in two- to six-fold lower AUC for CYP2D6 substrates during pregnancy than in the non-pregnant state in patients given the same dose. **B:** Concentration–time curves for a CYP1A2 substrate during pregnancy represented by the solid line and in the same subject 10 days postpartum represented by the dotted line. The inhibition of metabolism that occurs during pregnancy results in a higher AUC for CYP1A2 substrates during pregnancy than in the non-pregnant state.

or lower (Figure 3.2B) drug dosage to maintain concentrations within the therapeutic range. The changes in medication pharmacokinetics during pregnancy in some cases are so great that altered medication selection should be considered. For example, oral metoprolol concentrations are two- to four-fold lower during pregnancy than in the non-pregnant state [1, 2]. Given the magnitude and variability in metoprolol concentrations during pregnancy, for those patients that require a beta blocker, selecting another agent such as atenolol, which is renally eliminated, should be considered. Even with the changes in renal function that are expected during pregnancy, atenolol will give much more consistent and reliable drug concentrations in pregnant patients than metoprolol [1–3]. Although there are fetal risks with the utilization of beta blockers during pregnancy, such as intrauterine growth restriction, if a beta blocker is required during pregnancy, selecting an agent that will consistently and reliably achieve the desirable therapeutic effect requires consideration of pharmacokinetic changes in medication selection.

The following sections will discuss the commonly estimated pharmacokinetic parameters, their application and how they might

be altered by pregnancy. The actual calculation of these parameters will not be discussed in this chapter. However, the reader is referred to the many publications that discuss in detail the mathematical equations used to determine the pharmacokinetic parameters [4, 5].

3.2.1 Extraction ratio

Extraction ratio (ER) is the fraction of drug that is removed from the blood or plasma as it crosses the eliminating organ (e.g. liver or kidney). Knowing whether a drug has a high (ER >0.7; e.g. morphine, metoprolol, verapamil), intermediate (ER 0.3–0.7; e.g. codeine, midazolam, nifedipine, metformin, cimetidine) or low (ER <0.3; e.g. phenytoin, indomethacin, cyclosporine, amoxicillin, digoxin, atenolol) extraction ratio is important in predicting which factors, such as intrinsic clearance, protein binding, and/or blood flow, will alter the pharmacokinetic parameters for the drug.

3.2.2 Area under the concentration–time curve (AUC)

The area under the concentration–time curve is a measure of the overall systemic drug exposure (Figure 3.1B). Since we rarely can measure the drug concentration at the site of action (e.g. brain, lung or heart), blood, plasma or serum concentrations are typically used to determine systemic drug exposure. The AUC is dependent on the dose, clearance, and bioavailability of the drug. For some medications, AUC is the key determinant of medication efficacy and safety; while for other medications, either the maximum concentration and/or minimum concentration are better correlated with outcomes. For low extraction ratio drugs (both oral and intravenous administration), an increase in enzyme activity and/or a decrease in plasma protein binding will lead to a lower total drug AUC with changes in blood flow having no effect. For high hepatic extraction ratio, intravenously administered drugs, a decrease in blood flow will increase the total AUC; whereas, enzyme activity and protein binding have no effect on the total AUC. For high hepatic extraction ratio, orally administered drugs, the decrease in clearance caused by a decrease in blood flow is equal to the decrease in bioavailability such that changes in blood flow have no effect on oral AUC. However, increased enzyme activity or decreased plasma protein binding will decrease the total AUC through their effect on oral bioavailability.

3.2.3 Bioavailability

Bioavailability is the fraction of the dose administered that reaches the systemic circulation unchanged. Sometimes, the bioavailability

term is used to encompass both the rate and extent of absorption from the site of administration to the systemic circulation. For orally administered drugs, the bioavailability is affected by the amount of drug that is absorbed across the intestinal epithelium as well as first pass metabolism as the drug crosses the intestine and liver on its way to the systemic circulation. An increase or decrease in bioavailability directly impacts the oral AUC or total drug exposure. For low hepatic extraction ratio drugs, bioavailability is not affected by enzyme activity, hepatic blood flow or protein binding. In contrast, for high hepatic extraction ratio drugs, bioavailability is decreased by an increase in enzyme activity, decreased hepatic blood flow and/or a decrease in plasma protein binding. In addition to the above described changes in enzyme activity, protein binding and blood flow which can alter medication pharmacokinetics, other physiologic changes that occur during pregnancy which might influence the bioavailability of drugs include: gastric acidity, gastrointestinal transit time, and hypertrophy of duodenal villi, which can alter drug absorption [6–9].

3.2.4 Clearance

Clearance is a parameter used to describe how well the body can metabolize or eliminate drug. The clearance directly affects total drug exposure as well as average steady state drug concentrations and is utilized to determine maintenance dosage. There are three major determinants of hepatic drug clearance: hepatic blood flow, protein binding, and the intrinsic activity of hepatic drug metabolizing enzymes. Hepatic blood flow plays an important role in determining the hepatic clearance of drugs, particularly those with high extraction ratios. Physiologic, pathologic, and drug-induced changes in hepatic blood flow can alter the systemic clearance and oral bioavailability of many important therapeutic agents, resulting in changes in patient response. For high hepatic extraction ratio drugs, clearance is directly affected by hepatic blood flow such that an increase in blood flow will increase clearance. The rate-limiting step for metabolism of high hepatic extraction ratio drugs is the delivery of the drug to the liver. Visualizing this process in which everything that is delivered to the eliminating organ, such as the liver, will be cleared from the body can be helpful. This process will proceed so that the faster the drug is delivered to the eliminating organ, the faster the drug is eliminated from the body.

In contrast, for low extraction ratio drugs, the rate-limiting step is not blood flow; therefore, a change in organ blood flow does not alter clearance. Instead, clearance is affected by the enzyme activity and protein binding, such that an increase in enzyme activity or a decrease in protein binding will increase the drugs'

total clearance. For intermediate extraction ratio drugs, clearance will be dependent on changes in enzyme activity, protein binding, and organ blood flow.

3.2.5 Protein binding

As described above, plasma protein binding can affect the pharmacokinetics of medications. There are multiple issues to consider with regards to protein binding of medications. Some of the plasma proteins are known to be altered both in normal pregnancy as well as pathologic conditions [10]. In normal pregnancy, albumin concentrations decrease on average by approximately 1% at 8 weeks, 10% at 20 weeks, and 13% at 32 weeks [11]. In pregnant patients with pathologic conditions, albumin concentrations can be substantially lower. Changes in albumin concentrations are important for many medications (e.g. phenytoin, valproic acid, carbamazepine). Other plasma proteins such as α-1-acid glycoprotein are involved in binding of drugs like betamethasone, bupivacaine, lopinavir, and lidocaine. Plasma α-1-acid glycoprotein has been reported to be 52% lower in late pregnancy (30–36 weeks' gestation) than postpartum (2 to 13 weeks) [12]. In addition, some agents (e.g. cyclosporine, tacrolimus) concentrate within the red blood cells. For these agents, binding might be altered as a result of anemia during pregnancy. Hematocrits are known to fall during normal pregnancy by 2% at 8 weeks and 4% at 20–32 weeks [11]. Some medications, disease states or conditions during pregnancy can lead to severe anemia, which would be expected to have a much greater effect on binding of these medications.

Drug binding is important for many reasons. The first reason is that the unbound drug is in equilibrium with the site of action and is therefore considered the active moiety as well as being able to cross membranes including the placenta. Unbound drug will cause not only beneficial effects, but also potentially toxic effects. For drugs that are highly bound to albumin, such as phenytoin, these changes in albumin during pregnancy can be associated with alterations in protein binding. Yerby et al. reported a significant increase in the percent of unbound phenytoin during the second and third trimesters of pregnancy as well as labor and delivery as compared to the pre-pregnancy state [13]. This is particularly important clinically because phenytoin is a highly protein bound drug with a narrow therapeutic range, which undergoes therapeutic drug monitoring.

The second reason is that understanding protein binding is critical in the interpretation of total drug concentrations. For phenytoin, when interpreting total drug concentrations, knowing

whether protein binding has been altered or not is critical. Figure 3.3A illustrates that the total concentration for the drug in plasma is measured to be 10, and the unbound concentration is 1. In contrast, in Figure 3.3B the total drug concentration is 5, but the unbound concentration is still 1. In this example, although the total concentration is reduced in half, since the unbound concentration is still the same, no dosage adjustment should be made clinically because the active form of the drug (unbound concentration) is the same. This would be expected to occur if there was a change in protein binding and no change in enzyme activity, leading to a change in total clearance, but no change in unbound clearance. This scenario can occur with phenytoin, in which the total drug concentration is lower but no dosage adjustment is needed because the unbound concentration has not changed.

An alternate situation could occur in which there is no change in total clearance, but a change in protein binding, leading to no change in total drug concentration, but an increase in unbound drug concentration and toxicity. So it is critical in the case of highly bound drugs with narrow therapeutic ranges either to measure the unbound concentration or to mathematically account for the changes in protein binding if total concentrations are measured, such as in pregnant patients with low albumin concentrations. If protein binding is not accounted for and the total drug concentration is measured in a patient with an increase in the fraction unbound, when there is no change in unbound clearance, the

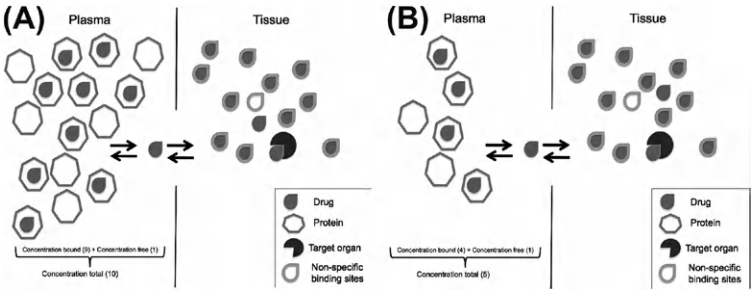

Figure 3.3 **A:** Drug with a total plasma concentration of 10, unbound concentration of 1, and bound concentration of 9. It is the unbound drug that is in equilibrium with the bound drug and is available to cross membranes and get to the site of action. **B:** Drug with a total plasma concentration of 5, unbound concentration of 1, and bound concentration of 4. Although the total drug concentrations are 50% in B compared to the example in A, in both cases, the unbound or active form of the drug are the same. A and B are adapted with permission from figures included in reference (4).

total concentration will be lower but the dosage should not be adjusted. If the clinician does not account for the altered protein binding and increases the dose, the patient might develop drug toxicity.

The physiologic changes that occur during pregnancy can translate into changes in multiple pharmacokinetic parameters that can alter the interpretation of drug concentrations. For example, you often have changes in both protein binding and unbound clearance during pregnancy, as is the case with phenytoin. These patients require consideration of both factors in interpreting the implications of total phenytoin concentrations. It is important to note that not all highly protein bound drugs have increased percent unbound during pregnancy. Some highly protein bound drugs such as midazolam and glyburide have little to no change in protein binding during pregnancy, but significant changes in their clearance [10, 14].

3.2.6 Organ blood flow

Changes in hepatic and renal blood flows can alter drug clearance. As described above, changes in organ blood flow are particularly important for high extraction ratio drugs. During pregnancy, cardiac output is markedly increased, which potentially can increase organ blood flow. On average, during normal pregnancies, cardiac output has been reported to be 35% increased in the second trimester and 40% increased in the third trimester as compared to postpartum [15]. One would suspect that the increased cardiac output during pregnancy may result in changes in hepatic blood flow. In non-septic critically ill patients, there is a good correlation ($r=0.92$) between cardiac output and effective hepatic blood flow [16]. In an animal model of reduced cardiac output, there was an associated decrease in portal venous flow [17]. Unfortunately, there is limited information available evaluating the effects of pregnancy on hepatic blood flow. Nakai et al. [18] studied the effects of pregnancy on hepatic arterial and portal venous blood flows during the first trimester of pregnancy ($n=13$), second trimester ($n=25$), third trimester ($n=29$), and in non-pregnant women ($n=22$). They found an increase in total liver blood flow (2.98 ± 1.13 L/min, $p<0.05$) and portal vein blood flow (1.92 ± 0.83 L/min, $p<0.05$) during the third trimester of pregnancy as compared to the non-pregnant women (1.82 ± 0.63 L/min and 1.25 ± 0.46 L/min, respectively). Rudolf et al. [19] reported indocyanine-green clearance in 16 women with hyperemesis gravidarum with all but one subject within the upper limit of normal. Robson et al. [20] found no change in hepatic blood flow in 12

women at 12–14 weeks', 24–26 weeks', and 36–38 weeks' gestation as compared to 10–12 weeks after delivery. Probst et al. [21] conducted a study in seven healthy pregnant women during labor and delivery and compared them to non-pregnant controls. They found that hepatic blood flow was decreased to 70% of the control value during labor. All of the studies were underpowered and in most cases did not have the pregnant women serve as their own control. At this point, it is unclear whether hepatic blood flow is increased or unchanged during pregnancy.

In contrast, pregnancy is associated with increased renal filtration, creatinine clearance, and renal clearance of drugs [3, 10, 22, 23]. During normal pregnancy, effective renal plasma flow increases on average 50–85%, with a corresponding 50% increase in glomerular filtration rate [24, 25]. Because the estimated tubular extraction ratio for metformin is moderately high, the gestational changes in the metformin's net secretory clearance can in part be explained by enhanced renal plasma flow [26].

3.2.7 Intrinsic clearance

The intrinsic clearance generally refers to the liver's inherent ability to metabolize drug. It is a term used to describe enzyme activity and is independent of protein binding and hepatic blood flow.

3.2.8 Metabolism

Drug metabolism is the conversion of one chemical structure to another. The formation of metabolites often occurs via drug metabolizing enzymes. There are many drug metabolizing enzymes involved in both phase I (e.g. CYP3A4, CYP3A5, CYP2D6, CYP1A1, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP2A6, CYP2B6, esterases, epoxide hydrolase, dihydropyrimidine dehydrogenase, alcohol dehydrogenase) and phase II (e.g. UDP glucuronyltransferase, sulfotransferase, methyltransferase, N-acetyltransferase, catechol-O-methyltransferase, thiopurine S-methyltransferase, histamine methyltransferase, glutathione S-transferase) metabolism. Phase I metabolism usually precedes phase II metabolism, but not always. Phase I reactions typically include: oxidation, reduction, hydrolysis, cyclization and decyclization reactions. Phase II reactions involve conjugation with glucuronic acid, sulfate, glutathione or amino acids. Occasionally, there is back conversion of metabolites to the parent compound. For some medications that are administered as inactive compounds (prodrugs), metabolism is necessary to convert the drug to active compound.

As described above, many different drug metabolizing enzymes exist. The enzyme involved in the metabolism of a drug is dependent on the chemical structure of the agent. For some medications, only one enzyme is involved in the metabolism. For other drugs, multiple enzymes with differing affinities are involved in the formation of the metabolites. One method that has been used to evaluate the effects of pregnancy on drug metabolizing enzymes is to use probe substrates as markers for enzyme activity. A probe substrate is a drug that is primarily metabolized by a single enzyme. The drug is administered and a pharmacokinetic study is completed. From this, drug clearance, urinary excretion of metabolite, metabolite formation clearance, area under the concentration–time curve or metabolite to parent concentration ratio are used as surrogate markers for enzyme activity. The discussion below will describe the effects of pregnancy on key drug metabolizing enzymes.

3.2.8.1 CYP3A

CYP3A is responsible for the metabolism of more drugs than any other P450 enzyme. Examples of CYP3A substrates can be found in Table 3.1. Midazolam is one of the "gold standard" probes for CYP3A activity. We conducted a study evaluating the effect of pregnancy on CYP3A activity utilizing midazolam as the probe drug. Mean midazolam area under the concentration–time curve and maximum concentration were markedly lower during pregnancy than postpartum. This corresponded to an average of 108% increase in midazolam apparent oral clearance and 123% increase in 1′-hydroxymidazolam formation clearance during pregnancy as compared to postpartum. Apparent oral unbound midazolam clearance and unbound 1′-hydroxymidazolam formation clearance were on average 86% and 99% higher, respectively, in pregnancy than postpartum [10]. Other CYP3A substrates (dextromethorphan N-demethylation, nelfinavir, indinavir) have also been studied during pregnancy. N-demethylation of oral dextromethorphan was increased by 35–38% during pregnancy [27]. Similarly, nelfinavir was reported to have a 25–33% increase in apparent oral clearance in pregnancy [28, 29]. Interestingly, indinavir has an approximately three-fold lower average AUC in pregnancy than postpartum [30]. These data are consistent with increased CYP3A activity during pregnancy as compared to the non-pregnant state.

Because CYP3A is involved in the metabolism of many medications, this finding has clinical implications for medication dosages during pregnancy. In particular, CYP3A substrates with narrow therapeutic ranges may fall below effective concentrations during

Table 3.1 Cytochrome P450 substrate examples

CYP3A	CYP2D6	CYP2C9	CYP2C19	CYP1A2
Alfentanil	Alprenolol	Diclofenac	Citalopram	Caffeine
Alprazolam	Amitriptyline	Flubiprofen	Clopidogrel	Clozapine
Amlodipine	Clomipramine	Glipizide	Escitalopram	Lidocaine
Amprenavir	Codeine	Glyburide	Esomeprazole	Olanzapine
Buspirone	Debrisoquine	Ibuprofen	Mephenytoin	Ondansetron
Chlorpheniramine	Dextromethorphan	Losartan	Omeprazole	Ramelteon
Citalopram	Doxepin	Naproxen	Proguanil	Ropivacaine
Cyclosporine	Flecainide	Omeprazole	Sertraline	Theophylline
Dapsone	Fluoxetine	Phenytoin		Triamterene
Diltiazem	Fluvoxamine	Piroxicam		
Efavirenz	Haloperidol	Sulfamethoxazole		
Erythromycin	Hydrocodone	Tolbutamide		
Felodipine	Imipramine	Voriconazole		
Fentanyl	Metoprolol	Warfarin		
Indinavir	Mexiletine			
Isradipine	Nortriptyline			
Itraconazole	Paroxetine			
Lidocaine	Promethazine			
Loratidine	Propafenone			
Methadone	Propranolol			
Midazolam	Resperidone			
Nelfinavir	Thioridazine			
Nicardipine	Tolterodine			
Nifedipine	Venlafaxine			
Oxycodone				
Simvastatin				
Sirolimus				
Tacrolimus				
Zolpidem				

pregnancy if dosage adjustments are not made. When CYP3A substrates are initiated during pregnancy and titrated to response, dosage reductions might be needed postpartum to avoid toxicity.

3.2.8.2 CYP2D6

CYP2D6 is responsible for the metabolism of the second highest number of drugs metabolized by P450 enzymes. Substrates for CYP2D6 can be found in Table 3.1. CYP2D6 is a particularly challenging enzyme to understand and study because of its genetic polymorphism. Genetic variation for this enzyme can result in some patients having no enzyme, some having a low amount of enzyme activity with only one active allele, some having two active alleles, and some having duplicate genes. Clinically, these

genetic differences result in poor, extensive, and ultra metabolizers for CYP2D6 substrates. Interestingly, CYP2D6 is not an inducible enzyme by known, classic mechanisms for enzyme induction. So the apparent increase in CYP2D6 activity described below is surprising and the mechanism by which it occurs is unknown.

Metoprolol is the "gold standard" probe for CYP2D6 activity. In a small study, oral metoprolol AUC was reported to be two- to four-fold lower during pregnancy than in the non-pregnant population [1, 2]. Other CYP2D6 substrates have also been studied during pregnancy. For example, dextromethorphan is primarily a CYP2D6 substrate (although its N-demethylation occurs via CYP3A as described above). Utilizing dextromethorphan as a CYP2D6 probe, Tracy et al. [27] reported an increase in CYP2D6 activity by ~25% at 14–18 weeks' gestation, ~35% at 24–28 weeks' gestation, and ~50% at 36–40 weeks' gestation. In addition, we have found clonidine to primarily be a CYP2D6 substrate [31]. The mean apparent oral clearance of clonidine is approximately 80% higher in pregnant women compared with the non-pregnant population. Of note, in the non-pregnant population, clonidine is primarily renally eliminated. However, only 36% of the clonidine was excreted unchanged in the urine in pregnancy compared with 59% in the non-pregnant population [32–35]. Interestingly, the increase in CYP2D6 activity during pregnancy is so great that the major pathway for elimination for clonidine switched from primarily renal to primarily metabolic.

3.2.8.3 CYP2C9

CYP2C9 is involved in the elimination of approximately 10% of the metabolized drugs from the list of top 100 drugs by US sales. Substrates for CYP2C9 can be found in Table 3.1. CYP2C9 is the primary metabolic pathway for phenytoin elimination. Because of the high protein binding for phenytoin, when considering phenytoin as a probe for CYP2C9, utilizing free phenytoin clearance is important given the known changes in phenytoin protein binding during pregnancy. CYP2C9 activity as measured by free phenytoin clearance is increased ~1.5-fold during all three trimesters of pregnancy as compared to the pre-pregnant state [13].

Glyburide is another agent that is metabolized by CYP2C9, although CYP3A and CYP2C19 are also involved in its metabolism *in vitro* [36–38]. *In vivo*, glyburide appears to be a CYP2C9 substrate in the non-pregnant population [39–42]. At equivalent doses, glyburide plasma concentrations were ~50% lower in pregnant compared to non-pregnant women [14]. The large gestational increase in unbound glyburide CL/F and unbound formation clearance of the primary metabolite 4-trans OH-glyburide

(>two-fold increase) suggest that higher dosages may be needed during pregnancy. The gestational increase in unbound glyburide CL/F most likely reflects induction of CP2C9 and CYP3A, since these activities have been previously shown to be increased (and CYP2C19 activity decreased) during pregnancy [10, 13, 43].

3.2.8.4 CYP1A2

CYP1A2 is involved in the metabolism of fewer drugs than the enzymes previously discussed. However, some agents that are substrates for CYP1A2 are being used more and more frequently during pregnancy, such as ondansetron (Table 3.1). A commonly used probe substrate for CYP1A2 activity is caffeine. The activity of CYP1A2 as determined by caffeine clearance is reported to be decreased by approximately 30% at 14–18 weeks' gestation, 50% at 24–28 weeks' gestation, and 70% at 36–40 weeks' gestation [27]. The apparent decrease in CYP1A2 activity potentially could result in increased toxicity for CYP1A2 substrates. This is in contrast to the effect seen with CYP3A, CYP2D6, and CYP2C9, which all have markedly increased activities during pregnancy and potentially will result in decreased drug efficacy.

3.2.8.5 CYP2C19

Substrates for CYP2C19 can be found in Table 3.1. Similar to CYP1A2, CYP2C19 activity appears to be inhibited during pregnancy. The ratio of proguanil to cycloguanil has been utilized as a probe for CYP2C19 activity. Although no significant changes are seen in CYP2C19 activity during pregnancy in poor metabolizers, in extensive metabolizers there is a doubling in the plasma ratio of proguanil to cycloguanil 6 hours after dosing when comparing women in their third trimester of pregnancy to women 2 months postpartum, suggesting a decrease in CYP2C19 activity in late pregnancy [43]. In light of these data, monitoring for medication toxicity and perhaps lower dosages for CYP2C19 substrates during pregnancy warrants consideration.

3.2.8.6 UGT1A4

UDP glucuronyltransferase 1A4 (UGT1A4) is a non-P450 enzyme involved in phase 2 metabolism. UGT1A4 metabolizes agents to glucuronide conjugates. There are many substrates for UGT1A4 such as amitriptyline, doxepin, imipramine, lamotrigine, and promethazine [44, 45]. The increase in UGT1A4 activity starts in the first trimester of pregnancy and is reported to return to pre-pregnancy baseline by 2–3 weeks postpartum. The clearance of lamotrigine has been reported to increase by 65% during pregnancy [46]. The increase in clearance translates to lower concentrations during pregnancy and

potential for a decrease in efficacy. Consistent with this, an increase in seizure frequency during pregnancy along with a decrease in lamotrigine concentration to dose ratio by ~50% between 11 weeks' gestation and term has been reported [47].

3.2.9 Renal

Almost one-third of the medication on the top 100 drugs list by US sales is primarily eliminated by the kidneys. During normal pregnancy, creatinine clearance increases by 45% at 9 weeks' gestation, and peaks in the mid-second trimester at 150–160% of non-pregnant values. In some women, clearances will decline over the last 6 weeks of pregnancy. Occasionally, creatinine clearance will return to the non-pregnant state over the last 3 weeks of pregnancy [22, 23]. Pregnancy has been reported to induce changes in tubular secretion of endogenous compounds such as glucose and amino acids [24]. Understanding and accounting for changes in kidney function during pregnancy is important for optimizing dosage for renally eliminated medications.

3.2.9.1 Filtration

Changes in renal filtration as measured by creatinine clearance during pregnancy have been associated with changes in the renal clearance of many medications [3, 10, 26, 48]. In some, but not all, cases these changes will require dosage adjustments during pregnancy. For example, changes in digoxin concentrations during pregnancy often require dosage adjustments to maintain therapeutic concentrations. On average, digoxin renal clearance increases 61% during pregnancy compared to 6–10 weeks postpartum [10]. There is a good correlation ($r=0.8$) between creatinine clearance and digoxin renal clearance [10]. Even though digoxin also has an active transport component to its renal elimination, the change in creatinine clearance appears to be a good surrogate marker for the expected change in digoxin renal clearance during pregnancy due to the large fraction of digoxin renal clearance accounted for by filtration compared to net secretion [10].

Metformin is eliminated almost entirely unchanged in the urine. In mid- and late pregnancy, metformin renal clearance increases on average by 49 and 29%, respectively, compared to 3–4 months postpartum. The change in renal clearance parallels the 29 and 21% increase in creatinine clearance during mid- and late pregnancy reported in the same study [26]. There are currently not enough data to determine if dosage increases for metformin are needed during pregnancy.

Atenolol is another drug that is primarily eliminated unchanged in the urine. Pregnancy as compared to 3 months postpartum results in significant increases in creatinine clearance, 42 and 50% in the second and third trimesters, respectively, and in atenolol renal clearance, 38 and 36% in the second and third trimesters, respectively. There is a very good correlation (r=0.7) between creatinine clearance and atenolol renal clearance [3]. However, changes in atenolol renal clearance during pregnancy do not translate into clinically significant changes in apparent oral clearance and therefore dosage adjustments are not necessary based on pharmacokinetic changes. However, changes in hemodynamics and pharmacodynamics over the course of gestation may result in the need for dosage adjustments for atenolol during pregnancy.

3.2.9.2 Secretion/Reabsorption

P-glycoprotein and organic anion transporter polypeptides

Digoxin has been considered the "gold standard" probe for P-glycoprotein activity because it mediates secretion of digoxin across the apical membrane of the renal tubular epithelium [49, 50]. However, other renal transporters are also involved in the net secretion of digoxin. There is evidence that digoxin is a substrate for organic anion transporter polypeptides (OATPs) [51, 52]. Human OATP4C1 (SLCO4C1) plays a primary role in the transport of digoxin on the basolateral membrane of the kidney [53]. Thus, digoxin renal tubular secretion appears to be a serial transport process mediated by P-glycoprotein and OATP. Although glomerular filtration rate increases during pregnancy, this increase does not completely explain the increased renal clearance of digoxin. Digoxin secretion clearance was 120% higher during pregnancy as compared to postpartum. Unbound digoxin secretion clearance was higher (on average 107%) during pregnancy than postpartum [10]. The doubling of digoxin net renal secretion clearance is consistent with an increase in P-glycoprotein renal activity, but may also be explained by an increase in renal OATP activity during pregnancy.

Organic anionic transporter, oligopeptide transporters

The transporters involved in renal transport of amoxicillin are still being worked out. *In vivo* studies with amoxicillin and probenecid (inhibitor of the renal organic anion transport system) have shown that the renal clearance of amoxicillin is significantly reduced by probenecid, suggesting that amoxicillin is a substrate for an organic anion transporter [54]. The oligopeptide transporters hPepT1 and hPepT2 are located on the apical membrane of the proximal tubule and are involved in reabsorption of endogenous

peptides [55]. Amoxicillin is an inhibitor and substrate for hPepT2 transport with a lower affinity for hPepT1 [56]. In both the second and third trimesters of pregnancy, the renal clearance and net renal secretion of amoxicillin are increased by more than 60 and 50%, respectively [48]. Renal secretion makes up more than half of the renal clearance for amoxicillin. The change in net renal secretion clearance may be a result of increased renal secretion, inhibition of reabsorption or both.

Organic cation transporters, multidrug and toxic compound extrusion transporter, and plasma monoamine transporter

Metformin is a substrate for OCTs, including OCT1, OCT2, the multidrug and toxic compound extrusion transporter (MATE) [57], and the plasma membrane monoamine transporter (PMAT) [58]. In humans, OCT2 plays an important role in metformin renal clearance [59–61]. Several studies *in vitro* and in animal species suggest that Oct2 expression and activity in the kidney can be regulated by the steroid hormones [62–64]. Metformin secretion clearance was on average 45 and 38% higher in mid- and late pregnancy than postpartum [26]. Metformin renal clearance correlates well with creatinine clearance (r=0.8), but even better with its net tubular secretion clearance (r=0.97), which is not surprising given metformin's high secretory clearance [26]. The increase in metformin net secretory clearance could in part be a result of upregulation in the renal tubular transport (i.e. OCT2 activity). Further research is necessary to determine which transporters are affected by pregnancy and the mechanism underlying these changes.

pH-dependent changes in secretion and reabsorption

Although the tendency is to assume that all drugs that are predominantly eliminated by the kidneys in the non-pregnant population will remain as such in the pregnant population, this is not always the case. For example, clonidine is a drug that is ~65% eliminated unchanged in the urine in the non-pregnant population with dosage adjustment recommendations for patients with renal disease. Therefore, it is reasonable to assume that the increase in creatinine clearance expected during pregnancy would increase the renal clearance of clonidine. However, even though the patients in our study had an increase in creatinine clearance during pregnancy, there was no change in clonidine renal clearance and a poor correlation (r=0.26) between clonidine renal clearance and creatinine clearance. In fact, the primary pathway for elimination of clonidine during pregnancy switches from renal to metabolic. The explanation for the discrepancy between changes in creatinine clearance and clonidine renal clearance during

pregnancy is related to the chemical properties of clonidine. Clonidine's pK_a is 8.05, which resulted in a strong correlation ($r=0.82$, $p<0.001$) between clonidine renal clearance, corrected for GFR, and urine pH (range 5.8–7.5) [32]. This example is a reminder that it is difficult to predict the effects of pregnancy on the pharmacokinetics of medications and that each medication requires evaluation.

3.2.10 Volume of distribution

Volume of distribution is not a physical space, but rather an apparent one. Volume of distribution is the apparent volume needed to account for the total amount of drug in the body if the drug was evenly distributed throughout the body and in the same concentration as the site of sample collection such as peripheral venous plasma. Some drugs (e.g. tolbutamide, phenytoin, gentamicin, warfarin) are known to have small volumes of distribution (0.1–1 L/kg) while others (e.g. meperidine, propranolol, digoxin) are known to have large volumes of distribution (1–10 L/kg). The volume of distribution for a drug affects the difference between peak and trough concentrations at steady state or maximum concentrations for single intravenous bolus dosing. The volume of distribution can be used to determine the loading dose needed to achieve a certain concentration.

There are many physiologic changes that occur during pregnancy that can result in altered volume of distribution for medications. For example, the recommended total weight gain during a singleton pregnancy depends on the BMI and stature of the pregnant woman, but ranges from 6 to 18 kg. Despite the recommendations, many women will exceed these weight gain guidelines. Of the weight gained, approximately 62% will be water, 30% will be fat, and 8% will be protein. Blood volume typically increases 30–45% and peaks between 28 and 34 weeks' gestation. Total body water increases 6–8 liters during pregnancy and peaks at term [65]. Increases in the volume of distribution for a medication will not alter the average steady state concentration, but will result in lower peak and higher trough concentrations. Apparent volume of distribution is dependent on the drug's lipid or water solubility, plasma protein binding as well as tissue binding. Metformin has a larger apparent oral volume of distribution during pregnancy than in women 3–4 months postpartum [26].

3.2.11 Half-life

Half-life is the time it takes for the drug concentration to be reduced in half and is useful in determining dosing frequency. Half-life is dependent on both clearance and volume of

distribution, such that a decrease in clearance, as might be seen with a CYP1A2 or CYP2C19 substrate, or an increase in volume of distribution will prolong the half-life and lead to a longer dosage interval. Medications with increased clearance (e.g. CYP3A, CYP2D6 or CYP2C9 substrates or those eliminated by the kidneys) or decreased volume of distribution will have shorter half-lives and require more frequent dosing. Since half-life is dependent on both clearance and volume of distribution, if there is a similar increase in both clearance and volume, there will be no change in the half-life for the drug as is the case for midazolam and metoprolol [1, 2, 10]. Although the changes in renal function during pregnancy are small relative to the magnitude of change seen with some of the hepatic enzymes, altered renal function can change the pharmacokinetics of some medications. We found that both renally eliminated drugs, atenolol and amoxicillin, have shorter half-lives during the second and third trimesters of pregnancy compared to the same women 3 months postpartum, although these changes were relatively small [3, 48]. In contrast, metformin, which is also eliminated by the kidneys, has a longer half-life in the second trimester of pregnancy than women 3–4 months postpartum, reflecting the increase in volume of distribution seen during pregnancy [26].

3.3 Summary

There is a tremendous amount of variability in patient response to medications during pregnancy. In part, this variability can be explained by changes in pharmacokinetics. The medication's chemical and pharmacokinetic characteristics influence the type of effect pregnancy can have on drug handling and response. Changes in protein binding are most important for highly protein bound drugs and should be taken into account when interpreting total drug concentrations. Hepatic blood flow will affect the hepatic clearance of high extraction ratio drugs. Medications that are eliminated by the kidneys as well as those metabolized by CYP3A, CYP2D6, CYP2C9, and UGT are likely to undergo increased clearance during pregnancy. Those metabolized by CYP1A2 and CYP2C19 might have decreased clearance during pregnancy. The physiologic changes that occur during pregnancy can have significant impact on medication pharmacokinetics, dosage, and selection. Taking into account the pharmacokinetic changes that occur during pregnancy will help to minimize the variability in patient response. This approach is particularly

important for medications with narrow therapeutic ranges. Pharmacokinetic changes should be taken as only one component in determining optimum medication selection and dosage.

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Medications and the Breastfeeding Mother

4

Cheston M. Berlin, Jr.

4.1 Medication use by the breastfeeding mother

Mothers may need medication both during and after pregnancy. In both cases it is important not only to protect the infant, but also to provide the mother with necessary drug treatment. The infant may be born having been exposed to maternal medication during gestation. It is important to remember, in addition to drug exposure of the infant during breastfeeding, that previous exposure during pregnancy may potentiate any adverse effects during lactation. This would

especially be true in the immediate postnatal period, but for some drugs, the window of adverse reactions in the infant may be longer (e.g. antidepressants).

4.2 Clinical pharmacology of drug transfer into breast milk

The determining factors for the transport of drugs from maternal circulation to the alveolar lumen in the mammary cell are: [1] molecular weight, [2] binding to maternal plasma proteins, [3] lipid solubility, and [4] degree of ionization. Drugs which are transferred most rapidly and/or in the highest amount are those with high lipid solubility, no electrical charge, low molecular weight, and low or no binding to maternal plasma proteins. There are four diffusion mechanisms for drug transfer into the mammary cell alveolar lumen: transcellular, intercellular, passive and inophore (transfer of polar compounds bound to carrier proteins) [1]. Transcellular diffusion probably accounts for most drug transfer. The intercellular diffusion route, which avoids the interior of the cell, may account for the appearance in milk of high molecular weight compounds such as immunoglobulins (from maternal plasma) and monoclonal antibody drugs such as etanercept (Enbrel®, molecular weight 52,000). High molecular weight compounds do appear in milk. Most obvious are antibodies from maternal plasma. Many of the newer pharmacological agents are high molecular weight entities such as monoclonal antibodies. For drugs like etanercept, the amount appearing in milk is extremely small (2–5 ng/mL) compared to the maternal serum level of 1450 to 2000 ng/mL [2]. Such a small amount of a protein is most likely pharmacologically inactive both because of the extremely small dose, and also because of lack of absorption from the infant's gastrointestinal tract. Because virtually all drugs of a molecular weight below 200 or 300 daltons will cross into milk, the dose that the child receives (concentration × volume) is usually pharmacologically insignificant. For most drugs, less than 1–2% of the maternal dose is potentially available to be excreted into breast milk [3].

4.3 During delivery

The obvious concern in this period of time is the type and anesthesia/analgesia that the mother may have received. This drug

exposure may delay the onset of lactogenesis, may affect the mother's mentation and ability to nurse, and the infant may show effects from transplacental transfer that interfere with latch and ingestion. An important concept is that regardless of the type of anesthesia and/or analgesia used after delivery, the amount of any agent potentially transferred to the infant would be less than the amount transferred during labor and delivery via the placenta.

4.4 General anesthesia

4.4.1 Volatile anesthetic agents

There are very little data on the concentration of these compounds in human milk. This is due to rapid washout after administration and by the time the mother wakens to nurse her infant, her plasma levels are very low or absent.

4.4.1.1 Halothane

There are no published reports measuring the amount of halothane in milk after general anesthesia to the mother. It has been reported that patients can exhale measurable amounts of halothane for 11 to 20 days after anesthesia [4]. A female anesthesiologist had levels of 2 ppm of halothane in her milk after working in an operating room for up to 5 hours [5]. Because of this observation, it is reasonable to assume that it would appear in the milk of a mother administered halothane for a cesarean section or any post-delivery complication.

4.4.1.2 Desflurane and sevoflurane

These two inhalation anesthetic agents are highly fluorinated and not very soluble in fat and other peripheral tissues. Thus induction and recovery are rapid. Although there are no reports of measurement of these two compounds in milk, the levels are very likely to be low or absent because of very low fat solubility.

4.4.2 Intravenous anesthetic agents

4.4.2.1 Ketamine

There are no reports of the measurement of ketamine in the milk of postpartum women. The half-life of ketamine is about 3 hours, so that permitting a mother to breastfeed several

hours after delivery would expose the infant to extremely small amounts of this drug.

4.4.2.2 Propofol

This drug is a lipid and must be administered to the mother via a lipid emulsion. The half-life of the drug is about 2 hours. The amounts found in milks are very low – usually 1 mg/L of milk or less [6]. Such low amounts would be unlikely to be absorbed by the nursing infant.

4.4.2.3 Etomidate

Concentrations of etomidate in milk are very low (less than 1 mg/L) and absent 4 hours after administration. Maternal half-life is about 3 hours [7].

4.4.2.4 Thiopental

Concentrations of thiopental in milk are usually 2 mg/dL or less depending on the time of sampling after intravenous administration to the mother. Serum concentrations usually decline to less than 1 mg/dL after 4 hours from the last dose [7]. One study compared the excretion of thiopental in both breastfed and non-breastfed infants and found no difference in the amount excreted [8]. It is unlikely that the breastfed infant would receive a significant amount of thiopental by the time lactation is established. This drug has been the subject of much debate because of its use as a component in lethal injection for capital punishment. It has not been manufactured in the USA since 2009 and its importation from foreign suppliers is a source of litigation.

4.4.3 A general statement

It is interesting to speculate on whether initial difficulty in breastfeeding (especially poor latch) may be due to residual general anesthetics (either inhalation or intravenous) in breast milk. It is safe for mother (and infant) to start or resume breastfeeding as soon as she emerges from a general anesthetic agent [9, 10].

4.5 Epidural anesthesia

The usual anesthetic agents employed in epidural anesthesia are bupivacaine or ropivacaine. The opioid fentanyl is frequently

added to the injection fluid. These local anesthetic agents provide rapid onset of pain relief and when used in the usual concentrations do not cause significant loss of muscle power. They are both highly bound to maternal plasma protein and hence transfer to milk is limited. Two recent, prospective, random allocated studies did not show any appreciable difference in breastfeeding between groups receiving epidural anesthesia with a local anesthetic and/or with fentanyl [11, 12]. There was a suggestion that women receiving only meperidine did have a lower rate of successful breastfeeding. Chang and Heaman reported on 53 women receiving either ropivacaine or bupivacaine for an average infusion time of 3.5 hours. There was no effect on neurobehavior including breastfeeding when compared to a group that received no anesthesia [13]. Both of these local anesthetic agents are poorly, if at all, absorbed from the gastrointestinal tract, so that even if a small amount was present in milk, the infant should not be affected. Rosen and Lawrence studied 83 mother–child pairs and found no difference between breastfed and bottle-fed infants on the ability to feed or initial weight loss [14].

4.6 Galactogogues

Several drugs and many dietary supplements have been tried to improve lactation both in initiation of milk formation and increase in milk supply. There are no studies which can confirm that any of these substances are effective [15, 16]. Mothers should be advised not to use dietary supplements as both their purity and efficacy are not established. There is no substitute for lactation support by the physician, the hospital, and a lactation consultant.

4.7 Immediate postpartum period

During the immediate postpartum period, the major concerns for drug administration to the mother are: [1] pain relief, [2] resumption of medications for chronic conditions that may have been interrupted by pregnancy, and [3] treatment of newly diagnosed conditions.

4.8 Pain

For immediate postpartum pain relief (cesarean section, episiotomy), acetaminophen or a nonsteroidal anti-inflammatory drug may be sufficient if appropriate dosing is used. There have been recent concerns over the use of higher doses of acetaminophen for chronic therapy particularly when associated with the use of alcoholic beverages. Should acetaminophen or NSAIDs (nonsteroidal anti-inflammatory drugs) provide insufficient pain control, a switch to a narcotic would be appropriate.

4.8.1 Morphine

Regardless of route of administration to the mother (oral, intravenous, epidural, intrathecal) the amount of morphine and its active metabolite, morphine-6-glucuronide, transferred in milk is very small and unlikely to cause symptoms in the infant except possibly in the very young term or premature infant. As an example, mothers given 4 mg of morphine epidurally had peak milk levels of 82 mcg/L. If the morphine was given parenterally (5–15 mg), the peak level was 500 mcg/L [17]. The half-life of morphine is about 3 hours (adult), so if the mother waited 3 hours after any dose of morphine, the level in milk would be quite low and most likely have no clinical effect.

4.8.2 Codeine

The active metabolites of codeine are morphine and the morphine metabolite morphine-6-glucuronide. The enzyme systems responsible for this metabolism are: CYP2D for codeine and UGT2B7 for morphine, codeine-6-gluronide, and morphine-6-glucuronide. Both of these systems are subject to genetic variation. Some patients are ultrarapid metabolizers of codeine and produce higher levels of morphine and active metabolites in a very short period of time after administration. These increased levels will produce increased side effects, especially drowsiness and central nervous system depression in both the mother and nursing child [18, 19]. One death has been reported from morphine poisoning [18]. It would be prudent to avoid using codeine in the immediate postpartum period and perhaps never in breastfeeding mothers regardless of the infant's age. Older infants, especially those receiving solid foods in addition to breast milk, may not have significant symptoms even though their mothers are ultrafast metabolizers [19].

4.8.3 Meperidine

Meperidine does appear in milk and in infant plasma after the administration of the drug for cesarean section and also for postpartum pain management [20, 21]. The infant's plasma level was found to be 1.4% of the maternal plasma level [20]. Meperidine given postpartum for pain control does produce decreased alertness in 3- to 4-day-old infants compared to equivalent doses of morphine [21, 22]. Hodgkinson et al. using the Early Neonatal Neurobehavioral Scale showed a suppression of most of the 13 items (including alertness, rooting, and sucking) on the first and second postpartum days. The effects were dose related [23]. Morphine appears to be the preferred opioid for intra- and postpartum pain.

4.8.4 Hydrocodone

Hydrocodone is metabolized to the more active metabolite hydromorphone and both are excreted into breast milk. If the daily dosage is limited to 30 mg per day, it is unlikely to affect the established nursing infant [24, 25]. The estimated median opiate dose to which the infant might be exposed is 0.7% of the therapeutic dosage for older infants.

There has been much concerned expressed over the potential toxicity of opioids delivered to the infant through breastfeeding. Adverse events are usually associated with high maternal dose in very young infants.

4.9 Methadone

Women who have been on methadone during pregnancy for narcotic addiction should be encouraged to breastfeed and continue to take methadone [26]. Babies who nurse from mothers on methadone have both a slower onset and less severe neonatal abstinence syndrome. They also have less need for pharmacological treatment of the abstinence syndrome [27]. Concentrations of methadone are low in breast milk: 21–314 ng/mL [28]. Only about 1–3% of the maternal dose is excreted into milk [29]. These infants will still require very close observation in the hospital and after discharge to monitor possible withdrawal symptoms.

4.10 Resumption of pre-pregnancy medications

With the possible exception of psychotropic drugs, almost all medications for acute and chronic maternal conditions are safe

for the breastfeeding infant. Adverse reactions in the infant to maternal drug administration are very rare and usually confined to infants under the age of 2 months [30, 31]. Anderson et al. found 100 reports of adverse reactions in several database searches from 1966 to 2002 [30]. None were considered definitely related to the drug used, 53 were possibly related, and 47 were probably related. There were three deaths among the 100 infants; one was a sudden infant death syndrome. These reports were before the concern about the use of codeine in mothers of very young infants. Only 4% of the reports were in infants older than 6 months of age. Information on approximately 1000 drugs is on the LactMed website [32] (see below).

4.11 Psycho- and neurotropic drugs

4.11.1 Antidepressants, antipsychotics, anxiolytics, antiepileptics, drugs for attention deficit hyperactivity disorder

These drugs are grouped together because they target the brain; the pharmacodynamic action of these compounds involves alterations of neurotransmitters within the central nervous system. These alterations may be in the amount of neurotransmitter, sensitivity of the receptor on the neuron, or number of active receptors. These drugs include antidepressants, antipsychotics, tranquilizers, antiepilepsy drugs, and drugs to treat attention deficient hyperactivity disorder. These compounds may be transmitted during both pregnancy and lactation. This group of drugs is perhaps the most significant challenge to the physician caring for the mother; she needs the drug or drugs, but what of the effect or effects on the infant? Since they all act by influencing transmitter function and since central nervous system receptors are developing in the fetus and young infant, will there be permanent effects on neurodevelopment? The evidence is far from complete; long-term studies are not available. Limited information suggests that the effect of these compounds on long-term development may not be significant or at the most difficult to measure because of so many variables such as genetic background, and social and economic status [33]. It is impossible to separate drug effect during breastfeeding from effect due to exposure during pregnancy. The important information to be given to the mother is: [1] all of these drugs if measured in breast milk do appear, [2] the amount in milk is very small and frequently the drug does not appear in infant plasma, and [3] long-term studies (over childhood and adolescence) are not available.

It appears that the sensitive period for exposure and adverse effects may be within the first weeks and months.

The antidepressants are of special interest for obstetricians because of the well-known incidence of depression during pregnancy as well as in the postpartum period. As many as 18–20% of women may experience depression either during pregnancy or during the first 3 months after delivery [34, 35]. Most of the antidepressants currently in use are members of the selective serotonin uptake inhibitors (SSRI) class. They all have prolonged half-lives of 15 to 36 hours [36]. Several of the SSRIs also have active metabolites (fluoxetine, sertraline) which may extend pharmacological action for a further 4–16 days. There is a neonatal withdrawal syndrome associated with the use of SSRIs. These symptoms can vary from infant to infant and usually consist of difficulty feeding, jitteriness, tremor, sneezing, and sleep difficulties [37]. Symptoms are usually mild and subside within 2 weeks [38].

4.12 Drugs not to give to the nursing mother postpartum

This list is quite small and would include:

- drugs of abuse (cocaine, heroin);
- several of the beta blocking agents such as atenolol and sotalol. These have a high percentage of maternal dose excreted and symptoms have been reported in the nursing infant [39];
- lithium – significant blood levels (from 11 to 56% of maternal levels) reported in nursing infants [40]. Twenty-four infants reported nursed without difficulty; four infants reported with symptoms (all under 2 months of age) [41];
- amiodarone – 3.5 to 45% of the maternal dose may be excreted in milk [42]. This drug contains 39% iodine and may interrupt thyroid function. The half-life in adults is 100 days [43]. Infant serum levels can be 25% of maternal serum levels [44].

4.13 Oral contraceptives (OCPs)

There have been two concerns with the use of oral contraceptives in the breastfeeding woman: quality and quantity of milk produced.

The quality of milk does not seem to vary between mothers not taking OCPs and mothers taking a variety of OCPs. There have been many studies showing decreased milk supply especially with the older high dose estrogen compounds and especially with starting in the first few weeks after delivery. Progestins seem not to inhibit lactation as much as the estrogen compounds do. The Academy of Breastfeeding Medicine places progestin-only compounds as a second choice for contraception and estrogen contraceptives as the third choice [45]. The first choices are: LAM (Lactational Amenorrhea Method), natural family planning, barrier contraception, and intrauterine devices. Mothers wishing to use LAM should be referred to a physician or lactation consultant for advice on how to use LAM. When used correctly it is 98% effective [46].

4.14 Summary

Important lessons for any drug that may be transferred in breast milk to the infant are: neonates up to 2 weeks of age are particularly susceptible to toxicity; most adverse reports are in infants less than 2 months of age; there is a dose (maternal) response (infant) relationship; there are significant interindividual variations in drug response; and both maternal and infant pharmacogenetics play a critical response in drug toxicity [47].

Finally, precise analytic methods have identified compounds in such extremely small (e.g. nanograms per liter of milk) amounts that it will be difficult to correlate with biological measures.

4.15 Where to find information

The most up-to-date, comprehensive and authoritative information is to be found in LactMed [32]. This is a website of the National Library of Medicine, TOXNET (Toxicology Data Network). Approximately 1000 drugs including herbal preparations are referenced; the information is peer reviewed, evidence based, and updated frequently during each year. LactMed can be accessed with a mobile device. The LactMed app for iPhone/iPod Touch and Android can be downloaded at: http://toxnet.nlm.nih.gov/help/lactmedapp.htm. Another source is Briggs et al. which also offers detailed information about the use of drugs during pregnancy [48].

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Fetal Drug Therapy

Erik Rytting and Mahmoud S. Ahmed

5

5.1 Introduction

When drugs are prescribed during pregnancy, most often the intention is to treat a condition affecting maternal health. Careful attention is placed on the appropriate selection of medication and dose to reduce transplacental drug transport and minimize any consequences of fetal drug exposure. However, this chapter focuses on the administration of drugs intended to treat medical conditions afflicting the fetus, rather than the mother. In order to achieve therapeutic drug concentrations in the fetus, efforts are made to circumvent the placenta's function as a barrier. In this case, it is imperative to reduce maternal exposure to medication that she does not need and which might even adversely affect her well-being.

The first section of this chapter will discuss a number of medical indications for which fetal drug therapy might be warranted. As the focus is on pharmacological therapy, the reader is referred to other sources for details regarding other fetal medical

interventions, such as prenatal repair of myelomeningocele [1], blood transfusions to treat fetal anemia [2], and others [3].

The second part of the chapter will describe strategies for fetal drug delivery, including transplacental transfer following maternal administration, direct fetal injection, gene therapy, stem cell transplantation, and nanomedicine. The chapter will conclude with a brief discussion of the ethics associated with this challenging subject (see also Chapter 8 which discusses the ethics of clinical pharmacology in pregnancy).

5.2 Indications for fetal therapy

Table 5.1 lists some common indications for fetal therapy and details regarding these conditions are provided below (see also Table 5.2). Nevertheless, as this table is not an exhaustive list, this section will identify a number of additional settings where fetal drug therapy may be beneficial.

Among the most common pharmacological interventions for fetal therapy is the administration of antenatal corticosteroids to promote *fetal lung maturation* in anticipation of preterm delivery. Dexamethasone and betamethasone are the most common drugs prescribed for this purpose, which has demonstrated clinically significant reductions in respiratory distress syndrome, neonatal mortality, cerebroventricular hemorrhage, necrotizing enterocolitis, intensive care admission, and systemic infections in the first 48 hours of life [4, 5].

Fetal *cardiac arrhythmias* affect 1% of pregnancies [6]. Although intermittent extrasystoles can be common and may not require

Table 5.1 Examples of indications for fetal drug therapy and medications used

Indication for fetal drug therapy	Medications
Cardiac arrhythmias	Digoxin, flecainide, sotalol
Endocrinological disorders	
Congenital adrenal hyperplasia	Dexamethasone
Fetal thyroid disorders	Levothyroxine
Hematological disorders	
Alloimmune thrombocytopenia	Gamma globulin
Erythrocyte alloimmunization	Anti-D immunoglobulin
Lung maturation	Dexamethasone, betamethasone

Table 5.2 Pharmacokinetic considerations for some medications used in fetal drug therapy (see Table 5.1)

Drug	Typical dosing	Notes	References
Digoxin	0.5 mg bid for two days, then 0.25–0.75 mg/day	Therapeutic concentration 1.0–2.5 ng/mL; fetal/maternal ratio: 0.3–1.3; hydrops reduces placental transfer; substrate for P-glycoprotein	[66–74]
Flecainide	100 mg, tid or qid	Therapeutic concentration 0.2–1.0 mcg/mL; fetal/maternal ratio: 0.5–1.0; crosses placenta even in the presence of hydrops	[66, 73, 75–79]
Sotalol	80–160 mg, bid or tid	Therapeutic concentration 2–7 mcg/mL (atrial flutter); fetal/maternal ratio 1.0 ± 0.5	[66, 78, 80–87]
Dexamethasone (for lung maturation)	6 mg, four intramuscular doses, 12 hours apart	Fetal/maternal ratio ranged from 0.20 (50 min after dose) to 0.44 (after 265 min); a fraction is metabolized in the placenta to the inactive 11-ketosteroid	[88–92]
Betamethasone	12 mg, two intramuscular doses, 24 hours apart	Fetal/maternal ratio: 0.28 ± 0.04; a fraction is metabolized in the placenta to the inactive 11-ketosteroid	[93–97]
Levothyroxine	Case studies report intraamniotic doses ranging from 50–800 mcg (median dose 250 mcg), every 1–4 weeks	Concurrent dose reduction of maternal antithyroid drugs may be necessary; it may be advisable to start with a low dose (150 mcg), then increase if necessary; cordocentesis should be limited	[15, 98–101]
Gamma globulin	1–2 g/kg/week IV, depending on risk	Prednisone is often used in combination	[102]
Anti-D immunoglobulin	1500 IU as a single intramuscular injection at 28 weeks of gestation	A two-dose regimen consisting of either 500 or 1250 IU each at 28 weeks and 34 weeks may be more effective in maintaining sufficient anti-D levels at term	[103–105]
Dexamethasone (for congenital adrenal hyperplasia)	20 mcg/kg/day based on pre-pregnancy body weight, divided in three doses	See notes on dexamethasone above	[11]

treatment, sustained fetal arrhythmias demand vigorous attention because this can lead to hydrops within 48 hours, a condition with poor prognosis [6–9]. Hydrops can impair transplacental transport, thereby necessitating fetal injection of medication [9]. The most common fetal arrhythmias are supraventricular tachycardia, atrial flutter, and severe bradyarrhythmia associated with complete heart block. Drugs used to treat fetal tachycardia include digoxin, flecainide, sotalol, procainimide, propranolol, amiodarone, and adenosine; questions remain regarding the use of steroids and sympathomimetics for bradycardia caused by heart block [7]. Attentive monitoring of response to most antiarrhythmic drugs is needed due to narrow therapeutic margins, and coadministration of digoxin and verapamil may cause fetal death [10]. Maternal side effects to fetal antiarrhythmic therapy include palpitations, second degree atrioventricular block, Wenckebach phenomenon, and hypotension [10].

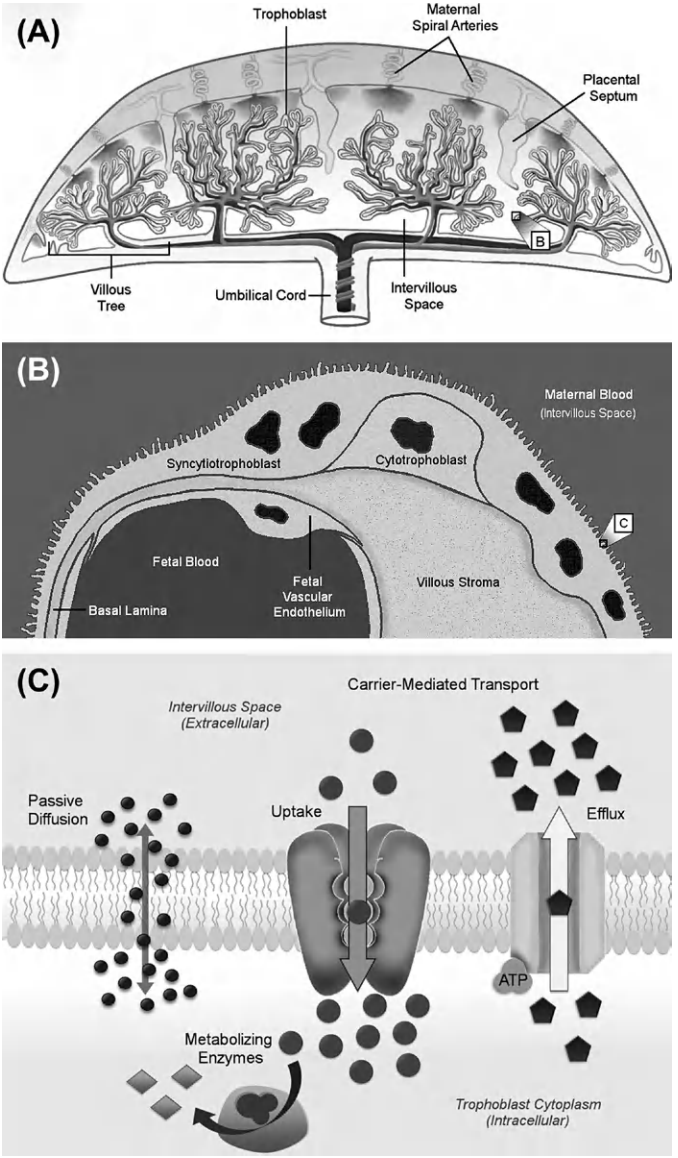
Congenital adrenal hyperplasia is most often due to a 21-hydroxylase deficiency (CYP21A2) [8]. Decreased cortisol production results in excess androgen synthesis, which causes virilization of female genitalia. A survey of 13 countries demonstrated an overall incidence of 1 in 15,000 births, but the rate is as high as 1 in 282 births among Yupik Eskimos [11]. *In utero* treatment with dexamethasone reduces the abnormal levels of androgens, and this therapy prevents the devastating consequences of wrong sex assignment in affected females. Differentiation of external genitalia occurs between 7 and 12 weeks of gestation, so therapy in at-risk pregnancies must begin earlier, preferably by the 5th week [11]. Cell-free DNA testing provides non-invasive determination of fetal sex at 7 weeks of gestation, thereby enabling rapid discontinuation of dexamethasone for male fetuses [12, 13]. Chorionic villus sampling (CVS) can be performed at 10–12 weeks, at which point therapy can be halted for unaffected females [11]. Dexamethasone treatment (three times daily) will continue throughout pregnancy for an affected female fetus. Maternal side effects of fetal dexamethasone therapy include edema, striae, excess weight gain, Cushingoid facial features, facial hair, glucose intolerance, hypertension, gastrointestinal problems, and emotional irritability [8, 11, 14].

Congenital hypothyroidism, which affects approximately 1 out of every 4500 pregnancies, is usually a secondary condition caused by treatment of maternal hyperthyroidism, such as Graves' disease [8]. Fetal goiter can interfere with fetal swallowing and lead to polyhydramnios and premature rupture of membranes. Furthermore, fetal goiter can cause tracheal compression and asphyxia at birth [8, 15]. Fetal hypothyroidism can be successfully treated with

levothyroxine. Levothyroxine is administered via intraamniotic injection due to its low transplacental transfer [8, 15].

Fetal hematological disorders that can be treated include alloimmune thrombocytopenia and erythrocyte alloimmunization. *Fetal and neonatal alloimmune thrombocytopenia* (FNAIT) has an incidence rate of 1 in 1500 and is caused by a maternal antibody-mediated response against a fetal platelet-specific antigen; this may lead to intracranial hemorrhage *in utero* [16]. Women at risk for a pregnancy with FNAIT are usually only identified after having a previous child with the disorder, but maternal administration of intravenous gamma globulin can successfully increase fetal platelet counts [8, 16]. *Erythrocyte alloimmunization* – the reaction of maternal antibodies with fetal erythrocyte antigens – can lead to hemolysis, fetal anemia, and hydrops fetalis [8]. The use of prophylactic anti-D immunoglobulin in Rh-negative women carrying an Rh-positive fetus can reduce the need for intrauterine blood transfusions to treat alloimmune hemolytic disease [17]. It should be noted that there are other types of red-cell alloimmunization besides anti-RhD without prophylactic immune globulins yet available [18].

In addition to the aforementioned indications, there are a number of fetal conditions for which experimental therapeutics are in various stages of testing. *Polyhydramnios* (excess amniotic fluid) affects approximately 1% of pregnancies, of which 55% are idiopathic and 25% are related to fetal diabetes [6, 19]. Amnioreduction and indomethacin administration have been investigated for polyhydramnios therapy, but not as randomized controlled trials [19]. Indomethacin likely decreases fetal urine production, with minor maternal side effects [6]. While some therapeutic options for *intrauterine growth restriction* currently under investigation require further study and randomized controlled trials to establish efficacy [20], it is clear that smoking cessation lowers rates of low birth weight and preterm birth [21]. Injection of picibanil into the pleural cavity for pleurodesis appears promising for the treatment of early second trimester, non-hydropic *fetal chylothorax* [22, 23]. Digoxin and furosemide have been injected into fetal intravascular space to treat idiopathic *non-immune hydrops fetalis* [24], and infection-induced non-immune hydrops fetalis has been treated with transplacental antiviral or antibiotic therapy [25]. *Fetal malignancies* are rarely diagnosed *in utero* [26], but this may represent a future area of potential fetal chemotherapy. There are also several examples of maternal prescriptions with direct or indirect fetal benefit, including tocolytics preventing preterm birth, penicillin to treat syphilis [6], spiramycin for toxoplasmosis [6], antibiotics before delivery to reduce neonatal sepsis [27], and


(A)
Trophoblast
Maternal Spiral Arteries
Placental Septum
B
Villous Tree
Umbilical Cord
Intervillous Space
(B)
Maternal Blood (Intervillous Space)
Syncytiotrophoblast
Cytotrophoblast
C
Fetal Blood
Fetal Vascular Endothelium
Villous Stroma
Basal Lamina
(C)
Carrier-Mediated Transport
Intervillous Space (Extracellular)
Passive Diffusion
Uptake
Efflux
ATP
Metabolizing Enzymes
Trophoblast Cytoplasm (Intracellular)

the reduction of maternal–fetal HIV transmission rates by the use of highly active antiretroviral therapy [28].

5.3 Strategies to achieve fetal drug therapy

5.3.1 Transplacental drug transfer

Many medications intended for the fetus are administered to the mother, with a portion of the dose crossing the placenta and reaching the fetal circulation. Although this method of drug delivery can cause maternal side effects, it is often preferred over the invasiveness and risks associated with direct fetal injection. To understand this process, it is important to provide a brief introduction to the role of human placenta as a functional barrier (see Figure 5.1).

Human placenta is a tissue of fetal origin localized at the interface between the maternal and fetal circulations. During gestation, placental functions include those of several organs in the newborn/adult. For example, the placenta is responsible for exchange of gases, uptake of nutrients from the maternal circulation, elimination of waste products, and the biosynthesis of specific hormones (steroids and proteins) that regulate autocrine and/or paracrine functions. Taken together, placental functions begin by ensuring implantation, supporting normal fetal organogenesis and development, and maintaining a healthy pregnancy until parturition.

In the early 20th century, the human placenta had been viewed as a barrier similar to the blood–brain barrier but with the role to "protect" the fetus from exposure to xenobiotics and environmental toxins. The thalidomide-induced birth defects of the

Figure 5.1 Mechanisms of maternal–fetal transfer. **A:** Overview of human placental morphology showing fetal vessels from the umbilical cord branching into villous trees, which are bathed by maternal blood entering the placenta via spiral arteries. Trophoblast cells on the surface of the villous structures separate the maternal blood in the intervillous space from the fetal circulation, as highlighted in B. **B:** Cellular components of a placental villus, wherein multinucleated syncytiotrophoblast cells are formed by fusion of the precursor cytotrophoblast cells. The trophoblast cells and the fetal vascular endothelial cells are separated by basal lamina. Several transport mechanisms within the trophoblast cell layer are highlighted in C. **C:** Transport mechanisms in trophoblast cells, with different molecules represented by different shapes. Passive diffusion is governed by the concentration gradient of any compound (xenobiotic or intermediary metabolite). Two types of carrier-mediated transport (uptake and efflux) involve transport proteins that span the phospholipid bilayer of the cell membrane. The biotransformation of molecules by metabolizing enzymes is also represented [59–65].

1960s shattered that concept and provided evidence for differences in transplacental transfer of compounds between placentas of human and other mammals. Currently, it is assumed that small molecules (<1000 Da, which includes most current medications) can freely cross the placenta between the maternal and fetal circulations by simple diffusion. However, the bidirectional transfer of compounds between the maternal and fetal circulations across the placenta by simple diffusion does not preclude the simultaneous involvement of two other transport processes, namely, facilitated diffusion and active transport [29, 30].

The transfer of a drug by either one of the two processes is mediated by a protein that is usually selective for a particular compound or group of compounds. The first process is facilitated diffusion and does not require metabolic energy where the transfer of the compound occurs down a concentration gradient until steady state equilibrium is reached. The second process is active transport, which is unidirectional, requires metabolic energy, and can transport compounds against a concentration gradient. For example, uptake transporters in the apical membrane are responsible for the transfer of many nutrients from the maternal to fetal circulation [31]. On the other hand, efflux transporters (such as P-glycoprotein, breast cancer resistant protein, and multidrug resistant associated proteins) are responsible for the extrusion of compounds from the fetal to maternal circulation [32]. Efflux transporters are crucial for decreasing fetal exposure to xenobiotics and each one of them is responsible for the extrusion of a diverse number of drugs.

Several trophoblast tissue metabolic enzymes are responsible for the placental biotransformation of drugs [33, 34]. Placental enzymes are occasionally identical to those in the liver, but in most cases their activity is ≤10% of the hepatic enzymes. One placental enzyme, CYP19/aromatase, which is known for its role in steroidogenesis, is also involved in the placental biotransformation of xenobiotics [35], thus catalyzing reactions which are performed by other hepatic enzymes that have not been identified in the placenta [36, 37]. For example, CYP3A4 is involved in the hepatic biotransformation of many drugs, but its activity in placenta has not been detected.

Thus, placental metabolic enzymes and efflux transporters define the human placenta as a functional barrier that regulates transplacental transport of drugs. The activities of these proteins are subject to regulation at the transcription and translational levels. Their activities vary widely between individuals and in the same individual with gestational age [38–41]. In terms of maximizing the transplacental transfer of maternally administered

medications intended for fetal drug therapy, substrates of uptake transporters are more likely to reach therapeutic levels in the fetal circulation. Drugs which are substrates for efflux transporters and/or metabolizing enzymes, on the other hand, are more likely to result in maternal side effects, as higher doses will be necessary to reach therapeutic drug levels in the fetal circulation.

5.3.2 Direct fetal injection

Ultrasound-guided injections can be introduced into the umbilical cord, amniotic fluid, intravenously, or into specific fetal tissues [2]. Such an approach may be advantageous when hydropic conditions or the chemical nature of the therapeutic agent limit its transplacental transfer [2, 4]. Nevertheless, there are important disadvantages to consider. Not only can fetal movement make the initial injection challenging, but it may also cause the needle to dislodge [27, 42]. The overall risk of fetal loss by CVS or amniocentesis is 0.5–1% [17]. When repeated injections are necessary, the risks of infection and fetal death are multiplied [2, 4].

5.3.3 Gene therapy

Fetal gene therapy could prove beneficial for a number of diseases, including cystic fibrosis, hemophilia, intrauterine growth restriction, Duchenne muscular dystrophy, and β-thalassemia [43]. The fetal period may present a unique window of opportunity for gene therapy and access to an expanding population of stem cells which may not be possible after birth. The comparative immaturity of the fetal immune system may allow for a circumvention of the type of immune response that would limit transgene expression. Furthermore, presentation of a vector to fetal thymus could induce lifelong tolerance to antigen, thereby enabling repeated injections of that same vector after birth, if necessary [43, 44]. Nevertheless, current utility is hampered by the selection of an appropriate vector and a series of unknown risks, such as increased chance of fetal loss upon injection during the first trimester, induction of preterm labor, infection, immune reaction, interference with normal fetal development, insertional mutagenesis, germline integration, and the chance that maternal harm may affect future pregnancies [43, 44].

5.3.4 Stem cell transplantation

Diseases where *in utero* stem cell transplantation might prove beneficial include hemoglobinopathies, immunodeficiencies, and inborn errors of metabolism [45]. As proposed for gene therapy, it has been anticipated that a naive fetal immune system would

readily accept stem cell transplantation, but to date, such therapy has only been realized in fetuses with immunodeficiencies that might facilitate engraftment [45, 46]. Sources of stem cells include maternal bone marrow, paternal bone marrow, fetal liver, and amniotic fluid [46, 47]. An advantage of using stem cells from amniotic fluid is eliminating the need for a donor source. Intraperitoneal injection of transduced amniotic fluid stem cells appears to be a promising strategy [47, 48].

5.3.5 Nanoparticles

Nanoparticles present a number of advantages for drug delivery, including sustained drug release promoting reduced dosing frequency and improved patient compliance, the potential for efficient drug targeting by passive and/or active targeting approaches, protection of therapeutic payload, and improved bioavailability for certain compounds. Besides traditional small-molecule drugs, nanoparticles can also be used to deliver peptides, proteins, genes, siRNA, and vaccines [49]. Examples of nanoparticles developed for drug delivery include liposomes, solid lipid nanoparticles, polymeric nanoparticles, polymeric micelles, and dendrimers. Multifunctional nanoparticles – combining both drug delivery and biomedical diagnostic imaging – have also gained recent attention as "theranostic" tools [50].

Targeted nanoparticle-based drug delivery systems offer the potential to increase the amount of drug reaching the fetus, thereby reducing the side effects associated with unnecessary maternal drug exposure. *Ex vivo* dual perfusion of human placental lobule is a representative model of *in vivo* placental transport and metabolism. To date, this model has been used with a few sets of nanoparticles to elucidate the effects of particle composition, size, and charge on the placental transfer of nanoparticles. Small, anionic liposomes increased the transplacental transport of thyroxine, with reduced metabolism to rT_3 [51]. Although PEGylated gold nanoparticles 15–30 nm in size were not transferred from the maternal circuit to the fetal circuit [52], minimal transplacental transport of a fluorescent fourth-generation polyamidoamine dendrimer (5–6 nm, fetal-to-maternal ratio of 0.073 ± 0.02) was reported [53]. Polystyrene beads with sizes up to 240 nm crossed the placenta, and higher fetal-to-maternal ratios were reported for 50–80 nm-sized particles [54]. These studies show that particle size is not the only determinant for transfer. This should not be surprising because macromolecules such as IgG and vitamin B_{12} can cross the placenta by carrier-mediated mechanisms, but the transport of other macromolecules such as heparin is negligible

[53]. Due to their size, most nanoparticles are unlikely to pass through tight junctions or trophoblastic pores [55], but nanoparticles for fetal therapy could take advantage of receptors in the placenta, such as F_cR, for receptor-mediated cellular entry [56]. Future developments in placental nanoparticle research must also include assessment of fetal safety to ensure improved drug delivery without adverse effects [55].

5.4 Special considerations

Maternal drug therapy during pregnancy requires balancing maternal benefit versus fetal risk, but in the case of drug therapy intended for the fetus, we must weigh maternal risks against potential fetal benefits. Despite the potential of a fetal medication causing maternal side effects, transplacental therapy is often preferred to avoid certain risks associated with fetal injections. In one extreme example of an attempted fetal intracardiac injection, the needle overshot its target, passed through to the other side of the fetal heart, and resulted in a severe adverse effect for the mother [57].

Although it is anticipated that targeted therapies would require lower doses and potentially lessen the resultant maternal side effects, the appropriate dose will need to be identified. Fetal drug therapy is associated with different pharmacokinetics than would be expected in adults or children. Compared to an adult, the fetus has more extracellular water, less fat, less metabolic enzyme activity, a lower renal secretion rate, less gastrointestinal absorption, and fetal brain receives a higher percentage of cardiac output [2, 10]. Furthermore, drug elimination is altered due to amniotic recycling [2].

Finally, the ethics of fetal drug therapy must be considered. Depending on gestational age, lung maturity, the availability of neonatal facilities, and maternal preference, in some instances, early delivery may be seen as an alternative to fetal therapies carrying high risk [7]. The risks and potential benefits of each disease are unique, and the recommendations of Noble and Rodeck serve as excellent guidelines [58]; it is important that the mother can give informed consent, meaning that she understands all the possible outcomes of each intervention. Protocols for fetal drug therapy must be approved by a research ethics committee. Invasive therapy must have a high probability of saving life or preventing disease; risks to fetal health must be minimized; and risks to maternal health must be negligible. Alongside the mother's right to consent is her right to refuse, and supportive counseling should be made

available to the family [58]. As if pregnancy and childbirth weren't challenging enough, it is inspiring to see the sacrifices of pregnant women participating in clinical trials, enduring undeserved side effects, and undergoing invasive procedures in order to offer their children more hope for a better future.

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Treating the Placenta: an Evolving Therapeutic Concept

6

Michael D. Reed and Donald R. Mattison

6.1 Introduction

Generally, from the perspective of clinical pharmacology, one thinks of the placenta as the passage from mother to fetus or the reverse [1–4]. With few exceptions it is generally not thought of as the target for therapy. However, we believe that as our understanding of placental function grows and as the science and application of obstetric-based clinical pharmacology broadens, the placenta may become an important therapeutic target for the mother, the fetus, or both. Clinically important diseases where such a strategy is employed today include the prevention of vertical HIV-1 virus transmission from mother to fetus and in the treatment of malaria where the placenta serves as an important reservoir of the malaria parasite. In this chapter we critically review what is known about placental functions and its modulations throughout gestation and how placental processes can and might be manipulated for therapeutic gain.

6.2 The placenta as the therapeutic target: the past

An early example of targeting placental function for therapeutic purposes that was both unsuccessful as well as resulting in unexpected tragic consequences is the experience with diethylstilbestrol (DES). The DES experience highlights the importance of the need for a good understanding of the disease process, drug pharmacodynamics and acute, chronic and generational toxicity before undertaking widespread drug-based manipulation of the maternal, placental, and/or fetal compartments [5]. Diethylstilbestrol is a synthetic estrogen structurally similar to estradiol with potent estrogen-like activity that is rarely used today. From the 1940s to ~1971 DES was commonly used for the prevention of spontaneous abortions. An innovative randomized controlled trial conducted at the Chicago Lying-In Hospital demonstrated that DES was actually not able to prevent pregnancy loss, and may have actually led to missed abortion [6]. Unknown at the time but recently described, DES beneficial clinical effects are most likely a result of the drug's positive effects on placentation and trophoblast stem cell differentiation [7]. Unfortunately, pharmacologic DES use maternally results in a high incidence of teratogenic effects on the reproductive tracts of males and females and the subsequent development of vaginal clear-cell adenocarcinoma in women of childbearing age [6–8]. Many environmental chemicals and pollutants either as the intact compound or metabolite can also have similar or unique devastating negative consequences on the mother, the placenta, and/or the fetus [5] complicating our assessment of individual compounds during pregnancy. These and many other tragic experiences underscore the importance of careful study of mother–fetal benefit–risk profiles of drugs intended to treat the placenta.

6.2.1 Placental function

The placenta provides a link between the mother and fetus, metabolizing and transferring nutrients for growth and development of the fetus as well as for its own growth and development. Metabolic waste products generated in the fetus or placenta are eliminated by transfer into the maternal circulation. A unique function of the placenta is its role as an endocrine organ producing steroid and protein hormones. These characteristics must be considered in thinking about treating the placenta – to enhance therapeutic success in placental, fetal or maternal disease. A detailed description of placental anatomy, physiology, and gestational maturation

are addressed in Chapter 5. However for completeness we provide a brief overview of those anatomic and physiologic functions important to understanding therapeutic targeting of placental function for maternal and fetal health.

Briefly, fetal and maternal circulations are separated by placental tissue that changes throughout pregnancy; anatomically, the surface area over which maternal–fetal exchange occurs increases and the distance between maternal and fetal blood decreases. Morphologically, the syncytiotrophoblast layer is reduced in thickness and the cytotrophoblast becomes discontinuous as gestation progresses. Changes in the villous structure are also observed, with an increasing number of microvilli facilitating exchange between mother and fetus. These villi and the syncytiotrophoblast layer permit the maternal and fetal circulations to be in close contact while providing a transport barrier between the two circulations [1, 9, 10].

In human placenta the syncytiotrophoblast arises from the fusion of cytotrophoblast cells, forming a syncytium over the surface of the placenta facing the maternal blood. The plasma membranes of the syncytiotrophoblast are polarized; the brush border membrane in direct contact with maternal blood and the basal membrane facing the fetal circulation. The brush border membrane possesses a microvillus structure that effectively amplifies the surface area, whereas the basal membrane lacks this structure.

Anatomic differences between species in the number of trophoblast layers and connection between maternal and fetal tissues result in species-specific variation in placental function that influences data gathered during the preclinical stages of drug development. The human placenta is unique in its villous structure. Factors such as diffusion, electrical potential across the placenta, magnitude of maternal and fetal blood flows, and differences in metabolism, transport proteins, and other mechanisms for exchange between maternal and fetal circulations should be considered as the placental transfer and metabolism of drugs varies dramatically among differing species. Discordant results for maternal–fetal drug disposition between humans and many animal species are often noted due to these anatomical differences in placental morphology and function [9–11]. The thalidomide tragedy was the most important event to dispel the erroneous belief that the placenta was a barrier and spawned regulation for controlled, animal-based preclinical teratology studies [11–13]. These anatomical and physiological differences can also lead to false implications for teratogenic effect(s). The widely used drugs diazepam and salicylates were shown to induce teratogenic effects in animals with no increased risk of any such effects in humans.

The previously widely used and therapeutically effective drug Benedictine (doxylamine plus pyridoxine) was shown in animal studies to cause cardiac and limb defects leading to enormous litigation and ultimately withdrawal from the US market though no increase in human teratogenic effects have been described [13], and this drug combination remains the most effective intervention for treating pregnancy associated nausea and vomiting (see Chapter 12**)**. These misleading and sometimes erroneous findings are directly attributable to the interspecies differences that exist in placental structure and function. Despite these disparities and the need for better mechanisms for screening possible placental toxins or teratogens, animal screening remains the best process today [11].

Drugs for treatment of placental disease should be concentrated within the placenta with little access to, and toxicity for, mother or fetus. Drugs developed for treatment of the mother should have minimal transport to fetal circulation and minimal impact on placental and fetal health. Drugs for treatment of fetal diseases should have unhindered access to the fetal circulation with minimal adverse impact on mother or placenta [1, 14].

6.2.2 Placental transport mechanisms

The syncytiotrophoblast, the outermost layer of the human placenta, is the main site of exchange for drugs and metabolites, nutrients, waste products, and gases between the maternal and fetal circulations. Efficient transfer of nutrients, gases, electrolytes, and solutes across the placenta is essential for fetal growth and development. There are several mechanisms by which transfer occurs, and depending on the mechanism of transfer the direction may be toward the maternal or fetal circulation.

As noted in Chapter 5 the placenta performs a multitude of important, complex, simultaneous functions at a differing functional capacity that changes as gestation progresses. Drugs may transfer from the maternal to fetal compartments via simple passive diffusion, facilitated diffusion, active transport, filtration or pinocytosis. The physiochemical characteristics of a drug substantially influence its maternal–fetal disposition profile. Structural modifications of a proposed drug's physical and chemical characteristics including molecular weight/size, degree of ionization at physiologic and pathophysiologic pH linked to water/lipid solubility and affinity for membrane transporters and drug metabolizing enzymes represent just a few of a multitude of targets for drug therapy. Xenobiotics with a molecular weight of <600 daltons can usually transfer across the placenta via passive diffusion

whereas compounds of 1000+ daltons, e.g. heparin and insulin, cross very poorly. With a small, highly lipid soluble, low plasma protein bound drug, its transfer across the placenta will primarily be dependent upon maternal and fetal blood flow combined with involvement, if any, of a membrane transporter. Important to the treatment of placental-based disorders (see below, e.g. malaria) a drug may have high affinity for placental tissue and bind to and/or accumulate within the syncytiotrophoblast [15]. Depending upon the inherent physiochemical characteristics of a drug, it may be released into the fetal circulation or be released back into maternal circulation without reaching the fetal compartment. The rates of these transfer processes can be very different than the individual or combined maternal or fetal clearance rates of the drug [1–5, 9, 10, 15–19].

6.3 The placenta: therapeutic targets

As noted above, the placenta is a multifunctional dynamic organ continuously evolving throughout gestation with the sole purpose of maintaining maternal–fetal homeostasis up to the time of optimal pre-programmed delivery of the newborn infant. The many perturbations that occur with each of these processes during gestation heighten the complexity of effectively targeting one or more functions as a therapeutic target [20]. Nevertheless, as our understanding of maternal–fetal physiology and pathophysiology increases in concert with advances in digital technology fostering more sophisticated patient monitoring and safer anatomical manipulation, therapeutic targeted strategies are a reality now and will continue to expand. With respect to possible therapeutics, enzymes capable of metabolizing (CYPs) or conjugating drugs (transferases) as well as uni- and bi-directional transporters facilitating or preventing drug movement from one location to another are ripe for pharmacologic manipulation to maximize maternal or fetal therapeutics [16, 19–25]. Similarly, a drug development plan focused on an analog's structure–activity relationship linked to specific manipulations of its physiochemical characteristics will foster safer and more effective therapy [1–4, 16, 18].

Tables 6.1, 6.2 and 6.3, respectively, outline placental expression of known CYPs, enzymes involved in conjugation and cellular transporters relative to gestational age that are active in maternal–fetal homeostasis. The overall influence of these placental-based processes on xenobiotic disposition must be considered in total with the functional activity of the mother and the fetus. Changes

in the functional capacity and activity of these processes important to drug disposition occur between the mother, placenta, and fetus throughout gestation. In general, fetal tissue activity of these processes increases whereas placental activity decreases with gestation such that at birth, placental metabolic activity is minimal [23]. This gestational ontogeny may be the basis for much of the conflicting data regarding placental drug disposition that exist in current literature. For example, the energy-dependent efflux placental transporter Pgp is of little importance in term placenta but very important during earlier stages of gestation in preventing xenobiotic access to the fetal compartment. This ontogenic pattern through gestation is very important to the rate and extent of digoxin placental transfer for the treatment of fetal arrhythmias (see Chapter 5) [22].

It is conceivable if not inevitable that drugs will be developed that function as a pure antagonist, i.e. high affinity with no intrinsic activity, which occupies a specific placental transporter, enzyme or other target antagonizing its effects. Such a compound could be used alone or in combination with other therapeutic compounds with the sole purpose of blocking drug transfer into the fetal compartment thus leading to maternal drug accumulation, or conversely, to block back transfer from the fetal compartment to maternal circulation leading to drug accumulation or persistence in the fetal compartment. Such a strategy is employed today with digoxin for fetal arrhythmias where Pgp inhibitors

Table 6.1 Placental expression of cytochrome P450 enzymes involved in drug metabolism

	Placental maturity		
Specific enzyme	**First trimester**	**Term**	**Inducible**
CYP1A1	R, P, A	A, P, R	Yes
CYP1A2	R	A, P	Yes
CYP2C8/9/19	R	ND	Yes
CYP2D6	R	ND	Yes
CYP2E1	A, R	A, P*, R*	Yes
CYP3A4-7	P, R	P* R	Yes

CYP – Cytochrome P450 isozyme.
A – Activity; ND – No substantive activity/excesses detected; P – Protein; R – mRNA.
*CYP2E1 has only been detected in the term placenta of heavy ethanol-consuming mothers.
Adapted from reference 23.

Table 6.2 The expression of cellular transporter proteins in human placenta

	Placenta		
Transporter	**First trimester**	**Second trimester**	**Third trimester**
ABCB1	R, P	R, P	R, P, A
ABCB4	R	NA	R
ABCC1	R	NA	R, P, A
ABCC2	R, P	R, P	R, P
ABCC3	R	NA	R, P, A
ABCC4	NA	NA	R, P
ABCC5	R	R	R, P, A
ABCC6	NA	NA	NA
ABCC10	NA	NA	NA
ABCC11	NA	NA	R
ABCG2	R, P	R, P	R, P, A
NET	NA	NA	R, A
SERT	NA	NA	R, P, A
OCT1	NA	NA	R, A
OCT2	NA	NA	R
OCT3	R	NA	R, P, A
OCTN1	NA	NA	NA
OCTN2	NA	NA	R, P, A
OAT1	NA	NA	NA
OAT4	P	NA	R, P
OATP1A2	R	NA	R
OATP1B1	R	NA	ND
OATP281	P	P	R, P, A
OATP3A1	R	NA	R
OATP4A1	R	NA	R, P

A – Activity; NA – Data not available; ND – Not detected; NET – Noradrenalin transporter; OAT – Organic anion transporter; OATP – Organic anion transporting polypeptide; OCT – Organic cation transporter; P –Protein; R – mRNA; SERT – 5-HT.
Adapted from reference 23.

Table 6.3 Therapeutic agents that are substitutes for P-glycoprotein and/or breast cancer resistance protein

Pgp	BCRP
Cyclosporine	Glyburide
Digoxin	Methotrexate
Erythromycin	Sulfated estrogens
Indenavir	Zidovudine
Levoflexacin	
Morphine	
Phenobarbital	
Phenytoin	
Ritonavir	
Saquinavir	
Veropamil	

Pgp – P-glycoprotein; BCRP – Breast cancer resistance protein.
Adapted from reference 18.

(e.g. verapamil) are coadministered to enhance fetal compartment digoxin concentrations [22]. As noted above, this strategy is of variable success but clearly dependent upon the fetus's gestational age [22].

6.4 The placenta as a therapeutic target today

6.4.1 Diabetes during pregnancy

Poorly or uncontrolled diabetes during pregnancy has been clearly shown to markedly increase maternal and fetal risk for a spectrum of untoward effects, many that are serious and attenuated or prevented with effective therapy [9, 26]. However, a major concern in the selection of drug therapy for maternal diabetes is strictly preventing fetal hypoglycemia [9, 17, 27–29]. The design of drug therapy for optimal treatment of maternal diabetes is a case study for the contemporary targeting of the placenta for successful therapeutics. In this case the target is exploiting the known influences the placenta has on drug distribution and overall maternal disposition to limit fetal exposure [9, 17, 27, 29].

The best example of manipulation of maternal and placental function to influence drug disposition for optimal maternal therapeutics is the story of glibenclamide (Glyburide) [9, 17, 27, 29]. Glibenclamide (GBC) is an oral hypoglycemic drug that stimulates the pancreatic beta cells to secrete insulin and is often used to treat diabetes, including diabetes during pregnancy. This particular drug dosing strategy capitalized on the known influences of drug protein binding, maternal drug clearance rate, and affinity for placental–fetal transporters to achieve the desired therapeutic effect. Glibenclamide is highly bound to maternal plasma proteins (primarily albumin) to the extent of 99.8%. This extensive degree of drug binding to circulating maternal plasma protein substantially reduces the amount of free active drug available for placental transfer. Augmenting this effect is the drug's relative short maternal elimination half-life ($t_{\{1/2\}}$), minimizing the duration of time the free GBC is present in maternal circulation for transplacental transfer. A third and extremely important characteristic of GBC is the drug's affinity as a substrate for multiple efflux proteins, P-glycoprotein (Pgp), multidrug resistant protein 1 (MRP1), 2 (MRP2) or 3 (MRP3) and breast cancer resistant protein (BCRP). Very recent data suggest that GBC may be preferentially transported from the fetal to the maternal circulations by BCRP [9, 15, 18]. When all three of these characteristics are combined, with the latter probably the most important to limiting drug access to the fetal compartment, highly effective and safe maternal therapeutic regimens can be constructed with easily achieved drug structure–activity relationships targeted at specific maternal and placental function.

6.4.2 Malaria in pregnancy

Malaria during pregnancy is a medical as well as public health concern owing to maternal (anemia, fever, cerebral infection, hypoglycemia, and death), placental, fetal (abortion, stillbirth, and congenital infection), and neonatal (prematurity, growth restriction, infection, and death) effects [14, 30, 31]. Therapy has been complicated by the emergence and rapid spread of drug resistance, necessitating combination therapy. In addition, malaria and HIV can be found in the same populations and interact to the detriment of the mother, placenta, and fetus [31, 32]. Finally, of special relevance are the interactions between malaria and the placenta, as placental malaria may be asymptomatic until adverse pregnancy outcome [33–35].

Drug development for malaria in pregnancy encounters two significant obstacles: malaria is a disease of developing countries and afflicts women during pregnancy [30, 31, 36, 37]. Existing

treatments are poorly characterized with respect to pharmacokinetics, pharmacodynamics, safety, and efficacy yet the tools for studying the existing drugs and new drug development are readily available. Further complicating this scenario is the fact that *Plasmodium falciparum*, the most common human malarial species, manifests differently in pregnant women than in non-pregnant women. In pregnant women *P. falciparum* expresses a different antigen variant to that found in non-pregnant women. Malaria-infected red blood cells possess adhesive proteins on their surface which appear to interact with chondroitin sulfate on the placental surface [34]. These and other cellular perturbations lead to infected erythrocytes preferentially accumulating in the intervillous space of the placenta resulting in a thickening of the trophoblast basement membrane. This later event appears to be an adaptive mechanism in response to the enormous amount of secreted cytokines released in response to the infection. The thickened trophoblast basement membrane damages the syncytiotrophoblastic surface of chorionic villi [35] leading to the negative maternal and fetal consequences associated with this parasitic disease. Thus, an effective therapeutic strategy must not only focus on parasite eradication at the placental and peripheral levels but might concurrently target antagonism of select chemokines and cytokines elevated with placental malaria [35].

6.4.3 HIV-1 infection in pregnancy

As noted above, referring to the placenta as a "barrier", the placental barrier has been discouraged for decades and for the most part falsely. This myth has been dispelled for many decades [1, 3, 12]. For some, however, the placenta does serve as a barrier to fetal transmission of viruses. Cytomegalovirus easily crosses the syncytiotrophoblast to the fetus whereas the HIV-1 virus crosses very poorly. In untreated HIV-1 infected mothers more than 90% of their offspring will be HIV-1 negative reflecting the maternal and placental focus of the infection [28]. Mother-to-child transmission of HIV-1 can be reduced to <1% with the use of antiviral drugs during pregnancy and in the neonate. The most common antiretroviral drug used to prevent maternal-to-child HIV-1 transmission is zidovudine – in 1994 maternal zidovudine (ZDV) monotherapy was clearly shown to decrease maternal-to-child HIV-1 transmission by two thirds [39]. Zidovudine is metabolized to its active moiety in the placenta and inhibits HIV-1 replication within placental cells [38].

The exact mechanism(s) of HIV-1 transmission *in utero* is poorly understood but the role of the placenta as the primary target

is clear. Histological examination of term placentas from HIV-1 positive women revealed HIV-1 infection in syncytiotrophoblast, cytotrophoblast, and villous endothelial cells. Similar histological examination of placenta at 16 weeks revealed syncytiotrophoblast and cytotrophoblast infection whereas chorionic villi were rarely involved [38]. All these data combined underscore the importance of the placenta as the primary therapeutic target for the prevention of mother-to-child transmission of HIV-1 infection. Further supporting this contention is the data showing increased expression of human beta defensins, a natural defense mechanism in the maternal–fetal interface, in HIV-1 seropositive mothers [40].

Like malarial infection during pregnancy many factors influence the efficacy of maternal HIV therapy in preventing mother-to-child transmission. Understanding and accounting for the changes in drug pharmacokinetics during pregnancy (see Chapter 3) is of paramount importance to the efficacy and safety of maternal and fetal drug therapy. Although the placenta is well perfused, inadequate prevention, the development of HIV-1 drug resistance or drug-induced toxicity can occur if maternal antiretroviral drug dose regimens do not account for the changes in drug disposition observed throughout gestation. Sub-therapeutic antiviral drug tissue and fluid concentrations can lead to inadequate fetal prevention and/or the development of HIV-1 drug resistance whereas too large doses may increase the risk of maternal and/or fetal toxicity.

6.5 The placenta as a therapeutic target in the future

The ideal drug for maternal therapy would be an agent that neither reaches the fetal compartment nor alters maternal physiology sufficiently to adversely affect placental function. Similarly, the ideal maternally administered drug targeting the fetal compartment would have no negative maternal or placental effects. To our knowledge this “ideal” drug does not yet exist – but soon “they” will. Furthermore, a drug may be maternally administered to the mother to inhibit or stimulate individual or multiple placental functions to achieve the desired therapeutic goal.

The value of nanosized materials as a method for drug delivery, and more specifically targeting specific anatomic site delivery, is gaining considerable interest. The number of nanoparticle polymer constructs supporting the engineering of compounds with novel

physical and chemical characteristics has increased dramatically over the last decade [41]. Based on the ability to manufacture nanosized compounds (e.g. drugs) of specific size, charge, and disintegration characteristics it is not surprising that the maternal–placental–fetal compartments are specific targets for ongoing research [41–43]. We envision that nanotechnology will foster the development of a number of specific compounds that target specific placental characteristics, i.e. targeting specific maternal sites, specific placental sites, and/or fetal compartment penetration and binding to specific fetal sites [41–43]. However, before these benefits are fully realized the methodical study of placental nanopharmaceuticals will provide tremendous insight into placental anatomy and physiology [43]. Advances in placental imaging, particularly of transport mechanisms [44] and other functions, should augment the rate at which such new therapies are realized.

Lastly, the genomics of placental function will further expand the therapeutic armamentarium for specific placental diseases and functions [45, 46]. Genetic technology has impacted greatly on the ability to detect perinatal genetic disorders and their susceptibility at multiple time points during gestation [45]. Pharmacogenomics in reproductive and perinatal medicine is in its infancy [46]. Although a few clinically useful drugs in perinatal medicine contain pharmacogenetic information in their official labeling, the relevance to contemporary perinatal care is extremely limited. Pharmacogenomics of placental receptors, transporters, enzymes, and other functions will be exploited for therapeutic purposes. As such, placental epigenetics are of great interest with respect to the treatment of placental disease as well as possible manipulation of the fetal compartment by using the placenta as the "gateway to the fetus" [47]. Much more information serving to define specific therapeutic targets is being described at a faster and faster rate as advances continue to occur in our technical capabilities. A recent example of such advances described differential expression of several human placental proteins between lean and obese pregnant women that could lead to a number of therapeutic strategies targeting many maternal, placental, and fetal perturbations [48]. This is just the beginning.

Conclusions

The placenta is the most important structure to the health and viability of the mother and the fetus and for fetal development up to delivery. Nevertheless, the majority of therapeutic strategies used during pregnancy today focus on manipulation of the placenta

for maternal or fetal therapeutics. Increasing information defines the importance of therapies directed at, or focused on, the placenta for maternal–fetal health. Advances in molecular biology, technology, imaging, and genomics are among just a few avenues that are fostering a much better understanding of placental anatomy, physiology, maturation, and pathophysiology and serving as the foundations for effective treatment of the placenta.

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What is Sufficient Evidence to Justify a Multicenter Phase 3 Randomized Controlled Trial in Obstetrics?

7

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7.1 Introduction

Randomized controlled trials (RCT) are the gold standard for the evaluation of a new drug or technology. From the perspective of industry, trials are a key component in the process of obtaining regulatory approval and a "successful" or "positive" trial is one that moves the drug further down the pipeline from first-in-human studies toward registration. Failure of a drug to complete this process is not

uncommon and many drugs fail at the level of the phase 3 trial. During a 10-year period (1991–2000) for 10 large US and European pharmaceutical companies, the overall "success rate" was 11%. The rate of success for trials in Women's Health was the lowest across sectors (less than 5%) [1]. Strand and Jobe [2] have noted the large number of negative trials in perinatal medicine and suggest that the situation requires a critical analysis.

Negative trials have a variety of costs, including financial as well as the exposure of participants to the potential toxicity of unproven experimental treatments without associated benefits. As well, there are "opportunity costs", as only a limited number of trials can be conducted at a given time. On the other hand, "negative trials give us important information about biologic and pathologic processes, and help us avoid ineffective therapies. They lead us from one path of investigation and point us in new directions. However, the large number of negative trials in the perinatal area does illustrate that we have poor preliminary information on which to base trials and little insight into what interventions may be beneficial" ([2], p. 348).

Over the last several decades, there has been a dearth of trials of new drugs conducted during pregnancy. Most of those that are conducted are investigator led, as pharmaceutical companies have focused their efforts elsewhere. The limited funding that is available is from government agencies. This creates an urgent need to "get it right": to invest in the evaluation of treatments for which there is a high probability of success. This begs the question: Can reasons for the failure of seemingly promising pregnancy drug trials be identified? In this review, examples of negative trials are provided and the degree and quality of evidence which served as the rationale for conducting these trials is explored. In doing so, we suggest that there is a great deal of variation regarding the level of evidence that is deemed sufficient to move forward with a phase 3 trial. We posit that we can learn from negative trials in order to be able to improve study design, to better select research questions and outcomes, and to better select among the various potential candidates for phase 3 trials.

In fact, the evidence required to justify the decision to conduct a phase 3 RCT in the area of maternal–fetal medicine has not been adequately defined. The main objective of this review is to propose criteria that may be applied by investigators and by funding agencies to assess if there is sufficient evidence to proceed to a phase 3 trial. In addition, we will attempt to identify risk factors for failure of phase 3 trials.

7.2 Evidence, equipoise, and the ethical considerations in deciding whether to conduct a trial

"A trial with methodological weaknesses is both a waste of resources and unethical" ([3], p. 141). The same could be said of a trial based on insufficient evidence.

A clinical trial is "warranted if there is sufficient but not definitive evidence that the intervention to be assessed would have a favorable risk–benefit ratio in the population to be enrolled" ([4], p. 165). Equipoise is an ethical standard, and it was proposed to identify scenarios where conducting an RCT would be unethical. Some authors take equipoise to be sufficient justification for a trial. However, this should not be the case. Equipoise is a necessary but not sufficient prerequisite to justify a trial. Phase 3 trials are costly and as such the number that can be conducted is limited – far fewer than the number of current and potential treatment approaches that could be tested. When the scientific community gives the green light for a given trial, they are in some ways "saying no" to others, as funds are limited and not every clinical question warrants its own trial.

A sharpened definition of equipoise has been proposed as "a state of genuine agnosticism or conflict in the expert medical community about the net preferred medically established procedure for the condition under study" [5]. Physician-researchers and members of institutional review boards (IRBs) "[…] have the responsibility to evaluate the extent to which a proposed randomized clinical trial solves a state of agnosticism or a knowledge conflict in the expert medical community" [5].

As stated by Strand and Jobe "large RCTs (phase 3) are performed to confirm preliminary information that suggests that a treatment or intervention will result in a clinically important improvement in outcomes for patients. The major roles of the large multicenter RCT are to verify the primary hypothesis, better quantify the magnitude of the clinical effect, better define potential risks because of the increased numbers of patients exposed to intervention, and establish if the intervention can be translated to clinical practice" ([2], p. 343). The hypothesis for a trial "usually arises from a scientific rationale and early empirical evidence, sometimes including information from laboratory or animal studies" ([6], p. 519). It is important to note that the decision to conduct a phase 3 trial requires not only empirical evidence, but a sound biological rationale and well conducted phase 2 studies.

7.2.1 Summarizing the evidence

A phase 3 trial is only warranted after the available evidence has been reviewed and assessed, usually through a meta-analysis. The proposed RCT must add to the existing knowledge base; thus, it is important to establish what information is missing from the current knowledge base so that the trial can be designed to fill these knowledge gaps. A thorough understanding of the available evidence is key to formulating the appropriate research question, in assessing the target population, in estimating the effect size, and in assessing feasibility.

"If available evidence is reliable and already provides a definitive answer, there is no need for a study, although there may be a need for a study in a specific target group or a larger study to refine therapeutic strategies or define optimal 'dosage'" ([3], p. 141). The philosophical question arises as to what constitutes sufficient evidence to consider that a treatment is efficacious. If the estimate derived from a number of small trials shows a significant effect, despite none of the individual trials showing a statistically significant effect, what conclusion should be drawn? Is an additional large RCT justified? This question is even more difficult to address given that studies have underlined the discrepancy between the findings of meta-analyses and the largest trials of the same therapy [7, 8].

A trial is warranted when there is "equipoise", that is when there is a "reasonable" balance between an existing treatment (or, in some cases, placebo when no effective treatment is available) and the experimental treatment. This is a delicate balance between the presence of insufficient evidence to justify a trial (in which case more preliminary/elementary research is needed) and a state of overabundance where an additional trial would not be ethically acceptable. Different IRBs can disagree markedly on the same protocol as to their opinion as to the presence or absence of equipoise [4]. This may reflect variations in the expertise on the IRB. As well, it reflects the absence of guidelines regarding what is evidence of sufficient quality to justify a trial.

7.3 Why are failure rates so high for pregnancy drug trials compared to other therapeutic areas?

An investigation into risk factors for failure of phase 3 trials may be informative in developing a set of criteria to be met to justify the decision to conduct such a trial. The stepwise process of drug

development seen in most major therapeutic areas such as cardiology and neurosciences is not frequently applied in development of drugs for use in pregnancy. Because few new drugs are developed specifically for obstetrical use, the process for "obstetrical drug development" is essentially "a repurposing" [9]. "For diseases with large populations eligible for therapy, drug development occurs through systematic searches for targets that can alter disease progression, and testing candidate drugs for efficacy, safety and pharmacokinetic characteristics in vitro and in animals (preclinical studies), followed by human studies if preclinical studies are successful. This research produces stepwise submission of data to a regulatory agency…for consideration of the drug for marketing with a specific disease indication and approach for a specific population (e.g. age, sex, race/ethnicity) as supported by the regulatory submission and described in the product label [4–6]. Unfortunately, drug development for women during pregnancy…is not addressed by a structured search for targets and therapeutic molecules [13–17]" ([9], p. 437) The lack of a systematic approach could very well be responsible for the lower success rates of obstetrical drug trials.

Following a selective review of a number of negative perinatal trials, Strand and Jobe ([2], p. 343) suggested reasons for failure to validate the primary hypothesis. In general, the rationale for negative trials was frequently based on the findings of small trials or a meta-analysis of multiple small trials which were not methodologically robust. "The weak preliminary information together with limited numbers of patients, problematic primary outcomes and a poor understanding of the biology of neonatal diseases has limited the ability to reliably design trials with positive outcomes" ([2], p. 343). A single small trial has the potential for alpha error and publication bias. On the other hand, other perinatal trials that were based on more compelling evidence have also yielded negative results ([2], p. 346). In some cases, changes in clinical care may have negated any benefit. Strand and Jobe [2] have noted that hypotheses may be based on a poor or erroneous understanding of the underlying biology of the targeted condition. Treatments that involve a failure or impossibility of blinding open the door to bias. Studies may be underpowered to detect small but clinically important differences. "Center effect" or variations across centers, particularly in the case of complex interventions, may dilute the effect and reduce power to detect a difference.

Gordion et al. [10] examined "attrition rates" (a failure of a new therapy to continue down the drug pipeline) in 656 phase 3 drug trials from a range of treatment areas undertaken between 1990 and 2002 by large pharmaceutical companies. Of these,

42% failed during phase 3. The causes of failure for 73 of the failed phase 3 trials (the only ones where enough public data were available to perform an analysis) were identified as efficacy, safety problems, and "lack of differentiation". An additional study [1] found very similar results. "The major causes of attrition…were lack of efficacy (accounting for approximately 30% of failures) and safety (toxicology and clinical safety accounting for a further approximately 30%)" ([1], p. 712). Gordion et al. [10] found "50 percent of the drugs failed in phase III because they could not be proved effective: the trials could not demonstrate that the drugs were more medically effective than the placebo" (lack of differentiation). This is surprising given that demonstrating efficacy is, after all, a primary objective of phase 2 trials. Among the remaining drugs that failed, 31% posed safety concerns. "An additional 19 percent were found to be neither safer (i.e. given similar efficacy, failure to demonstrate superior safety versus an active comparator) nor more effective (i.e. given similar safety profile, failure to demonstrate superior efficacy versus active comparator) than drugs currently on the market" ([10], p. 2).

A few factors have been identified which help to explain failure to show efficacy. "The less established the drug's mechanism and the less objective the endpoints, the higher the drug's risk of failure." Drugs combining the two higher-risk factors – novel mechanisms and less objective endpoints – failed 70% of the time, compared with 25% for drugs with known mechanisms and more objective endpoints ([10], p. 4). Studies of drugs involving novel mechanisms may involve hypothesized effects rather than proven effects.

How do we assess the plausibility of an effect of a drug involving a novel mechanism? Malek and Mattison's [9] criteria for the identification of promising pharmaceuticals for use in the perinatal period can be adapted to assist in considering the appropriateness of a drug proposed for the treatment of a perinatal condition as well as the selection of dose. The following questions should be addressed: [1] Among the **classes of molecules that have potential efficacy** [for] treating the condition of interest (maternal, placental or fetal condition), is the proposed molecule the best choice? **Are preclinical pregnancy models of the disease processes** available to help guide evaluation of the molecule prior to use in humans? [2] Among the classes of molecules available, **is the molecule proposed preferable for pharmacokinetic, pharmacodynamic, safety or efficacy reasons**? [3] In designing clinical trials, how will the results of dose finding and treatment be evaluated? Are **therapeutic concentrations** defined in media that can be sampled (e.g. maternal urine, blood, exhaled breath or

amniotic fluid)? **Do pharmacokinetics and pharmacodynamics change [occur] across the course of pregnancy and how will that alter dosing and therapeutic end points monitored?** [4] How will the clinical trial monitor drug toxicity or adverse events, and over what period of time will those potential adverse events be monitored? "Drug development should spring from our understanding of the maternal, placental or fetal disease we intend to treat, recognizing that there may be sites of drug activity (toxicity) away from the therapeutic targets" [9].

Lack of objectivity of endpoints in phase 2 precursor studies is another reason for failure of phase 3 studies. Trials with less objective endpoints at phase 2 failed approximately 10% more often than those with more objective endpoints [10]. An endpoint was considered objective if it could be measured with diagnostic tests whose results could be "easily reproduced, or with a scale that was both professionally measured and widely used" ([10], p. 3) Endpoints were considered less objective "if they relied on less easily reproducible measurements, uncommonly used scales, or self-reporting by patients" ([10], p. 3).

7.4 Role of phase 2 trials

Testing the biological activity, dosage, and safety profile of the drug in question requires thoroughness. An important risk factor for failure in phase 3 is a phase 2 clinical trial that has not been done or that has been poorly conducted. The goal of phase 2 trials is to determine if a pharmacological activity can be measured by a number of objective or subjective endpoints and how well this activity compares to that of a placebo or active control. Determination of drug dose and the collection of information pertinent to the design of a phase 3 program are other goals. Safety remains a strong component of phase 2 programs. Serious toxicities may be observed for the first time in a phase 2 trial.

In the area of critical care, many large clinical studies are based on "small pilot investigations with inadequate phase 2 trial data, and on limited mechanistic data…" ([11], p. S124). The same can be said of some large perinatal trials.

"A successful Phase 2 program should have established that the candidate drug has 'activity' in the indication tested and the target population of interest. A well-run Phase 2 program would also have provided information about the appropriate dose for the pivotal studies and provided an estimate for the sample size required for the Phase 3 trials. The team must then decide if the drug meets

the 'desirability quotient' for further development…" ([12], p. 6). To quote Retzios: "We can divide deficiencies in the Phase 2 clinical trials in the following categories: (a) inadequate design; (b) endpoints with a tenuous connection to clinical-benefit-based Phase 3 endpoints; and (c) improper execution. These categories are not mutually exclusive; a failed program may span a number of them" ([12], p. 7).

7.5 How to improve success rates

It is possible to build a framework for improved trial success centered on avoiding the above-identified risk factors for failure by systematically establishing and adhering to rigorous prerequisites for a trial. Many therapeutic areas boast higher success rates for phase 3 trials compared to obstetrics [1]. Success rates in obstetrics can be improved by drawing from strategies used in other clinical areas.

Failure at the phase 3 stage to demonstrate safety and efficacy frequently stems from inadequate understanding of underlying biological mechanisms and insufficient evidence from earlier stage clinical trials. Experimental medicine paradigms must be strengthened in obstetrics to improve the ability to predict and affect clinical outcomes. Funding bodies must improve efficiency in the overall scheduling and planning of clinical trials, with a sufficiently strong focus on proof-of-concept clinical trials in the early stages of drug development to justify larger later-stage studies. Finally, more predictive animal models must be used in the development of therapeutic agents for obstetrical populations [1]. While animal models play a significant role in perinatology research, their utility in the drug development process has been to some extent hampered by limited understanding of underlying biological processes in pregnancy. In addition, differences between human pregnancy and that in other animals present particular challenges in obstetrical research.

Small treatment effects can be of major clinical importance, and phase 3 trials must be adequately powered to detect such effects. Small but clinically important effects have been observed in phase 3 trials in other therapeutic areas. For example, the MRC/BHF Heart Protection Study of more than 20,000 high-risk individuals demonstrated a reduction in all-cause mortality from 14.7 to 12.9% ($p=0.0003$) and in coronary death from 6.9 to 5.7% ($p=0.0005$). Statin trials such as this have led to substantial changes in clinical care, despite showing smaller absolute effect

sizes (1.8 and 1.2% for all-cause mortality and coronary death, respectively) than nonsignificant effects found in smaller trials from other therapeutic areas [2].

Frameworks for improved trial success based on identified risk factors for failure have been proposed and utilized in several branches of medicine. A useful example comes from the area of critical care. Like obstetrics, critical care has suffered from multiple negative phase 3 trials. McAuley et al. [11] have proposed a stepwise approach to justify phase 3 RCTs in critical care in order to enhance the likelihood of positive results. The construction of this framework stemmed from an increasing recognition of the need to improve clinical trials in the area of critical care, a need that has not yet been saliently recognized in obstetrics.

The stepwise approach to justify phase 3 trials in critical care holds several valuable lessons for obstetrics. For example, one aspect common to pregnancy complications and critical care injuries is the heterogeneity of causes for a given condition. Accordingly, outcome definitions must be sufficiently specific and clinical trials designed to account for, or in some cases minimize, heterogeneity of the study population (appropriate patient selection). Also, phase 3 trials often fail to achieve planned sample size due to poor recruitment or high attrition rates. Effective recruitment and follow-up strategies may require a stronger commitment from funding bodies and study leaders.

7.6 Learning from experience – the example of antioxidants and preeclampsia

In addition to examining challenges faced in other clinical areas and drawing on their successes, we can learn from our own experience. A powerful and potent opportunity for such reflection can be found by examining the failure of phase 3 clinical trials to demonstrate effectiveness of antioxidants in the prevention of preeclampsia.

Oxidative stress is believed to play a role in a number of clinical disorders in obstetrics, including preeclampsia, a major contributor to maternal mortality and maternal and perinatal morbidity. There is a substantial body of evidence linking oxidative stress to preeclampsia, although it remains uncertain whether this is a primary or a secondary phenomenon.

In 1999, Chappell et al. [13] reported the results of a phase 2 trial of the effects of the prophylactic administration of antioxidant vitamins C and E in pregnant women. Women with risk

factors for preeclampsia were included in the trial, the most frequent being a positive screen on uterine artery Doppler. The trial was stopped before the full sample size could be achieved, as the proportion of women experiencing preeclampsia, as observed in an interim analysis, was reduced in the active treatment group. In fact, a biochemical indicator of endothelial dysfunction (PAI-1:PAI-2), and not preeclampsia, was the major endpoint of this phase 2 trial. However, the relationship of this marker to clinical disease was unclear. Furthermore, at the time that the study was initiated, little information was available as to whether the doses of vitamins C and E administered were those most likely to produce an antioxidant effect.

Thus, while the findings of this phase 2 study were exciting, it suffered from those limitations that placed subsequent phase 3 studies at high risk of failure: absence of data on dose-finding, uncertain mechanism of action, and high risk of alpha error due to early stopping of the phase 2 trial. Subsequently, nine large multicenter trials, including patients at high risk of preeclampsia and those where nulliparity was the only identified risk factor, were conducted to assess the role of vitamins C and E in the prevention of preeclampsia [14]. All yielded negative results. One of the trials was led by the senior author of the current chapter (WDF), and was stopped before recruitment was completed due to concerns raised in the intercurrent reporting of a separate trial about possible effects of the intervention on the risk of low birth weight [15].

Could this have been avoided? In retrospect, given the limitations of the initial phase 2 study, the most prudent approach might have been simply to attempt to replicate the findings using a rigorous design and predesigned stopping rules, while collecting more data on possible biological mechanisms. Or, at the very least, through international collaboration, could a single trial have been conducted rather than separate trials in Canada, the UK, the US, Australia, and Brazil?

The decision to conduct phase 3 studies in such a context should be based on a cross-disciplinary consensus, involving both basic scientists and clinical trialists. From a global perspective, in order to optimize the use of scarce resources, international expertise and collaboration should be brought to bear on prioritizing research questions, so that only studies meeting the most rigorous criteria at the phase 2 level are given priority for phase 3 research.

The result of this “cumulative” failure has been that even those who have been longstanding leaders and supporters of clinical research in preeclampsia expressed a skepticism regarding the impact of large trials. “Thus for over a decade now, many large and expensive multicentre randomized trials have failed to show

significant reductions in the incidence of preeclampsia, or, when positive results occurred, the significance was small and the number to treat large" ([16], p. 1119).

Conclusions and recommendations

As we have demonstrated in this chapter, one of the problems we are faced with is an absence of clear criteria about what constitutes sufficient evidence to move forward with a phase 3 obstetrical drug trial. The lack of systematic criteria is of significant concern because of the high stakes entailed by these studies: large well-conducted RCTs are expensive, time consuming, and a strain on finite resources [17]. Obstetrical trials also draw from a limited pool of patients. A negative phase 3 trial that could have been avoided with improved planning constitutes a significant waste of resources. Yet another crucial issue highlighted in this chapter is the absence in the scientific literature of the recognition of the need to establish such systematic criteria in the first place.

In order to be justified, phase 3 trials require rigorous phase 2 studies that [1] have been rigorously conducted from a methodological perspective; [2] demonstrate some measure of efficacy on unequivocal endpoints – either the disorder itself or on a marker that has been confirmed to be part of disease pathophysiology; and [3] when a new molecule is introduced, or when a medication is repurposed for an indication other than that for which it was initially intended, the mechanism of action should be clearly understood. Phase 2 studies should also produce a sufficient demonstration of safety and should determine the adequate dosage most likely to provide clinical benefit.

To compile and assess the phase 2 evidence on novel therapeutic agents, studies must be evaluated using carefully executed systematic reviews that sufficiently take into account the potential for publication bias and type I error in individual studies. In cases where phase 2 trials were not conducted with adequate statistical rigor or when results are statistically questionable, "promising" findings should be replicated with further phase 2 studies rather than moving prematurely to a phase 3 trial. When meta-analyses and RCTs on a subject are contradictory, careful consideration must be taken to ensure that the decision on whether to move ahead with a phase 3 study is based on a complete review of all available data.

Several steps can be taken to improve consistency in the IRB review of obstetrics trials. Summarizing and assessing the existing

evidence base on novel therapeutic agents is a complex task requiring time and skill. It is essential that funding agencies be equipped with the necessary expertise and resources to make such decisions. Investigators can help by including in phase 3 RCT proposals a demonstration of robust phase 2 evidence and a known biological mechanism of action.

Further collaboration between both basic science and clinical trial researchers across centers, as well as open dialogue between all experts in the field, could go a long way in optimizing the use of scarce resources in the area of obstetrical drug trials. For this reason, we urge all researchers active in this discipline to participate in evaluating and critiquing the studies published by their peers. Critical review of small or preliminary studies should make clear their merits and faults; this would undoubtedly aid in identifying promising avenues for further research and minimizing the risk for failure of any subsequent trials.

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Ethics of Clinical Pharmacology Research in Pregnancy

8

Marvin S. Cohen

There is no need for ethics in a world free from conflicts. In clinical research there is, however, one inherent conflict. Research subjects are at risk of incurring multiple harms without any guaranteed direct benefit. Instead they are exposed to variable risks solely for the possible benefits to themselves or to future generations in the form of generalizable knowledge. In 1979 the federal government commissioned the Belmont commission to recommend ways to guarantee safe and ethically sound research [1]. Their report canonized three principles of ethical research. The first principle of beneficence demands that all risks be minimized and proportionate to benefits, while the second principle of respect for autonomy should be fulfilled with a rigorous informed consent process. Justice, the third principle defined in the Belmont report, directed that all factions of society share equally the benefits and risks of research. Federal regulations establishing institutional review boards (IRBs) and review policies were enacted to ensure the implementation of these recommendations [2].

Yet, despite this effort to encourage safe and ethical research, studies on the specific effects of most drugs during pregnancy are lacking [3]. The Cochrane report on psychopharmacological agents in pregnancy recently bemoaned the sorry state of our knowledge of prescribing and using these agents in pregnant patients [4]. Anyone who is pregnant or whose loved one is pregnant has witnessed the consternation of not knowing whether to continue using these medicines or not. The occasional headache or upper respiratory infection can be a cause for hours of soul searching about whether the pregnant woman should take over-the-counter medications.

In 2009 the Hastings Center published a paper that demonstrated continuing biases among both medical professionals and the media about the risks of pregnancy. CT scans are rarely prescribed to pregnant patients with abdominal pain even though the risk of misdiagnosing an appendicitis is much greater than the risk of the exposure of the pregnant patient or the fetus to the radiation dose of a CT scan [5].

An online search for drugs that are safe during pregnancy repeatedly finds that even the best sites use language that can easily be understood to discourage the use of any medications during pregnancy. For example, the website "E-medicine" has this sentence in its introduction to the chapter on teratology and drug use during pregnancy: "Because any medication can present risks in pregnancy, and because not all risks are known, the safest pregnancy-related pharmacy is as little pharmacy as possible" [6]. The same article notes that while some studies quote the frequency of drug-related fetal complications at 1–3% the article authors could find no evidence to corroborate this number.

Table 8.1 summarizes the conditions that need to be satisfied to guarantee an ethical study.

Ethical research requires clinical equipoise. In order to begin a clinical research project there must be a lack of a scientific consensus for the optimal therapeutic option for a particular diagnosis. In other words, for a given clinical situation no specific treatment has been shown to be preferable among various alternatives. Usually one positive study is not enough to alter the clinical equipoise of the physician. Only after a number of studies have shown the same result can a therapy be considered a true advance.

Table 8.1 Necessary conditions for ethical clinical research [7]

Generates useful knowledge that has social benefit
Previous theoretical and animal studies have indicated a high chance of a positive result
A demonstrated need to include human subjects in order to ensure scientific validity
Clinical equipoise of both the researcher and subject
A favorable risk–benefit ratio
An equitable selection process of subjects
A thorough, informed consent process
Independent review, authorization and follow-up of the study design, protocols and results
Opportunity for subjects to withdraw at any time
Protocols for secure handling of all data and personal identifying information
Prompt notification and treatment of all complications

Clinical equipoise should also be clear to the research subject. If the potential subject enrolls in the study because she believes she will get optimal treatment, there is a risk that she will mistake the research study for a proven treatment. This mistake is called the therapeutic misconception. In many studies the clinical researcher may be part of the clinical team treating the patient. It is easy for a patient to assume that her treating physician would only want the best treatment for her and therefore agreeing to participate in the study is the best treatment. This is the therapeutic misconception since in reality there is no "best treatment".

Ensuring a favorable risk–benefit ratio requires a detailed understanding of both the risks and benefits of a study. The benefits of research participation to the individual include direct benefits to the subjects from possible exposure to new and improved therapies. Indirect benefits include more access to the medical team, a promise of hope, and the psychological benefits of being a Good Samaritan. Reimbursements and minimal payments are also an acceptable benefit if provided at a level that is not unduly coercive to disadvantaged populations. The risks of research participation include the complications of the medical procedures and of the experimental therapy itself, the inconveniences of multiple visits, and the possible violation of privacy.

The necessary components of a rigorous informed consent process are delineated in Table 8.2.

What differentiates research on pregnant patients from any other clinical study? With pregnancy we have two subjects instead of one; mother and fetus. The risks and benefits of the research must be balanced for both of these patients. However, the fetus is clearly not able to give consent to this calculation. It is, therefore, the joint responsibility of the mother and the researcher to guard the interests of the pre-viable fetus, but it is the mother who must give her informed consent to participate in the study.

Drs Chervenak and McCullough have published extensively on the ethics of research with pregnant subjects. Their suggestions are a productive way to work through the ethical issues surrounding

Table 8.2 Necessary components of informed consent [8]

Competency
Disclosure
Absence of coercion
Choice
Authorization

research with pregnant subjects. They understand the fetus to have dependent moral status [9, 10]. Accordingly, the pre-viable fetus has moral status only because the mother has decided to bring the baby to a live birth. This moral status is therefore conferred by the mother and could be withdrawn at any time before viability. It is the mother that must consider the research risks and benefits to the dependent fetus as well as her own risks and benefits. This approach expresses respect for the pregnant patient's autonomy as she is authorized to give consent. It protects both the fetus and mother from undue harm since possibilities of harm to both entities are taken into account. It ensures the woman's active involvement in her care without interference by others. Finally, it supports her personal freedom of choice within the therapeutic milieu.

Federal regulations and case law agree with this approach. Part B of these regulations mandates that only the mother needs to give informed consent to participate in research that may benefit either herself as a pregnant subject or both herself and the fetus [11]. (Phase I studies where there is no benefit to the mother or researcher will be considered below.) The regulations make an exception for research that only benefits the fetus, in which case the federal regulations stipulate that an attempt must be made to obtain paternal consent. Some drugs that may be studied are given in pregnancy for the sole benefit of the fetus. These include steroids for fetal lung maturity and digoxin for fetal tachycardia. One example of such research that benefits only the fetus is a study to determine the efficacy of Flecainide as an alternative to digoxin for fetal supraventricular tachycardia [12]. Both the obstetric community and many women's groups are disputing the inclusion of paternal consent in this type of research by impugning the autonomous rights of the pregnant women.

In the past the pregnant patient has been excluded from most drug-related research. In 1977 the FDA (Food and Drug Administration) issued "General Considerations for the Clinical Evaluation of Drugs" [13]. These regulations excluded all women of childbearing potential from participating in phase 1 and early phase 2 studies. The FDA in 1993 attempted to remedy this situation by issuing more liberal guidelines dedicated to include all populations in research projects [14]. However, as we have seen above there is still a lack of pharmacological research on pregnant subjects.

In dedicating a section in the federal regulations to pregnant women, in addition to other populations such as children and prisoners, the government may have dangerously strengthened the idea that pregnant women are a vulnerable population. It is true that pregnant subjects can be considered a special subset because they have responsibilities to both fetus and themselves.

But it must be clearly stated, "Being pregnant does not by itself result in diminished decision-making capacity" [15]. Grouping pregnant patients with vulnerable populations unnecessarily obscures this fact. This unfortunate label is one reason IRBs are unduly hesitant to approve research involving pregnant women.

Ethical research including pregnant patients is generally understood to require balancing the risks and benefits to the patient and fetus. But Brody rightly pointed out that Part B as written requires us only to minimize the risks [16]. It does not mention balancing risks and benefits. Minimizing risks can be accomplished by a stepwise process beginning with adequate animal studies done only on drugs that have a sound theoretical basis for assuming their safety and efficacy. Those drugs that have been shown to be safe and promising in animals should then be studied in non-pregnant humans to minimize the risk to pregnant women. Only after this should studies include pregnant women. In addition many drugs have been in wide clinical usage without reports of serious or frequent side effects in pregnant patients, although they have never been formally studied in pregnancy. These drugs should be the first drugs of a certain class to be studied in pregnant subjects. In 2005 the European Medicines Agency's (EMEA) Guideline on the Exposure to Medicinal Products During Pregnancy encouraged the systematic collection of data on complications in these drugs as a way of increasing our knowledge where randomized double blind studies are lacking [17]. Pharmacokinetics studies of these drugs can also be done with minimal risk as they would have been prescribed for the patient even without the study.

Studies such as phase 1 inquiries with no therapeutic benefit require the more stringent criterion of minimal risk to the fetus because there is no direct benefit to either the mother or fetus in these studies. But this concept of "minimal risk" can be ambiguous. Minimal risks are defined in the federal regulations as the risks which research subjects accept while performing their daily activities [2]. These risks might include the danger of being hit by a car when crossing the street or drowning when swimming in the sea. But should these be daily risks of a generic person? Or perhaps it should be a sick person who clearly experiences greater daily risks from hospitalization or treatment? In general the daily risks incurred by the specific subject should be used in determining minimal risk, as this is the most stringent criterion.

The process of informed consent with a pregnant subject should be very vigorous since including a pregnant woman in research involves two subjects. Many of the decisions affecting a pre-viable fetus may be irrevocable. The subject must be able to articulate her understanding of the risk–benefit calculations for both herself and

her fetus. A written record of this understanding is preferable, as it will insure that the subject has made the necessary determinations.

Regulations regarding pregnant teens are governed by individual states. Every researcher must be familiar with the standards applicable in her region. In most instances one parent of the adolescent research subject must give consent while the adolescent herself should articulate her understanding and consent to the research project.

Unforeseen complications may arise during the research protocol that may necessitate decisions about termination of the pregnancy. The research team should not be involved in these decisions. Instead, the primary care provider should be consulted. This possibility is a good reason to include the patient's primary physician at the earliest stages of the consent process.

There have been many recent disclosures of serious misconduct in research due to apparent conflicting interests of the researchers [18, 19]. Although such deviations have not yet been reported in pharmacologic research in pregnant patients, this probably is a result of the paucity of such studies. Conflict of interest in research occurs when the researcher, who is entrusted with the public trust, is unduly tied to secondary interests that compromise his primary trust. The primary responsibilities of researchers must be the best interests of the research subject and the scientific validity of the study. This is self-evident, yet research is being compromised because it seems that fortune and fame are unquenchable human drives that can cloud the judgment of anyone, including academic scientists [20]. A desire for academic promotion and recognition is another example of the stumbling blocks that all of us must be wary of. The old adage of "publish or perish" that has been replaced by "get funded or get fired" creates a very competitive academic climate.

A study from 2003 published in JAMA [21] found that over 25% of academic researchers had financial relationships with industry. The same study found that industry-sponsored research sometimes used flawed control arms, and that the published conclusions tended to be overwhelmingly positive. Although no direct connection was found, the inference was made that privately funded research can be biased towards reporting positive results.

Even the appearance of conflict of interest can taint many subjects' willingness to enroll in a study. They may ask, "Why should I put myself at risk when only the researcher stands to materially benefit from my sacrifice?"

To minimize conflicts of interests and to fulfill our duty to respect our subjects, disclosure of all pertinent financial interests is now mandated [22]. It is hoped that by openly acknowledging possible conflicts the researcher will be more focused on his

primary responsibilities, and the subject will be better informed about her total exposure to risks. These conflicts must be disclosed to the IRB and through their reporting to the sponsoring institutions and to the NIH (National Institutes of Health) or FDA if appropriate. The same standards of disclosure also apply when publishing research results. In general you should disclose anything you feel uncomfortable revealing to the subject, institution, or company.

Protecting the personal health information (PHI) of patients and research subjects is a major concern in this age of electronic data. See Table 8.3 [23].

Preventing PHI from being made public without consent demonstrates respect for personhood. More practically it can avert the multiple harms that breaches of privacy can cause. These harms include economic loss, social embarrassment, psychological damage, and legal complications.

Successful strategies can minimize breaches of privacy. It is important to choose an innocuous study name. Stringent protocols to code electronic data and secure all paper data and electronic storage must be implemented. Staff should undergo ongoing training including instructions to limit oral communication about individual subjects' private spaces.

In the case of a breach of privacy, the subjects must be immediately informed and the breach reported to the supervising authorities.

This chapter reviewed the ethical issues surrounding clinical research with pregnant subjects. The principles of bioethics applicable to research are beneficence, autonomy, and justice. Researchers must minimize the risks to both the mother and the fetus. Pregnant women must consider not only their own risks and

Table 8.3 PHI (1)

Names
Addresses more specific than state
Social security numbers
Medical record number
Health plan registration
Telephone and fax numbers
Email addresses
Web addresses
Any other information that can be used to identify an individual

benefits, but also the risks and benefits of their fetus. Conflict of interest must be minimized and privacy protections guaranteed. Finally, it is important to emphasize that any methodology or system can only hope to minimize the inherent ethical challenges of our human endeavors. The only guarantee of proper ethical conduct in a clinical research study is the virtuous and ethical behavior of the researcher.

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Questions for further discussion

1. A woman prefers a certain treatment for cosmetic reasons but without any scientific evidence that proves better efficacy or fewer complications. Is this still a state of clinical equipoise?
2. How can we assure that the informed consent process is individualized to the needs of each subject if there is a uniform consent process and form?
3. Should researchers be prohibited from owning stock in pharmaceutical companies?

Pharmacogenomics in Pregnancy

9

David M. Haas and David A. Flockhart

9.1 Pharmacogenomics

> "If it were not for the great variability among individuals, medicine might as well be a science and not an art."
>
> Sir William Osler, 1892

While much drug development and many clinical practice guidelines do not directly address variability in drug response, and in many cases assume that the effects of drugs on patients can generally be predicted, the evidence indicates otherwise. Significant numbers of patients do not respond to many medications, and adverse events that accompany drug therapy often compromise the quality of life of patients, limiting compliance with therapy, and can even be fatal in rare circumstances. The reasons for this variability in drug response often lie in easily accessible clinical factors including disease severity, age, weight, gender, ethnicity

or drug–drug interactions. Other factors may also be important, however, and in situations where readily available clinical predictors such as these are inadequate alternative biomarkers of drug response can be used. In many situations the need for new biomarkers is urgent, perhaps most clearly in the case of diseases such as psychiatric disease or cancer, where considerable morbidity is incurred when therapy is ineffective or impossibly toxic for individual patients.

While improved efficacy is clearly a goal of the new era of "personalized medicine" heralded by the development of increasingly sophisticated new biomarkers of drug response, the occurrence of unanticipated adverse effects is also of great concern. It is clear that considerable damage is done to the public health by such adverse events. In the largest study of in-hospital morbidity published to date, the incidence of serious adverse drug reactions (ADRs) was 6.7%, and of fatal ADRs was 0.32%, and it was estimated that of 2 million patients 216,000 experienced serious ADRs and over 100,000 had fatal ADRs in one year, making these reactions between the fourth and sixth leading cause of death [1]. The cost was estimated at more than 100 billion dollars per year in 1994. It follows that biomarkers that can *predict* and also *prevent* adverse events would also be of great potential value.

Biomarkers of drug response in clinical practice are far from new. Tests such as the international normalized ratio (INR) used to monitor warfarin response, the presence of estrogen or progesterone receptors on breast tumors used to guide anti-estrogenic therapy, and the testing of patients with HIV or hepatitis C for viral loads are all a routine part of daily practice that health care professionals have become comfortable with. We have learned that clinically useful biomarkers of drug response are of most value in situations where there is great variability in response, and a clear clinical decision, such as a change in drug, dose or therapeutic approach results from a test. It is equally clear that a test must have iterative value over existing easily available clinical predictors in order to be useful. For example, a test designed to predict the efficacy of an antihypertensive agent that had less predictive ability than routine measurement of blood pressure would be of little value.

The advent of genomics has brought a series of powerful new tools to this predictive science. While proteomics and metabolomics show great promise, it is with germline genomics, the study of the genetic sequence that we inherit from our parents, that we have the most experience. There are a number of reasons why the science of pharmacogenetics (or pharmacogenomics) appears valuable in this context. Not least among these are the simple facts

that DNA is very stable and easy to amplify, and that there exists a map of the human genome and of the international hapmap (http://www.genome.gov/10001688). In addition, the cost of DNA testing continues to drop dramatically.

While many definitions of the differences between the science of pharmacogenetics and that of pharmacogenomics have been put forward, a useful distinction appears to be simply that "pharmacogenetics" refers to the study of individual candidate genes, while "pharmacogenomics" refers to the study of whole pathways of genes, and indeed the entire genome.

9.2 Genetics and polymorphisms

Genetic variation in the sequence of about 3 billion nucleotide pairs that make up our DNA comes in many forms, but the most common differences between people are in the form of single nucleotide polymorphisms (SNPs). These are single letter nucleotide changes and they are referred to as a "polymorphism" if they occur in 1% or more of the population. This is because variants that are that common tend to be stably present in a given population, whereas variants present at less than 1% tend to drift out. There are 12–15 million such variants, and they have been meticulously catalogued by the human genome project in the publicly available database called dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/). Since SNPs are the most common and easily accessible form of variability they form the basis of the first genome-wide association testing studies (GWAs) that have been used to test for associations between common variants in the genome and nearly every form of human pathology (http://www.genome.gov/gwastudies/).

Other important forms of variation include deletions and insertions of sequence, variable number tandem repeats of short sequences that are clustered together and oriented in the same direction [2] and copy number variation: regions of the sequence that are copied with high fidelity within the genome itself. It has been estimated that such regions constitute up to 12% of the entire sequence in the genome [3].

Since only about 1.5% of the human genome sequence is used for the ~24,000 genes that code for proteins in humans, we presume that not all of it is relevant to therapeutic response, and that not all of this variability has functional or clinically meaningful consequence. That said, large numbers of variants that influence function via "nonsynonymous" changes in coding SNPs (cSNPs) have been

found, and a growing number of functionally important variants in intronic and regulatory regions have also been identified [4].

The use of GWAs to identify new genetic associations between SNPs and drug response has begun and already a significant number of important discoveries have resulted. These include the discovery of the SLC transporter with the muscle toxicity incurred by the use of the statin class of drugs [5], and of a gene in the IL17 pathway with the musculoskeletal toxicity associated with the use of aromatase inhibitors in patients with breast cancer [6]. It is widely appreciated that a large number of new patterns of multiple genetic associations will result from this effort [7], such that tests that involve large numbers of variants organized into a predictive pattern will become commonplace. The use of such predictive patterns is already commonplace in breast cancer, where arrays that test for 20–100 RNA species in a tumor at once are routinely used to predict the value of chemotherapy in individual patients [8].

Within this large field of research, our understanding of genetic factors that affect drug disposition far exceeds our understanding of the factors affecting response. This is in part because pharmacokinetic changes are relatively easy to measure whereas the "phenotype" of overall drug response is more complex. In addition, cloning of most drug-metabolizing enzymes and drug transport proteins within the past 20 years combined with the genetic polymorphism information generated by the sequencing of the human genome and catalogued in dbSNP have allowed a comprehensive characterization of variability in drug metabolism and transport. As the practice of searching for, identifying and then using determined genetic characteristics as predictors of drug effect becomes more common, it is clear that physicians, pharmacists, and nurses, the clinical community of health care providers, will have to play an increasing role as the value of carefully defined, valuable, clinical phenotypes and their individual genetic and genomic associations increases.

9.3 Genes that influence pharmacokinetic variability

It is well recognized that pharmacokinetic variability is most apparent for drugs that are metabolized, and that the majority of this variability is in turn due to inconsistencies in the ability of enzymes in the liver and gastrointestinal tract to carry out drug metabolism. A growing body of literature also makes clear

that differences in the activity of drug transporters in the kidney, blood–brain barrier, liver, and at the level of individual tissues between people contribute significantly to pharmacokinetic variability [9].

In terms of metabolic variation, the key enzymes involved include the cytochrome P450 family of drug metabolizing enzymes that carry out phase 1 drug metabolism, but also the phase 2 enzymes including the enzymes that carry out acetylation, glucuronidation, sulfation, methylation, and the addition of glutathione, all of which increase the solubility of hydrophobic small molecules, and catalyze their removal from the body.

The first genetic associations with drug therapy observed were those involving glucose 6 phosphate dehydrogenase (G6PDH) and sulfa drugs in African American soldiers, and in N-acetyl transferase in patients taking isoniazid for tuberculosis. Since then, 50 years of research on drugs metabolized by the cytochrome P450 enzymes has clearly documented CYP2B6, CYP2C9, CYP2D6, CYP2C19, and CYP3A5 as the most important enzymes that exhibit important genetic alterations.

Cytochrome 2B6 is the primary metabolic route for the metabolism of drugs used in the treatment of HIV, including the NNRTIs (non-nucleoside reverse transcriptase inhibitors), nevirapine, and efavirenz [10], but also contributes importantly to the metabolism of methadone [11], of cyclophosphamide [12], and of ketamine [13]. The enzyme has reduced function in patients who carry the *6 allele [10], and this variant has been associated with reduced rates of metabolism, and higher concentrations of all these drugs.

CYP2C9 is widely recognized as the principal enzyme involved in the clearance of the active S-enantiomer of warfarin. Genetic variants that notably reduce activity result in higher S-warfarin concentrations and in turn lower required warfarin doses, and this effect was obvious even when a genome-wide association study testing thousands of genes was carried out as identified [14].

CYP2D6 is the most studied of the genetically variable cytochrome P450 enzymes. Variants that result in complete "knockout" or loss of enzyme activity are present in 7% of Caucasian populations, and in 2–5% of African and Asian populations [15]. In addition, the *10 allelic variant that decreases, but does not eliminate, activity is present in more than 40% of Asians, and similarly the *17 allele reduces activity in 10–20% of Africans [15]. These changes result in clinically important changes in the metabolism of more than 40 drugs (www.drug-interactions.com) that include codeine [16], tamoxifen [17], a large number of the beta-blocker class of drugs that are metabolized, and the majority of clinically available antidepressants, including fluoxetine,

paroxetine, and venlafaxine. Changes in the concentrations of these drugs and their metabolites brought about by CYP2D6 genetic variability have been intensely investigated [18], and those with venlafaxine appear to be sufficient to result in clinically significant changes and recommendations for dosing changes [19]. A notable example of genetic variation within the CYP2D6 gene is the presence of copy number variation, such that up to 13 copies of the entire gene have been shown to exist in some families, and to be passed down through the generations in a Mendelian manner [20].

CYP2C19 is also genetically variable, with loss-of-function variants designated as *2 and *3 that are present in 15–30% of Asian populations, and 2–5% of Caucasians and Africans. While a large number of drugs are metabolized by this enzyme [21], it is the dominant route for the metabolism of clopidogrel to its active metabolite, and this has resulted in a huge amount of attention because of the widespread use of this drug in cardiology. Plasma glucose variability in CYP2C19 has been clearly associated with alterations in platelet function during clopidogrel therapy [22] that have been clearly associated with cardiovascular outcomes in a large number of studies, but not all [23].

Recently, important variations in the genetics of CYP3A5 that influence concentrations of vincristine [24], cyclosporine, tacrolimus [25], and notably of nifedipine used in tocolysis [26] have been described. These variants associate with higher concentrations of the parent drugs and result in clinically significant toxicities.

While these genes represent some of those most studied among pharmacogenetic "VIP" genes, recent results of GWAs studies and targeted approaches across a wide range of genes involved in specific diseases have resulted in the development of clinical tests. An easily accessible catalogue of such genes has been collected by the Pharmacogenetics and Genomics Knowledge Base (PharmGKB) at www.pharmgkb.org

9.4 The current state of pharmacogenetic testing

Pharmacogenetic testing has the potential to aid in the diagnosis and treatment of multiple conditions. In fact, as of July 2011 there were 15 different drugs or drug classes that had commercially available pharmacogenetic tests (Table 9.1).

Several pharmacogenetic tests have risen to become the standard of care in medical therapy. Patients with colon cancer are

Table 9.1 Fifteen drugs/therapies and their available pharmacogenetic tests as of July 2011

Drug/therapy	Test
Abacavir*	HLA-B*5701
Cetuximab for colon cancer*	KRAS
Imatinib*	BCR-ABL
Chemotherapy for breast cancer (various)	Oncotype Dx® and MammaPrint®
Carbamezepine*	HLA-B*1502
Clopidogrel	CYP2C19
Tamoxifen	CYP2D6
Metformin	OATP3
5-Fluorouracil	DPYD-TYMS
Clozapine	2 SNPs in HLA-DQB1
QT-interval prolonging drugs	Familion™
Irinotecan	UGT1A1
Azathioprine and mercaptopurine	TPMT
Warfarin	CYP2C9 and VKCoR
Interferon	IL 28b

*Standard of care in some clinical settings.

often treated with anti-epidermal growth factor (EGRF) monoclonal antibody therapy in the form of cetuximab. A mutation in the KRAS gene codon 12 or 13 leads to resistance to cetuximab therapy [27]. Thus, the American Society of Clinical Oncology (ASCO) has recommended that all patients with metastatic colorectal carcinoma who are candidates for anti-EGRF therapy should have their tumor tested for KRAS mutations. If codon 12 or 13 mutations are detected, then the patients should not receive anti-EGRF therapy as part of their treatment [27].

The cutaneous adverse drug reaction Stevens–Johnson syndrome (SJS) is a serious concern for people taking drugs such as abacavir and carbamazepine [28, 29]. Pharmacogenetic screening for the HLA-B*5701 can help identify those who are most at risk for developing this severe adverse drug reaction with abacavir. Carriers of this HLA-B allele should not be given abacavir. This test is now widely used for screening patients in need of abacavir to avoid SJS in the developed world [30]. In addition, HLA-B*1502 testing is becoming the standard of care for Asians prescribed carbamazepine to avoid severe cutaneous drug reactions [28].

For those with chronic myelogenous leukemia, imatinib inhibits the BCR-ABL-activated tyrosine kinase, interrupting signal transduction pathways that would otherwise lead to leukemic transformation. In this way, imatinib has led to impressive survival benefits in these patients [31]. However, a mutation in the BCR-ABL gene negates the benefits of imatinib. As imatinib is an expensive therapy, pharmacogenetic testing is employed in this scenario to avoid prescribing a costly therapy that would not be as beneficial in patients with the mutation.

Commercially available pharmacogenetic testing panels such as Oncotype Dx® and MammaPrint® have been promoted for women about to undergo chemotherapy for breast cancer [32, 33]. ASCO and other organizations have included some of these tests in their guidelines as options to predict benefit, particularly from tamoxifen therapy [34]. These are examples of commercially available tests that are not yet standard of care recommendations. Other tests that similarly have data supporting their potential role for individualizing therapy are the CYP2D6 testing for tamoxifen [35, 36] or venlafaxine [19], CYP2C19 testing for clopidogrel antiplatelet therapy [23], and CYP2C9 and VKCoR testing for those starting warfarin therapy [37–39].

Other tests are available for different conditions and/or drug therapies. At the time of writing of this chapter, however, the remaining tests have not developed the cache of evidence or treatment guideline support to become commonplace in practice. However, with the advent of new pharmacogenetic tests, pharmacogenetic modeling strategies, and the need for individualized pharmacotherapy to avoid adverse events, pharmacogenetic testing will likely expand greatly in the next several years.

9.5 Potential therapeutic areas for pharmacogenomics in pregnancy

Most pregnant women take drugs for various conditions. Epidemiologic studies have documented that over 90% of pregnant women take a prescription drug, with most taking more than one [40, 41]. Even after eliminating prenatal vitamins and supplemental iron, over 70% of pregnant women take a prescription drug during the course of their pregnancies [41]. Many of the drugs commonly consumed by pregnant women are potential candidates for pharmacogenetic testing. Based on the drug metabolism pathway or receptors that serve as targets, pregnancy therapeutics may be a ripe area for pharmacogenetics.

As the cause of the majority of neonatal morbidity and mortality, preterm labor is a major focus of obstetric care and research. The use of tocolytic medications to stop uterine contractions is commonplace but of varying success [42]. Many tocolytics are substrates for polymorphic drug metabolizing enzymes. Nifedipine is a calcium channel blocker commonly used in obstetrics to stop contraction and delay birth. Nifedipine is metabolized by the CYP3A family. Recent studies have documented that CYP3A5 polymorphisms and concomitant use of known CYP3A inhibitors can impact the concentration of nifedipine in maternal blood [26]. Another potential pharmacogenetic target in preterm labor therapy includes indomethacin. Indomethacin, a nonsteroidal anti-inflammatory drug used to inhibit contractions, is metabolized by the polymorphic CYP2C9 and CYP2C19 [43]. SNPs in these enzymes can affect the concentrations of these tocolytics. As these two drugs may be the better first line agents for preterm labor [44], these pharmacogenetic implications should be further interrogated.

Depression is common in pregnant women. The selective serotonin reuptake inhibitors (SSRIs) are the first line agents to treat depression and other mood disorders in pregnancy. The SSRI drugs are metabolized by many different polymorphic enzymes (Table 9.2). Depression is commonly noted to be undertreated in pregnancy. It is possible that some of the undertreatment may be due to the combination of pregnancy physiology impacting the drug concentration as well as pharmacogenetic polymorphism causing reduced drug concentrations. The impact of SNPs in these enzymes on the effectiveness of SSRI therapy is an area of active investigation [45, 46].

Table 9.2 Drug metabolizing enzymes for SSRIs

Drug	Enzymes responsible for metabolism
Fluoxetine (Prozac)	CYP2D6, CYP2C9
Sertraline (Zoloft)	CYP2D6, CYP2C9, CYP2B6, CYP2C19, CYP3A4
Venlafaxine (Effexor)	CYP2D6
Paroxetine (Paxil)	CYP2D6
Fluvoxamine (Luvox)	CYP1A2
Buproprion (Wellbutrin, Zyban)*	CYP2B6
Citalopram (Celexa)	CYP3A4, CYP2C19
Escitalopram (Lexapro)	CYP3A4, CYP2C19

*Buproprion is not an SSRI but rather a serotonin-norepinephrine reuptake inhibitor

Nausea and vomiting of pregnancy (NVP) affects up to 80% of pregnant women [47, 48]. Both mild and severe cases of NVP have a significant impact on the quality of a woman's life and contribute significantly to health care costs and time lost from work [48, 49]. Many anti-emetic drugs are used with various mechanisms of action to counter NVP. These include vitamin B6, doxylamine, promethazine, metoclopramide, and ondansetron to name a few. Learning from anesthesia research, emesis and the effectiveness of anti-emetic drugs are potential pharmacogenetic targets. Ondansetron is metabolized by CYP2D6. Extensive and ultrarapid CYP2D6 metabolizers have been linked to ondansetron failure [50]. Also, the polymorphic serotonin receptor 5-HT3 facilitates the role of serotonin as a mediator of nausea and vomiting [51]. Variants in the 5-HT3B receptor are linked to increased nausea and vomiting due to increased response to serotonin binding [52]. 5-HT3 receptor variants are also associated with the severity of NVP (personal communication, data from our center). Thus, it is possible that identifying women with receptor variants with NVP may lead providers to utilize different medication to control a woman's NVP. The individualized treatment of NVP using pharmacogenetics is also an area of investigation.

These are just a few of the areas of drug therapy in pregnancy where pharmacogenetics may play a role [46, 53, 54]. As obstetrics moves into the genomics era, active pharmacogenetic research to help individualize therapy is ongoing. Maximizing the benefit for the mother and minimizing the risks to both the mother and fetus are the tenets of individualized pharmacotherapy. With both a mother and fetus to consider, optimizing therapeutics in pregnancy is pivotal. As a tool, pharmacogenetics may provide insights to help achieve maximal benefit with minimal risk.

9.6 Study designs and approaches to pharmacogenetics trials

Gathering quality trial data in pharmacogenetics is often difficult. Genetic testing is expensive and new SNPs are discovered frequently. However, there are key components of pharmacogenetic analyses that can help propel the field forward.

In general, analyses of trials focus on the mean changes in outcome measures of two or more groups. The outliers are often eliminated or statistically compensated for. However, in the field of pharmacogenetics, it is often those same outliers, the subjects in the tails of the bell-shaped curve, who are the most important to analyze. The subjects who have the most robust response to a drug

or the poorest response to a drug are often the ones who may have a genetic polymorphism in the metabolic or receptor pathway that is causing this. For instance, subjects who receive no benefit from a drug may have an SNP in an enzyme like CYP2D6 that makes them an ultrarapid metabolizer and thus not enough drug is available for effect. In that case, knowing the CYP2D6 status ahead of time could lead to either increased dose or utilizing a different drug.

Prospectively obtaining genotype information in a randomized clinical trial setting is difficult logistically. While genotyping costs are decreasing, the approach to genotyping needs to be considered. Assaying for particular candidate pathway genes may be efficient but could miss a key contributor. Using GWA assays or full DNA sequencing may be too expensive and give extraneous data. In addition, these become analytically complex. Using a pathway-informed GWA approach may be a practical way to limit the data needed and improve the efficiency of using the information.

Because of the expense and time needed to genotype a screening population for entry into a trial, newer adaptive trial designs have been utilized to make mid-study adjustments [55]. These adjustments may be based on genotypes. For instance, halfway through a drug trial, the subjects in the study could be genotyped in a batch to save on cost. Then an interim analysis might indicate that subjects with a certain SNP did not benefit at all at current doses. An adaptive trial design can then allow for dose adjustments for subjects with those SNPs for the remainder of the trial. In this way, adaptive trial designs can improve the efficiency of trials, allowing researchers to demonstrate effectiveness or ineffectiveness sooner, improving subject safety and yielding substantial time and cost savings [55].

As pharmacogenetic studies become more prevalent and the cost of genotyping is reduced, clinical trials of individualized pharmacotherapy will become more common. Up-front genotyping and stratified randomization based on genotyping are beginning to appear in studies. In these ways, pharmacogenomics is becoming an increasingly important tool that will be available for providers in the future for individualizing drug therapy.

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Analgesics and Anti-Inflammatory, General and Local Anesthetics and Muscle Relaxants

10

Sarah Armstrong and Roshan Fernando

10.1 Introduction

As with all drug use in pregnancy, the challenges of general and regional anesthesia include optimization of maternal physiological function, preservation and maintainance of utero-placental blood flow and oxygen delivery while avoiding unwanted effects of fetal exposure to drugs.

The likelihood of maternal and fetal exposure to anesthetic drugs in delivery has increased dramatically in recent years. It has been estimated that in developed countries 1–2% of pregnant women undergo anesthesia during pregnancy for surgery unrelated to the pregnancy. Of these procedures, approximately 42% are performed during the first trimester, 35% during the second, and 23% during the third [1]. Elective surgery and therefore anesthesia

should be avoided in pregnancy if at all possible and only after the first 6 postpartum weeks to allow resolution of the physiological changes of pregnancy. If necessary current opinion suggests that it should be delayed to the second trimester of pregnancy to reduce the risk of both teratogenicity and miscarriage although there is no firm evidence to support this approach. Emergency surgery must proceed regardless of gestational age in order to preserve the life of the mother.

Intervention rates involving the use of general or local anesthetics at delivery vary widely across the world. Overall epidural rates (including operative delivery and labor analgesia) are as high as 95% in some regions in the US. There is also an increasing overall rate of cesarean delivery worldwide, the highest being currently in China at around 46% in 2008 [2]. The increasing incidence of these procedures necessitates an increasing incidence of maternal and fetal exposure to anesthetic drugs. For cesarean delivery, regional anesthesia is more widely used and preferred where possible over general anesthesia. Regional anesthesia minimizes risks associated with general anesthesia including pulmonary aspiration of gastric contents, failed intubation, maternal awareness, maternal gastric ileus postoperatively, and fetal exposure to drugs. No studies have shown a beneficial effect on the outcome of pregnancy after regional anesthesia compared to general anesthesia. Before the initiation of any anesthetic technique, resuscitation facilities should be available for both mother and fetus.

10.2 General anesthesia

General anesthetics may be divided into intravenous and inhaled volatile anesthetics. Indications for general anesthesia in pregnancy are listed in Table 10.1 and include maternal disease requiring urgent surgery or cesarean delivery where regional anesthesia is not appropriate. As stated in other chapters, pharmacokinetic and

Table 10.1 Indications for general anesthesia in pregnancy

Maternal disease/trauma requiring emergency surgery unsuitable for regional technique
Urgent delivery of fetus (fetal or maternal threat)
Maternal refusal of regional techniques
Contraindications to regional technique (e.g. coagulopathy or infection)
Failed or inadequate regional technique
Delivery if at risk of obstetric major hemorrhage (e.g. placenta previa or accreta)

pharmacodynamic profiles are altered in pregnancy and drugs for general anesthesia should be titrated as a result.

The utero-placental circulation is not autoregulated and so fetal perfusion is critically dependent on maternal systolic driving pressure. Hypotension in general anesthesia is common, particularly due to decreased systemic vascular resistance induced by volatile or intravenous anesthetic agents, hypovolemia and aortocaval compression which is further exacerbated by the supine position. Obstetric patients after the first trimester should undergo general anesthesia in the supine position with 15 degree left lateral tilt to reduce aortocaval compression by the gravid uterus and meticulous attention should be paid to the maintenance of maternal systolic blood pressure through the use of intravenous fluids and vasopressors.

10.3 Inhalational anesthetics

The minimum alveolar concentration (MAC) of volatile agents is a term used to describe the potency of anesthetic vapors. It is defined as the concentration that prevents movement in response to skin incision in 50% of unpremedicated subjects studied at sea level (1 atmosphere), in 100% oxygen. Hence, it is inversely related to potency and the more potent the agent, the lower the MAC value.

Although it is more than 160 years since the first use of modern anesthetic agents, the mechanism of action of volatile anesthetics still remains elusive [3]. Inhaled anesthetic agents are thought to act in different levels of the central nervous system with both pre- and postsynaptic effects having been found. They may disrupt synaptic transmission by interfering with the release of excitatory or inhibitory neurotransmitters from the pre-synaptic nerve terminal, by altering the reuptake of neurotransmitters or by changing the binding of neurotransmitters to the postsynaptic receptor sites [4]. There is a high correlation between lipid solubility and anesthetic potency suggesting inhalational anesthetics have a hydrophobic site of action and direct interaction with the neuronal plasma membrane is likely.

In pregnancy neural tissues show increased sensitivity to effects of volatile anesthetics. The minimum alveolar concentration is reduced by 30% under the influence of progesterone and endogenous endorphins [5, 6]. The 25% increased alveolar minute volume from the first trimester (caused by both increases in respiratory rate (by 15%) and tidal volume (by 40%)) leads to a more

rapid induction of general anesthesia if an inhalational induction technique were to be used. In most cases of general anesthesia in the parturient, preoxygenation with 100% oxygenation precedes rapid sequence intravenous induction with cricoid pressure to secure the airway and to reduce the likelihood of pulmonary aspiration. This is followed by maintenance with 0.5–1.0 MAC of volatile anesthetic agents in either an air/oxygen or nitrous oxide/oxygen mix. Nitrous oxide has a rapid alveolar uptake and remains an important adjunct to reduce the risk of awareness during emergency cesarean delivery. Nitrous oxide if administered in high concentrations for long periods (more than 50% concentration for over 24 hours) has been shown to be a weak teratogen in rodents. Studies voicing concerns regarding nitrous oxide teratogenicity are not supported in clinical practice to date [7]. Insufficient general anesthesia or analgesia may cause awareness and substantial maternal catecholamine release which is generally considered to be more detrimental to the fetus.

The high lipid solubility and low molecular weight of all commonly used volatile anesthetics (Enflurane, Isoflurane, Sevoflurane, Desflurane, and Halothane) facilitate rapid transfer across the utero-placental unit to the fetus. If induction to delivery time is prolonged, it has been shown to result in lower Apgar scores in the fetus [8]. Low doses of volatile anesthetics in combination with nitrous oxide may improve uterine blood flow but may also induce uterine relaxation. After the fetus is delivered, increasing concentrations of nitrous oxide, systemic opioids, and IV oxytocin may be used to reduce the amount of volatile anesthetic required and to encourage uterine contraction. Nitrous oxide is poorly soluble and may be eliminated from the blood into the alveoli very rapidly. This effectively dilutes alveolar air, and available oxygen, so that when room air is inspired hypoxia may result. This "diffusion hypoxia" may occur in the neonate after delivery and so it would seem prudent to administer supplemental oxygen to any neonate exposed to high concentrations of nitrous oxide immediately before delivery [9].

10.4 Intravenous anesthetics

Rapid sequence induction (RSI) is the administration of a potent intravenous anesthetic agent to induce unconsciousness followed by a rapidly acting neuromuscular blocking agent to achieve motor paralysis for tracheal intubation. The choice and dose of intravenous induction agent is crucial to ensure a balance between

excellent intubating conditions with minimal maternal recall and high maternal blood concentrations with subsequent adverse maternal hemodynamic effects and fetal transfer. The lipophilic characteristics of intravenous anesthetic agents enhance their transfer across the placenta.

10.4.1 Thiopentone

Thiopentone is the most extensively studied intravenous anesthetic agent and has been shown to be safe in obstetric patients. It is administered in a dose of 3–7 mg/kg with 4 mg/kg being generally agreed to be unlikely to lead to fetal depression while doses in excess of 7 mg/kg are liable to do so [10]. Thiopentone rapidly crosses the placenta and has been detected in umbilical venous blood within 30 seconds of administration. However, as a result of rapid equilibration in the fetus thiopentone does not produce fetal neuronal levels high enough to sedate the neonate. Approximately 80% of thiopentone is protein bound and both maternal–fetal and feto-maternal transfer is strongly influenced by maternal and fetal protein concentrations. High fetal–maternal ratios suggest that thiopentone is freely diffusible but many factors must be involved in placental transfer as demonstrated by a wide intersubject variability in umbilical cord concentrations at delivery [1]. Some anesthesiologists use methohexital rather than thiopentone for induction of anesthesia and evidence from *in vitro* perfusion studies suggests rapid maternal to fetal transfer and vice versa.

10.4.2 Propofol

Propofol is now the most widely used drug in anesthetic practice and produces a rapid, smooth induction of anesthesia. It attenuates the cardiovascular response to laryngoscopy and intubation more effectively than barbiturates and does not appear to adversely affect umbilical cord gases at delivery. Increased maternal blood flow accentuates placental tissue uptake and rapid transfer across the placenta [11]. It is highly protein bound and so placental transfer is affected by changes in plasma protein concentrations and may be increased by reduced protein concentrations in the maternal blood. There are concerns over its capacity to produce neonatal depression and provide an adequate depth of (maternal) anesthesia [12]. An additional disadvantage of propofol is a long equilibration time from administration to effect site which may prolong the time period from injection to hypnosis. In one study comparing thiopentone 5 mg/kg with propofol 2.4 mg/kg maternal electroencephalograms were studied. Fifty percent of those women receiving propofol showed rapid low voltage (8–9 Hz) waves

on their electroencephalogram suggestive of a light plane of anesthesia and therefore potentially awareness compared to 10% of the thiopentone group [13]. This concern regarding the failure of propofol to produce maternal anesthesia has been found in other studies [14, 15]. Some studies have shown that propofol use may result in lower Apgar scores when compared to thiopentone even at lower doses where maternal awareness is a distinct possibility. As a result there are currently no major advantages to its use over thiopentone in pregnancy [16].

10.4.3 Ketamine

This phencyclidine derivative is used in a dose of 1–2 mg/kg for induction in obstetric patients in <2% of general anesthetics [17]. It has a rapid onset and provides analgesia, hypnosis, and reliable amnesia and may be useful in patients with asthma or modest hypovolemia. It rapidly crosses the placenta and a dose of 1 mg/kg appears not to be associated with an increase in uterine tone unlike larger doses. Its use is limited in preeclampsia and hypertension due to its sympathomimetic effects, and due to the risk of increased uterine tone and asphyxia it should not be used in the first two trimesters. There are practical concerns regarding hallucinations and emergence phenomena although both are dose related and are thought to occur less frequently in obstetric patients [18]. Apgar scores and umbilical cord gases appear to be similar as with other IV induction agents.

10.4.4 Etomidate

This carboxylated imidazole has been used in pregnant women who are hemodynamically unstable when it is important to maintain baseline systolic blood pressure. However, there are currently no adequate and well-controlled studies in pregnant women. Potential side effects include pain on injection, postoperative nausea, myoclonus, and adrenal suppression. Etomidate should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus.

10.4.5 Benzodiazepines

This class of drugs is rarely used as the sole anesthetic agent due to their relatively slow maternal onset and offset and neonatal depressive actions. They may be used as co-induction agents. Benzodiazepines have been associated with cleft lip and palate in animal studies but the association in humans is controversial and a single dose has not been associated with teratogenicity

[19, 20]. Long-term use should be avoided due to the association with neonatal withdrawal.

10.4.6 Systemic opioids in pregnancy

As part of general anesthesia short- and long-acting systemic opioids may be administered for analgesia, facilitation of intubation, and attenuation of the stress response to surgery. Placental transfer to the fetus of systemic opioids is passive; however, opioids have been safely used for pain relief in pregnancy for decades. As with the non-pregnant population, maternal opioid administration is associated with a number of adverse side effects including nausea and vomiting, pruritis, sedation, respiratory depression, urinary retention, and constipation.

In addition neuraxial anesthesia may be contraindicated or refused in labor or at cesarean delivery necessitating the use of intravenous patient-controlled analgesia using opioid drugs such as fentanyl or remifentanil. Remifentanil is a short-acting mu-opioid receptor agonist [21]. It has the advantage of a rapid onset and offset of action (context-specific half-life of 3 minutes in both maternal and neonatal studies) being hydrolyzed by non-specific tissue esterases and excreted in the urine. Both drugs can cause significant respiratory depression and thus it is mandatory that all laboring women using this technique have adequate supervision and monitoring with maternal pulse oximetry and fetal heart rate monitoring.

Meperidine intravenously results in rapid transfer across the placenta and fetal/maternal ratios may exceed 1.0 after only a couple of hours. This is thought to be due to maternal metabolism exceeding fetal metabolism of the drug [22]. It has been associated with neonatal central nervous system and respiratory depression.

Morphine also rapidly crosses the placenta (although transfer is membrane-limited and there appears to be a fast placental washout) and has been shown to be associated with a reduction in fetal biophysical score [23]. Fentanyl is highly lipophilic and rapidly transferred to the placenta. It has been detected in early pregnancy in both the placenta (which acts as a drug depot) and fetal brain [24]. Maternal alfentanil administration has been associated with a reduction of 1-minute Apgar scores despite a relatively low fetal/maternal ratio [25–26]. Maternal sufentanil administration results in a very high fetal/maternal ratio of 0.81. Human placental studies have confirmed this rapid transfer across the placenta which is influenced by fetal pH and differences in maternal and fetal plasma protein binding [27].

10.5 Neuromuscular blocking agents

In pregnancy individual drug metabolism is heterogeneous reflecting the separate pregnancy-related changes in each drug-metabolizing organ system. Neuromuscular blocking agents are required for general anesthesia in nearly all cases where endotracheal intubation is required and may be depolarizing or non-depolarizing agents. They are highly polar, fully ionized molecules that do not cross the placenta in significant amounts and fetal blood concentrations of muscle relaxants are 10–20% of that of maternal blood [28]. Neonatal hypotonia is rarely seen following induction of general anesthesia with muscle relaxation.

- Depolarizing muscle relaxants include suxamethonium which acts by depolarizing the plasma membrane of the skeletal muscle fiber making it resistant to further stimulation by acetylcholine. It induces rapid paralysis (within 30–90 s) with a short offset time (2–5 min) in order to safely facilitate tracheal intubation in the presence of increased risk of aspiration as found in the second and third trimesters. It is metabolized by plasma cholinesterases.
- Non-depolarizing neuromuscular blocking agents act by competitively blocking the binding of acetylcholine to its postsynaptic receptors. This class of drugs includes the aminosteroids (pancuronium, vecuronium, and rocuronium) and the benzylisoquinolines (atracurium, doxacurium, and mivacurium). These drugs have a longer onset time (1.5–3 min) and offset time (20–60 min) compared to suxamethonium. The aminosteroids undergo in general a combination of hepatic and renal metabolism and excretion. Atracurium is broken down to inactive metabolites by ester hydrolysis (the minority) and spontaneous Hoffman degradation (the majority) to laudanosine.

The marked physiological reduction of plasma cholinesterase levels in pregnancy (by 30% from early in the first trimester to several weeks postpartum) theoretically causes suxamethonium to have a prolonged effect. This is, however, counterbalanced by the increased maternal volume of distribution. Maternal doses of more than 300 mg (recommended dose 1–2 mg/kg) are required before the drug can be detected in umbilical venous blood [29]. Fetal pseudocholinesterase deficiency or repeated high doses of suxamethonium may lead to neonatal neuromuscular blockade [11, 30]. Rocuronium demonstrates an unaltered onset time at a dose of 0.6 mg/kg but shows a longer duration of action in pregnancy [31] whereas vecuronium shows a faster onset at a standard dose of 0.2 mg/kg but also an extended duration of action [32]. The advent of sugammadex, a reversal agent for rocuronium and to a

lesser extent vecuronium, may herald the increased use of these drugs in obstetrics although more studies are required to establish the safety of this drug in obstetrics and postpartum [33, 34]. Non-depolarizing muscle relaxants are often administered in bolus form, which may result in an increase in fetal blood concentration over time even though the transfer rates are relatively low [35].

At cesarean delivery usually only a single dose of suxamethonium is needed but may be followed by small boluses of a short-acting, non-depolarizing neuromuscular blocking agent. For other surgery requiring neuromuscular blockade longer-acting, non-depolarizing neuromuscular blockers may be employed but time should be allowed for adequate reversal of effects. Monitoring of neuromuscular function is recommended in all cases. Magnesium sulfate is known to decrease requirements of non-depolarizing neuromuscular blockers and prolong their effects and this should be considered in cases of preeclampsia and eclampsia.

10.6 Regional anesthesia

The advantages of maternal regional anesthesia for incidental surgery in pregnancy, analgesia in labor and for operative or instrumental delivery are substantial and advantages of central neuraxial blockade are listed in Table 10.2. Infiltration of local anesthetic may be employed, for example in episiotomies and paracervical blocks. It should be noted that there are significant contraindications and complications associated with regional techniques and of which the patient should be made aware when consenting for regional anesthesia.

Table 10.2 Advantages of regional anesthesia in obstetrics

Greater maternal satisfaction
Enables maternal participation
Reduces catecholamines and potentially improves placental blood flow
For operative anesthesia:
Reduced risk of GA (↓ maternal aspiration, ileus, awareness, ↓ fetal exposure to drugs used for general anesthesia)
Improved respiratory function
Reduced intra-operative blood loss
Improved maternal bonding, earlier breastfeeding, less postnatal depression
Good postoperative analgesia
Increased mobility with low-dose epidural (e.g. 0.125% bupivacaine and 2 mcg/mL fentanyl)

Local anesthetic drugs are weak bases and exist predominantly in the ionized form at physiological pH as their pK_a exceeds 7.4. Each possesses an aromatic lipophilic group and a hydrophilic group and they are classified as either esters or amides, the name describing the linkage between the groups. Commonly used local anesthetics in obstetrics have low molecular weight, high lipid solubility, and low ionization and include bupivacaine, levobupivacaine, lidocaine and ropivacaine (amides), and chloroprocaine (ester). These agents work by binding to the receptor sites of sodium channels, blocking ion movement across nerve cell membranes and preventing the initiation and propagation of the action potential and subsequent sensory nerve transmission. Local anesthetics cross the placenta by simple diffusion. Due to a relative fetal acidosis there is fetal accumulation of local anesthetic (also known as "ion trapping"). Transfer to the fetus is also affected by total dose, site of administration, and use of adjuvants such as epinephrine.

Choice and concentration of local anesthetic depends on the onset time of block required, the desired indication (operative (incidental surgery or for delivery) or labor analgesia) as well as maternal and fetal conditions. Bupivacaine has a pK_a of 8.1 compared to lidocaine's pK_a of 7.9. This means that at physiological pH bupivacaine consists of a greater fraction in the ionized form which is unable to penetrate the phospholipid membrane, resulting in a slower onset of action. The duration of action is correlated with the extent of protein binding. Those drugs that are highly protein bound will have a lower materno-fetal transfer attributed to restricted placental transfer (for example, bupivacaine is 90% protein bound compared to lidocaine's 50%). In pregnancy altered protein binding (physiological hypoalbuminemia combined with an increase in α_1-glycoprotein concentration) changes the unbound fraction of the drug and reduces the doses required and at which toxicity may occur [1]. The sensitivity of neural tissue to local anesthetics also increases and this contributes to the risk of toxicity.

The volume of the subarachnoid and epidural spaces is reduced due to compression of the inferior vena cava causing distension of the epidural venous plexus. This results in a greater risk of inadvertent intravascular injection and leads to more extensive spread of local anesthetic in central neuraxial blockade, both of which may increase the risk of complications.

10.6.1 Bupivacaine

Bupivacaine (0.125–0.5%) is used frequently in both epidural and subarachnoid blocks – the higher the concentration, the

greater the motor blockade. It has a slower onset and longer duration than lidocaine (approximately 120–180 min). Bupivacaine toxicity has been associated with refractory ventricular fibrillation leading to the isolation and commercial preparation of the S(−) enantiomer of bupivacaine, levobupivacaine. This has been shown to be less neuro- and cardiotoxic than racemic bupivacaine.

10.6.2 Lidocaine

Lidocaine has an intermediate onset time between 2-chloroprocaine and bupivacaine and concentrations of 1.5–2% are often used in epidural anesthesia. Epinephrine is often used with lidocaine as an adjunct to decrease systemic absorption, prolong the duration of the block and increase the intensity of the blockade (both sensory and motor). Without it there may be an increased risk of inadequate anesthesia and a risk of local anesthetic toxicity especially with additional lidocaine doses. Bicarbonate may also be used to buffer lidocaine, increasing the amount of unionized drug and speeding its penetration into the nerve tissue. Some studies have found differences in neonatal neurobehavior following lidocaine compared to bupivacaine in epidural anesthesia but these differences have been shown to be not clinically significant [36, 37].

10.6.3 2-Chloroprocaine

As an ester local anesthetic, 2-chloroprocaine is rapidly metabolized and placental transfer is limited compared to amide local anesthetics. As a result it is used widely in the US in the situation of epidural anesthesia requiring instrumental or operative delivery and a decompensating fetus as it has an extremely rapid onset (approximately 5 minutes), it is less likely to participate in ion trapping and there is less risk of toxicity. It should not be used in the subarachnoid space due to the risk of adhesive arachnoiditis.

10.6.4 Ropivacaine

This amide anesthetic has an onset intermediate between lidocaine and bupivacaine and its safety in cesarean delivery has been established. It has a duration similar to bupivacaine (120–180 min) but exhibits less cardiac toxicity as it is supplied in the S(−) enantiomer form. Ropivacaine may provide anesthesia and analgesia with less motor blockade when compared to bupivacaine but this may not be clinically important [38].

10.6.5 Adjuvant opioids

The rationale behind using opioids in obstetric regional anesthesia is to minimize maternal systemic and fetal effects of both local anesthetics and opioids. There have been extensive numbers of both human and animal studies confirming the synergism between opioids and local anesthetics in neuraxial anesthesia which may reduce the required local anesthetic dose by up to 30%. This may reduce both the risk of local anesthetic toxicity and the incidence of motor blockade which may be undesirable for the laboring parturient. Neuraxial opioids improve the quality of analgesia and are thought to exert their effects via a direct action on spinal and supraspinal opioid receptors. Dose ranges of commonly used opioids are shown below in Table 10.3.

When considering specific opioids, fentanyl is the most commonly used and most widely studied adjuvant opioid in obstetric anesthesia. It is a highly potent lipophilic phenylpiperidine derivative that rapidly binds dorsal horn receptors in the spinal cord after neuraxial administration leading to rapid analgesia within 5 minutes intrathecally and 10 minutes epidurally. Cephalad migration and the incidence of central respiratory depression are reduced compared to less lipid-soluble opioids such as morphine. Sufentanil has an analgesic potency that is around five times more potent than fentanyl and has an even more rapid onset. Early respiratory depression, however, may occur due to rapid systemic absorption of these drugs and the side effects are equipotent with equivalent doses of either drug. Their fast onset of action makes these opioids desirable for labor analgesia and emergency delivery but limits their use for postoperative analgesia after a single dose.

Morphine is a hydrophilic phenanthrene derivative which is approximately 100 times less potent that fentanyl. It has a slower onset (15 minutes intrathecally and 30 minutes epidurally) compared to fentanyl and sufentanil and a significantly longer duration of action (12–24 hours). Poor lipid solubility leads to a delay in binding to dorsal horn receptors in the spinal cord and may

Table 10.3 Dose ranges of commonly used neuraxial opioids

Opioid	Epidural dose	Intrathecal dose
Fentanyl	50–100 mcg	10–25 mcg
Sufentanil	25–50 mcg	2.5–15 mcg
Morphine	2.0–3.0 mg	100–200 mcg
Diamorphine	4.0–6.0 mg	200–400 mcg

contribute to the accumulation of free drug within the cerebrospinal fluid (CSF) which may migrate cranially and cause delayed respiratory depression. In both intrathecal and epidural anesthesia morphine has been shown to have a ceiling effect (at 100 mcg intrathecally and 3.75 mg epidurally) above which there is little analgesic benefit and an increased incidence of adverse effects [39, 40]. Neuraxial morphine has been shown to be as effective as fentanyl for labor and cesarean delivery analgesia and more effective than fentanyl in postoperative pain relief. However, increased incidence and magnitude of side effects such as nausea, vomiting, sedation, urinary retention, respiratory depression, and pruritis when compared to fentanyl limit its effects. There is new interest currently in extended-release epidural morphine (EREM) where morphine is encapsulated in lipid foam particles which may lead to a prolonged duration of action and fewer side effects [41].

Diamorphine is a suitable alternative to intrathecal morphine and is primarily used in the United Kingdom. It is more lipophilic than morphine and therefore has a faster onset of action. Despite a short half-life in the CSF it is metabolized into its active components (morphine and 6-acetylmorphine) increasing its duration of action. Intraoperative analgesia is of similar quality to fentanyl with the additional advantage of prolonged postoperative analgesia [42]. Side effects, however, are dose dependent with pruritis occurring in up to 90% of women after a 200 mcg dose at cesarean delivery [43].

10.6.6 Fetal effects of neuraxial opioids

Spinal and epidural opioids will diffuse into the maternal bloodstream and will be rapidly transported to the uterus. All commercially available opioids have low molecular weights and rapidly cross the placenta by diffusion. The risk of neonatal depression with morphine increases with reduced inter-dosing interval and with increasing dose due to higher maternal systemic morphine levels. The risk of neonatal depression with fentanyl appears less and has only been reported at very high repeated epidural doses leading to maternal systemic accumulation [44].

10.7 Summary

General anesthesia utilizes pharmacological agents to render the parturient unconscious and unaware. It requires a rapid sequence induction with neuromuscular blockade to secure the airway after

the first trimester due to the risk of aspiration. These drugs cross the placenta in varying amounts and may be implicated in neonatal depression. Intravenous agents should be carefully titrated to minimize fetal exposure while ensuring maternal anesthesia and analgesia. In many cases regional anesthesia and analgesia may be more appropriate with less potential risk of harm to both mother and fetus.

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The Management of Asthma During Pregnancy

11

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11.1 Introduction

Asthma is one of the most common potentially serious medical problems to complicate pregnancy, and may adversely affect both maternal quality of life and perinatal outcomes. Optimal management of asthma during pregnancy is thus important for both mother and baby. This chapter reviews the assessment and management of asthma in pregnant women.

11.2 Effect of pregnancy on the course of asthma

Asthma course may worsen, improve, or remain unchanged during pregnancy, and the overall data suggest that these various courses occur with approximately equal frequency. In a recent

large prospective study of 1739 pregnant asthmatic women, severity classification (based on symptoms, pulmonary function, and medication use) worsened in 30% and improved in 23% of patients during pregnancy [1]. Asthma also appears to be more likely to be more severe or to worsen during pregnancy in women with more severe asthma before coming pregnant [2].

The course of asthma may vary by stage of pregnancy. The first trimester is generally well tolerated in asthmatics with infrequent acute episodes. Increased symptoms and more frequent exacerbations have been reported to occur between weeks 17 and 36 of gestation. In contrast, asthmatic women in general tend to experience fewer symptoms and less frequent asthma exacerbations during weeks 37–40 of pregnancy than during any earlier gestational period [3].

The mechanisms responsible for the altered asthma course during pregnancy are unknown. The myriad of pregnancy-associated changes in levels of sex hormones, cortisol, and prostaglandins may contribute to changes in asthma course during pregnancy. In addition, exposure to fetal antigens, leading to alterations in immune function, may predispose some pregnant asthmatics to worsening asthma [4]. Even fetal sex may play a role, with some data showing increased severity of symptoms in pregnancies with a female fetus [5].

There are additional factors that may contribute to the clinical course of asthma during pregnancy. Pregnancy may be a source of stress for many women, and this stress can aggravate asthma. Adherence to therapy can change during pregnancy with a corresponding change in asthma control. Most commonly observed is decreased adherence as a result of a mother's concerns about the safety of medications for the fetus. One study found that women with asthma significantly decreased their asthma medication use from 5 to 13 weeks of pregnancy. During the first trimester, there was a 23% decline in inhaled corticosteroid prescriptions, a 13% decline in short-acting beta-agonist prescriptions, and a 54% decline in rescue corticosteroid prescriptions [6].

Physician reluctance to treat may also affect the severity of asthma during pregnancy. A recent study found that less than 40% of women who classified themselves as "poorly controlled" reported use of a controller medication during pregnancy [7]. Another study identified 51 pregnant women and 500 non-pregnant women presenting to the emergency department with acute asthma. Although asthma severity appeared to be similar in the two groups based on peak flow rates, pregnant women were significantly less likely to be discharged on oral steroids (38% vs. 64%). Presumably related to this undertreatment, pregnant women were

three times more likely than non-pregnant women to report an ongoing exacerbation 2 weeks later [8, 9].

Infections during pregnancy can certainly affect the course of gestational asthma. Some degree of decrease in cell-mediated immunity may make the pregnant patient more susceptible to viral infection, and upper respiratory tract infections have been reported to be the most common precipitants of asthma exacerbations during pregnancy [10]. Sinusitis, a known asthma trigger, has been shown to be six times more common in pregnant compared with non-pregnant women [11]. In addition, pneumonia has been reported to be greater than five times more common in asthmatic than nonasthmatic women during pregnancy [12].

11.3 Effect of asthma on pregnancy

One of the largest controlled studies that have evaluated outcomes of pregnancy described 36,985 women identified as having asthma in the Swedish Medical Birth Registry. These outcomes were compared with the total of 1.32 million births that occurred during the years of the study (1984–1995). Significantly increased rates of preeclampsia (OR 1.15), perinatal mortality (OR 1.21), preterm births (OR 1.15), and low birth weight infants (OR 1.21), but not congenital malformations (OR 1.05), were found in pregnancies of asthmatic versus control women [13]. The risks appeared to be greater in patients with more severe asthma, which was confirmed in a more recent Swedish Medical Birth Registry report [14]. A recent meta-analysis, derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women (over 1,000,000 for low birth weight and over 250,000 for preterm labor), indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse perinatal outcomes including low birth weight, small for gestational age, preterm labor and delivery, and preeclampsia [15].

Mechanisms postulated to explain the possible increase in perinatal risks in pregnant asthmatic women demonstrated in previous studies have included [1] hypoxia and other physiologic consequences of poorly controlled asthma, [2] medications used to treat asthma, and [3] pathogenic or demographic factors associated with asthma but not actually caused by the disease or its treatment, such as abnormal placental function.

Several recent prospective studies [16–24] have shown that the pregnant asthmatic with mild to moderate severity can have

excellent maternal and fetal outcomes. In contrast, suboptimal control of asthma or more severe asthma during pregnancy may be associated with increased maternal or fetal risk [22, 25, 26].

11.4 Asthma management

The ultimate goal of asthma therapy in pregnancy is maintaining adequate oxygenation of the fetus preventing hypoxic episodes in the mother. The management of asthma can be summarized in four categories: assessment and monitoring, education of patients, control of factors contributing to severity, and pharmacologic therapy [27].

The first step is assessment of severity (in patients not already on controller medications) or assessment of control (in patients already on controller medications). Severity is assessed in untreated patients based on the frequency of daytime and nighttime symptoms, rescue therapy use, activity limitation, and pulmonary function (ideally spirometry, minimally peak flow rate) (Table 11.1). Based on this, severity assessment controller therapy is initiated. Patients should be monitored monthly for asthma control (Table 11.2), and if not responding adequately to treatment should have their level of treatment adjusted (Table 11.3).

Table 11.1 Classification of asthma severity in pregnant patients*

Asthma severity	Symptom frequency	Nighttime awakening	Interference with normal activity	FEV_1 or peak flow (predicted percentage of personal best)
Intermittent	2 days per week or less	Twice per month or less	None	More than 80%
Mild persistent	More than 2 days per week, but not daily	More than twice per month	Minor limitation	More than 80%
Moderate persistent	Daily symptoms	More than once per week	Some limitation	60–80%
Severe persistent	Throughout the day	Four times per week or more	Extremely limited	Less than 60%

Abbreviation: FEV_1 – forced expiratory volume in the first second of expiration.
*Data from Dumbrowski MP, Schatz M; ACOG Committee on Practice Bulletins - Obstetrics. ACOG practice bulletin: clinical management guidelines for obstetrician -gynecologists number 90, February 2008: asthma in pregnancy. Obstet Gynecol 2008;111:457–464.

Table 11.2 Assessment of asthma control in pregnant women*

Variable	Well-controlled asthma	Asthma not well controlled	Very poorly controlled asthma
Frequency of symptoms	≤2 days/week	>2 days/week	Throughout the day
Frequency of nighttime awakening	≤2 times/month	1–3 times/week	≥4 times/week
Interference with normal activity	None	Some	Extreme
Use of short-acting β-agonist for symptoms control	≤2 days/week	>2 days/week	Several times/day
FEV_1 or peak flow (% of the predicted or personal best value)	>80	60–80	<60
Exacerbation requiring use of systemic corticosteroid (no.)	0–1 in the past 12 months	≥2 in the past 12 months	≥2 in the past 12 months

*Data from Schatz M, Dombrowski M. Asthma in pregnancy. N Engl J Med 2009;360:1862–1869.

Table 11.3 Steps of asthma therapy during pregnancy*

Step	Preferred controller medication	Alternative controller medication
1	None	–
2	Low dose ICS	LTRA, theophylline
3	Medium dose ICS	Low dose ICS + either LABA, LTRA or theophylline
4	Medium dose ICS + LABA	Medium dose ICS + LTRA or theophylline
5	High dose ICS + LABA	–
6	High dose ICS + LABA + oral prednisone	–

ICS – inhaled corticosteroids; LTRA – leukotriene receptor antagonists; LABA – long-acting beta-agonists.
*Data from Schatz M, Dombrowski M. Asthma in pregnancy. N Engl J Med 2009;360:1862–1869.

11.5 Pharmacologic therapy

Asthma medications generally are divided into long-term control medications and rescue therapy. Long-term control medications are used for maintenance therapy to prevent asthma manifestations and include inhaled corticosteroids, cromolyn, long-acting beta-agonists, leukotriene receptor antagonists, and theophylline. Rescue therapy, most commonly inhaled short-acting beta-agonists,

provides immediate relief of symptoms. Oral corticosteroids can either be used as a form of rescue therapy or as chronic therapy for severe persistent asthma.

11.5.1 Inhaled corticosteroids

Inhaled corticosteroids are the mainstay of controller therapy during pregnancy. Many studies have shown no increased perinatal risks (including preeclampsia, preterm birth, low birth weight, and congenital malformations) associated with inhaled corticosteroids [23, 28–33]. A recent study of over 4000 women who used inhaled corticosteroids during pregnancy found no increased risk of perinatal mortality associated with inhaled corticosteroid use during pregnancy [34]. Several large studies support the lack of association of inhaled corticosteroid use with total or specific malformations [33, 35–37]. One study [38] has suggested a relationship between high dose inhaled corticosteroids and total malformations, but confounding by severity is a possible explanation, based on the relationships between exacerbations and congenital malformations demonstrated by the same group [26].

Because it has the most published human gestational safety data, budesonide is considered the preferred inhaled corticosteroid for asthma during pregnancy. That is not to say that the other inhaled corticosteroid preparations are unsafe. Therefore, inhaled corticosteroids other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy, especially if it is thought that changing formulations may jeopardize asthma control. Doses of inhaled corticosteroids are categorized as low, medium, and high (Table 11.4).

11.5.2 Inhaled beta-agonists

Inhaled short-acting beta-agonists are the rescue therapy of choice for asthma during pregnancy. Inhaled albuterol is the first-choice short-acting beta-agonist for pregnant women because it has been studied the most extensively [28], although other agents may be used if uniquely helpful or well tolerated. In one recent case–control study, the use of bronchodilators during pregnancy was associated with an increased risk of gastroschisis among infants (OR, 2.1; 95% confidence interval (CI), 1.2 to 3.6) [39]. Also, in another cohort study involving 4558 women, there was an increased risk of cardiac defects exposed to bronchodilators during pregnancy (OR, 1.4; 95% CI, 1.1 to 1.7) [35]. A more recent case–control study also supported this association (OR 2.20; 95% CI, 1.05 to 4.61) [40]. However, this observation may be a result of confounding. Asthma exacerbations may be associated with both

Table 11.4 Comparative daily doses for inhaled corticosteroids*,**

Corticosteroid	Amount	Low dose	Medium dose	High dose
Beclomethasone HFA	40 mcg per puff	2–6 puffs	More than 6–12 puffs	More than 12 puffs
	80 mcg per puff	1–3 puffs	More than 3–6 puffs	More than 6 puffs
Budesonide	90 mcg per inhalation	2–6 puffs	More than 6–12 puffs	More than 12 puffs
	180 mcg per inhalation	1–3 puffs	More than 3–6 puffs	More than 6 puffs
Ciclesonide	80 mcg per actuation	2–4 puffs	More than 4–8 puffs	More than 8 puffs
	160 mcg per actuation	1–2 puffs	More than 2–4 puffs	More than 4 puffs
Flunisolide HFA	80 mcg per puff	4 puffs	More than 4–8 puffs	More than 8 puffs
Fluticasone HFA	44 mcg per puff	2–6 puffs	–	–
	110 mcg per puff	2 puffs	More than 2–4 puffs	More than 4 puffs
	220 mcg per puff	1 puff	More than 1–2 puffs	More than 2 puffs
Fluticasone DPI	50 mcg per inhalation	2–6 puffs	–	–
	100 mcg per inhalation	1–3 puffs	More than 3–5 puffs	More than 5 puffs
	250 mcg per inhalation	1 puff	More than 1–2 puffs	More than 2 puffs
Mometasone	110 mcg per actuation	2 puffs	3–4 puffs	More than 4 puffs
	220 mcg per actuation	1 puff	2 puffs	More than 2 puffs

Abbreviations: DPI – dry powder inhaler; HFA – hydrofluoroalkane.
*Total daily puffs are usually divided into a twice-per-day regimen.
**Data from [27] and Kelly HW Comparison of inhaled corticosteroids: an update. Ann Pharmacother 2009;43:519-27.

increased use of bronchodilators and congenital malformations. In addition, factors such as obesity or lower household socioeconomic status may be associated with both more severe asthma requiring more bronchodilators and congenital malformations. In general, patients should use up to two treatments of inhaled albuterol (two to six puffs) or nebulized albuterol at 20-minute intervals for most mild to moderate symptoms; higher doses can be used for severe symptom exacerbations.

The use of long-acting beta-agonists is the preferred add-on controller therapy for asthma during pregnancy. This therapy should be added on when patients' symptoms are not controlled with the use of medium-dose inhaled corticosteroids. Because long-acting and

short-acting inhaled beta-agonists have similar pharmacology and toxicology, long-acting beta-agonists are expected to have a safety profile similar to that of albuterol. Two long-acting beta-agonists are available: salmeterol and formoterol. Limited observational data exist on their use during pregnancy. A possible association between long-acting beta-agonists and an increased risk of severe and even fatal asthma exacerbations has been observed in non-pregnant patients. As a result, long-acting beta-agonists are no longer recommended as monotherapy for the treatment of asthma and are available in fixed combination preparations with inhaled corticosteroids. Expert panels suggest that the benefits of the use of long-acting beta-agonists appear to outweigh the risks as long as they are used concurrently with inhaled corticosteroids [41].

11.5.3 Leukotriene modifiers

Both zafirlukast and montelukast are selectiveleukotriene receptor antagonists indicated for the maintenance treatment of asthma. Both are pregnancy category B; however, data on the use of leukotrienereceptor antagonists during pregnancy are more limited. There is one published study, involving 96 patients, that supports their safety during pregnancy [42]. Another study of 180 montelukast-exposed pregnancies found no increase in baseline rate of major congenital malformations [43]. Montelukast is available as a once daily medication with doses variable based on age. For adults, the typical dose is 10 mg daily.

11.5.4 Cromolyn and theophylline

Given the superiority of inhaled corticosteroids over cromolyn and theophylline in the prevention of asthma symptoms, the latter are considered alternative treatments for mild persistent asthma. Theophylline is also an alternative, but not preferred, add-on treatment for moderate to severe persistent asthma. Reassuring data on the use of cromolyn and theophylline in pregnant women have been published [41]. Theophylline use is also limited by its many adverse side effects and potential drug interactions resulting in possible toxicity. Serum levels should be monitored during pregnancy and maintained between 5 and 12 mcg/mL. Cromolyn is now only available as a nebulizer solution.

11.5.5 Oral corticosteroids

Some patients with severe asthma may require regular oral corticosteroid use to achieve adequate asthma control. Oral corticosteroids are also typically part of the discharge regimen after an acute

asthma episode. Doses are typically 40–60 mg in a single dose or two divided doses for 3–10 days. Oral corticosteroid use has been associated with an increased risk of preterm birth [23, 28] and low birth weight infants [28] in 52–185 exposed women. An increased risk of orofacial clefts was reported in a meta-analysis of case–control studies [44], but this increased risk was not confirmed in a recent large cohort study [36]. Since these risks would be less than the potential risks of a severe asthma exacerbation, which include maternal or fetal mortality, oral corticosteroids are recommended when indicated for the management of severe asthma during pregnancy [41].

Conclusion

Asthma is a common medical problem that may worsen during pregnancy. In addition to affecting maternal quality of life, uncontrolled asthma may lead to adverse perinatal outcomes. Awareness of proper treatment options for asthma during pregnancy is important for clinicians who care for pregnant patients.

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12 Updated Guidelines for the Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum

Caroline Maltepe, Rachel Gow and Gideon Koren

12.1 Introduction

Nausea and vomiting of pregnancy (NVP) is a common medical condition, one that is perhaps least understood, which occurs in up to 85% of all pregnancies. The commonly used term "morning sickness" is misleading, as symptoms (nausea, retching and/or vomiting) can persist throughout the day and/or night [1–5]. The severity of NVP can range from mild to severe, beginning between 4 and 9 weeks and worsening between 7 and 12 weeks gestation. Importantly, symptoms that begin after 10 weeks' gestation should be investigated for other causes (see differential diagnosis). Typically, symptoms subside between 12 and 16 weeks; however, up to 15% of women will experience symptoms beyond 16 weeks or for the duration of their pregnancy [1–5].

NVP symptoms, whether they are mild, moderate or severe, can have a negative impact on the overall well-being of pregnant

women, affecting family, work, and social life. The impact on quality of life is not only physical but also emotional. Women often describe feelings of isolation, fatigue, helplessness, depression, anxiety, frustration, difficulty coping, and irritability [6–10]. Up to 70% find that their parenting abilities are affected, with women spending less time with their children, and approximately 82% report that their usual activities are disrupted [8–9]. Furthermore, the financial burden of NVP can be quite significant. In 2007, Piwko et al. reported on the weekly cost (including costs to society, the patients, and the health care system) of NVP in women with mild–severe symptoms. Total cost of NVP per woman-week with mild symptoms was $132, $355 for moderate, and $653 for severe [10].

Health care practitioners are often uncertain as to how best to treat their patients with NVP. Both patients and physicians often fear the use of pharmacological therapies during pregnancy due to the concerns of potential risks to the fetus. Physicians can considerably improve their patients' quality of life, reduce the risk of both maternal and fetal complications, and hopefully prevent hospitalization by implementing early symptom management using counseling and evidence-based guidelines.

12.2 Hyperemesis gravidarum

Approximately 0.5–2% of women are affected by the most severe form of NVP, known as hyperemesis gravidarum (HG) [3]. HG is defined as severe and persistent nausea and vomiting, weight loss greater than 5% of pre-pregnancy weight, dehydration, electrolyte imbalances, and nutritional deficiencies, typically requiring hospitalization [3, 11–13]. The following complications have been reported in women with HG: Wernicke's encephalopathy due to vitamin B_1 deficiency, coagulopathy secondary to acute vitamin K deficiency, anemia or peripheral neuropathy due to vitamin B_{12} and vitamin B_6 deficiency, hyponatremia, renal damage, and Mallory Weiss tears [11, 13–14]. Furthermore, a study showed the recurrence risk for hospital admission to be 29 times higher if the woman had also been hospitalized for HG in her previous pregnancy [15].

Women with HG may have more severe psychosocial morbidities, including depression. In some cases, women may choose to terminate otherwise wanted pregnancies [16]. Negative maternal effects have been reported postpartum, such as longer recovery time from the pregnancy, muscle pain, and food aversions, particularly with those women with extreme weight loss [17–18]. In addition, hospitalization and treatment for HG has a great

financial impact on the patient and society overall. A 2005 study found that the average cost of HG admission to hospital is $5900 per patient, with an average stay of 2.6 days [19]. A study investigating preemptive therapy demonstrated that initiating treatment prior to or on first day of symptoms effectively lessened the severity of symptoms and reduced the recurrence of HG [20].

12.3 Etiology and risk factors

The etiology of NVP/HG is multifactorial and still largely unclear. The most common theory is hormonal changes during the first trimester of pregnancy, specifically human chorionic gonadotropic (hCG) hormone, estrogen, and progesterone [14]. Women with multiple pregnancies will have higher hCG levels, which, in turn, often worsen symptoms of NVP. Nausea during the first trimester is also associated with gastric slow wave dysrhythmias which correlate closely with symptomatology [21]. Additionally, genetic influences (such as familial recurrence and carrying female fetus), underlying psychological problems, liver abnormalities, other hormonal imbalances such as thyroid disorders, elevated cytokine levels, vitamin deficiency/ies (such as vitamin B_6, B_1, and K), *Helicobacter pylori* infection, as well as the evolutionary adaptation theory (maternal and embryonic protection from toxins) have been proposed as part of etiology [11–14, 19, 21–24].

12.4 Differential diagnosis

When symptoms occur daily in early pregnancy, they are typically caused by NVP itself. However, when symptoms present after 10 weeks of gestation, they are almost certainly due to other causes. Many conditions related or unrelated to pregnancy can cause nausea and/or vomiting, such as gastrointestinal disorders, genitourinary tract disorders, metabolic and neurological disorders, drug toxicity or intolerance, psychological disorders, and pregnancy-related complications [1, 3, 11, 21, 24]. It is important to investigate for differential diagnosis (see Table 12.1), as serious complications could occur if not detected. Furthermore, a thorough medical history and symptomatology must be taken, as patients may not disclose all relevant information. The presence of signs and/or symptoms, such as abdominal tenderness or pain, fever, headache, diarrhea, constipation or goiter, can also point to

Table 12.1 Other contributors to nausea and vomiting* [1, 3, 11, 21, 24]

Central nervous system disorders

- Migraine, headache
- Tumors
- Balance disorders (e.g. Meniere's disease, labyrinthitis, motion sickness)
- Psychologic and psychiatric disorders (e.g. depression, anxiety)
- Increased intracranial pressure (e.g. pseudotumor cerebri, hemorrhage, hydrocephalus)

Gastrointestinal disorders

- Pancreatitis
- Gastroesophageal reflux disease
- Gastroenteritis
- Hepatitis
- Appendicitis
- Intestinal obstruction
- *Helicobacter pylori* infection
- Irritable bowel syndrome
- Peptic ulcer disease
- Biliary tract disease
- Achalasia
- Gastroparesis
- Cholecystitis

Metabolic and endocrine disorders

- Hyperthyroidism/Hypothyroidism
- Hypercalcemia
- Addison's disease
- Diabetes mellitus
- Diabetic ketoacidosis

Genitourinary tract disorders

- Uremia
- Kidney stones
- Ovarian torsion
- Porphyria
- Pyelonephritis

Pregnancy-related conditions

- Preeclampsia
- Acute fatty liver of pregnancy
- Gestational trophoblast disease
- HELLP syndrome
- Multiple pregnancies

Other

- Viral and/or bacterial infections
- Drug toxicity, intolerance or dependence

*Permission to adapt by the Association of Professors of Gynecology and Obstetrics.

other conditions [1]. Ultrasound can be useful to detect multiple or molar gestation, as well as gallbladder, liver, and kidney disorders. Of note, laboratory abnormalities (such as elevations of liver enzymes, bilirubin, amylase, and lipase) may be present with severe NVP/HG and could influence differential diagnosis [1, 3, 11].

12.5 Management of NVP and HG

The symptoms and impact of NVP and/or HG can vary among women; therefore treatment must be tailored to the individual. It is important to advise all women on dietary and lifestyle changes, non-pharmacological and pharmacological treatments. For some women, dietary and lifestyle changes may be difficult to maintain, non-pharmacological approaches may lack effectiveness, and therefore pharmacological approaches may be warranted.

12.5.1 Dietary and lifestyle approaches

Food and odor aversions caused by pregnancy and NVP can greatly impact a woman's daily routine and, for some, may lead to weight loss and dehydration. To reduce symptoms, common dietary strategies include eating small, frequent meals or snacks of high-carbohydrate and low-fat types every 1–2 hours to avoid an empty stomach or feelings of hunger, thus preventing low blood sugar and gastric distension [5, 25–27]. Importantly, Jednak et al. demonstrated that nausea is reduced significantly when ingesting protein-predominant meals, therefore protein (meat and/or alternatives) should be added to all meals and snacks [26]. For women who are having difficulty eating solid foods, liquid nutritional products may be added. It is important to drink colder fluids between meals and snacks and to keep well hydrated [5]. See Table 12.2 for additional symptom management.

Table 12.2 Symptom management for NVP [1, 5, 25–31]

Dietary

- Eating every 1–2 hr smaller portions
- Dry, salty, bland, and soft foods may help
- Add protein or its alternates to all meals and snacks (e.g. nuts, seeds, beans, dairy, nut butters)
- Drink 20–30 min prior to and after solid foods
- Liquid intake should be 2 liters per day; colder fluids, such as slushies, popsicles, ice chips, will help maintain hydration
- Electrolytes can be added to prevent dehydration (e.g. sport drinks, vitamin waters)
- To minimize bitter or metallic taste, add candies, gums and colder fluids
- For constipation, increase dietary fiber, such as psyllium, fruits; and, if needed, add docusate sodium daily
- For gas and/or bloating, switch to lactose-free and, if needed, add simethicone daily or prn
- For symptoms of acidity, such as burping, burning, indigestion, reflux, modify diet and, if needed, add antacids, H_2-blockers or PPIs daily or prn

Lifestyle and other

- For heightened sense of smell, try to sniff lemons, limes or oranges, ventilate the area, consume room temperature/cold meals or snacks
- Women experiencing ptyalism, advise to spit out excessive saliva and use mouthwash more frequently
- Avoid brushing teeth after eating meals or snacks
- Get plenty of sleep and rest, try not to get overly tired
- When rising, snack beforehand and try to get up slowly
- Try not to lie down after meals
- If possible, ask for help from family members or friends
- If iron deficient, to continue with prenatal vitamins, break in half and take in divided doses for tolerability. If not, avoid for first trimester and switch to children's chewable multivitamin along with folic acid; resume with prenatal vitamin after 12 weeks

12.5.2 Treatment for acidity and indigestion

Given that symptoms of dyspepsia and/or gastroesophageal reflux disorders are common in pregnancy (affecting 40–85% of women) and that gastric dysrythmias are associated with NVP, it is important for physicians to investigate if their patients are experiencing any symptoms of acidity and/or digestive issues [28].

A 2009 study demonstrated that adding acid-reducing medications (e.g. antacids, H_2-receptor antagonists, and/or proton pump inhibitors) resulted in a significant reduction of NVP symptoms, without making changes to the antiemetic regimen [28]. Acid and indigestion have been safely treated in pregnant women using antacids, H_2-blockers (such as calcium carbonate and ranitidine) and proton pump inhibitors (omeprazole more commonly used) [28–31]. Proton pump inhibitors (PPIs) have been studied in over 5000 pregnant women and have not been associated with increased risks of major malformations [30–31].

Further, many studies and a meta-analysis have shown an association between *Helicobacter pylori* infection and HG and/or severe NVP [32–33]. Screening for *H. pylori* should be standardized for all women who have a previous pregnancy with HG, or who are currently experiencing moderate to severe NVP. Subsequent treatment of *H. pylori* with antibiotics and PPIs may improve NVP symptoms [1, 5, 32–33].

12.5.3 Non-pharmacological approaches

With increased fear of taking medications in the pregnancy, non-pharmacological treatments offer a good alternative. Vitamin B_6 and ginger are most commonly used for NVP. Vitamin B_6 has been well studied and can be taken safely in pregnancy with doses up to 200 mg/day [1, 5, 34]. The effectiveness of ginger has been shown in randomized trials and can be taken safely with doses of up to 1000 mg/day (dried ginger root powder equivalent) [1, 3, 5, 35]. In addition, traditional acupuncture or acupressure of the P6 (Neiguan point) can be safely used to treat NVP. With regards to efficacy, data are limited [1, 3, 5, 36]. Small studies and case reports have been published using psychotherapy and medical hypnosis for the treatment of NVP [1, 37–38]. When women are experiencing unrelenting and more severe symptoms, many researchers recommend counseling and supportive therapy [38, 39].

12.5.4 Pharmacological approaches

There are many antiemetics that have been given either as monotherapy or polytherapy to help alleviate NVP with varying levels

of safety and effectiveness [1, 3, 5]. It is important to note that all pregnancies have a 1–3% baseline risk of having a baby with a birth defect by chance alone [25]. Health care providers should assess the best course of treatment, not only based on the severity of symptoms, but also on the patient's self-report and impact on her daily life. Importantly, many of these antiemetics have anticholinergic properties and therefore, if the patient reports anticholinergic drug reactions, modifications in treatment regimen, dose or schedule may be needed [11–13]. Physicians should reiterate to their patients the importance of adherence in order to sustain the management of symptoms and, upon improvement, gradually taper down their medication(s).

The Motherisk Program at the Hospital for Sick Children in Toronto has the only specialized NVP Helpline worldwide dedicated to counseling women and has produced an algorithm for the treatment for NVP based on best available evidence (see Figure 12.1) [5]. The combination therapy of doxylamine succinate and vitamin B_6 is recommended as first-line therapy for the treatment of NVP by the Canadian and American Colleges of Obstetricians and Gynecologists [3, 40] and the Association of Professors of Gynecology and Obstetrics [1]. This formulation was originally known as Bendectin, which was voluntarily removed in 1983 due to concerns of teratogenicity; however, since this time many studies including two meta-analyses have confirmed its safety [41, 42]. In Canada, this medication, known as Diclectin®, is the only drug labeled for pregnancy by Health Canada due to its large safety profile. Furthermore, the use of Diclectin® during pregnancy was not associated with any long-term effects on neurodevelopment in a 2009 study [43]. In regards to its efficacy, a randomized placebo-controlled trial published in 2010 showed Diclectin® was effective over placebo in 280 American women [44].

Metoclopramide use in pregnancy has not been associated with increased risk of birth defects in several prospective studies [45–47]. A study published in 2009 did not show an increased risk of birth defects following first trimester use in over 3400 women [47]. As a stomach motility agent, it may be helpful for those women also suffering with heartburn and indigestion. Importantly, women should be advised to eat within 30 minutes after taking metoclopramide.

Domperidone has reportedly been used to treat NVP; however, no case reports or studies have been documented [45, 46]. In 2009, a preliminary study by Choi et al. investigated 146 women unintentionally exposed to domperidone in early pregnancy for gastrointestinal tract symptoms and found no increased risk of major malformations [48]. Its safety profile is limited, but seems reassuring.

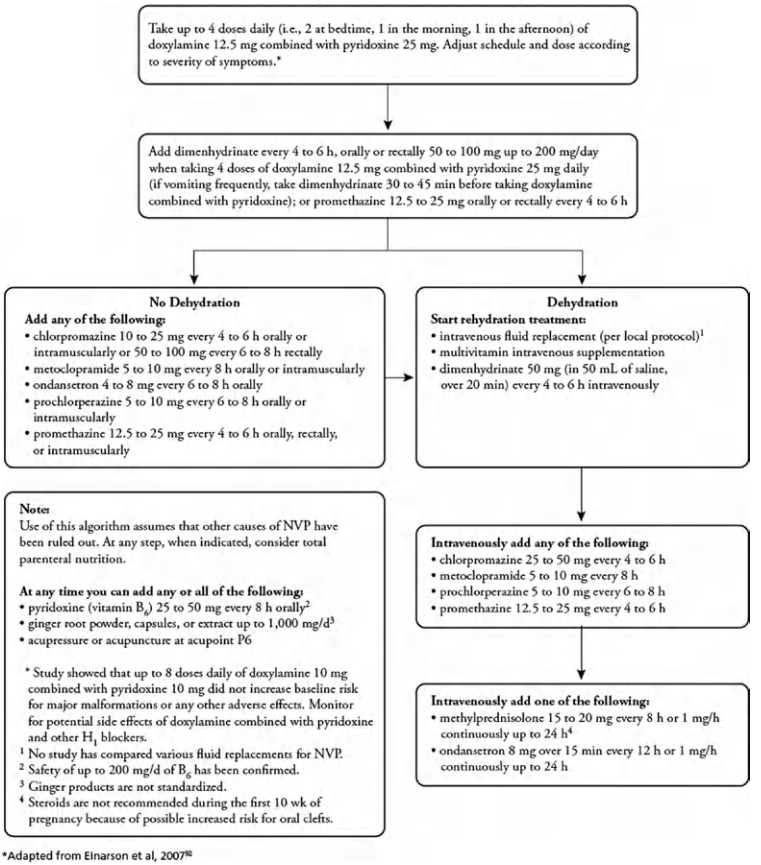

Figure 12.1 Algorithm for treatment of NVP. (If no improvement proceed to next step.) Permission to reprint by the Association of Professors of Gynecology and Obstetrics.

Phenothiazines, such as prochlorperazine, promethazine, and chlorpromazine, are commonly used antiemetics and antipsychotics. With regards to NVP/HG, numerous studies have not shown an increased risk for major malformations [1, 13, 15, 56]. When used continuously into the third trimester, neonatal withdrawal, including extra-pyramidal effects, have been reported in newborns [13].

Ondansetron is a selective serotonin 5-HT3 receptor antagonist known for its use in treating chemotherapy-related nausea and

vomiting. Despite its cost and limited safety profile, it is commonly used. Studies and case reports are available on approximately 230 women exposed to ondansetron in pregnancy, none of which have reported any increased risk of birth defects [1, 45, 49]. Of note, a stool softener may be needed, as constipation is a common side effect [1].

Droperidol is a butyrophenone tranquilizer that has been used in the treatment of hyperemesis gravidarum [45, 50, 51]. In 2001, Turcotte et al. found no differences in any pregnancy outcome between their treatment group receiving droperidol and diphenhydramine ($n=28$) and the control group ($n=54$) [50]. In a 2003 study, Ferreira et al. looked at two different doses of droperidol combined with diphenhydramine (total $n=101$) and found an increase in major malformations; however, the differences were not significant compared to controls ($n=54$) [51]. These two nonrandomized, prospective studies found a reduction of nausea and vomiting symptoms following treatment.

Trimethobenzamide is an older antiemetic that is structurally similar to antihistamines and has been reported to reduce NVP symptoms. In over 1000 women exposed in pregnancy, many in the first trimester, trimethobenzamide was not associated with increased risk of major malformations [46, 52–54].

For breakthrough relief, antihistamines such as dimenhydrinate or meclizine have been widely used in the treatment of NVP and may be taken daily or as needed until symptoms improve [1, 3, 5, 45, 55]. Numerous studies have documented their effectiveness. A meta-analysis including over 24 different studies have shown no increased risk of birth defects [46, 55].

As a last resort, corticosteroids, specifically methylprednisolone, have been used in the treatment of NVP/HG, though reports of efficacy are conflicting [56–58]. They are recommended to be used *after* the first trimester since corticosteroids are associated with a slight increased risk of facial clefts [56, 57]. It has been observed that the use of corticosteroids throughout pregnancy has been associated with a higher rate of preterm births and reduced birth weight [58]. Of note, it may be necessary to monitor fetal growth, as well as maternal blood pressure and blood sugar.

12.5.5 Management of HG

When a pregnant patient presents herself with persistent nausea, dehydration, uncontrollable vomiting, and/or excessive weight loss, hospitalization may be required. For most patients, symptoms will improve with IV hydration and antiemetics. For some women who fail to respond to treatment and experience ongoing symptoms and weight loss, enteral or parenteral nutrition should

Table 12.3 Nutritional support of the hyperemesis patient*

Assessment

- >5% loss of pre-pregnancy body weight
- Nutrient reserves before pregnancy
- Individual physiologic needs *and* added requirements pregnancy
- Any disease process or current therapy that might affect nutrient requirement or nutrient tolerance
- Clinical and laboratory findings (urine output, peripheral pulse, temperature, skin color, muscle strength, general fatigue, electrolyte abnormalities)

Correct Hypovolemia

(i.e. acidosis. decreased serum bicarbonate, increased serum lactate, electrolyte imbalances)

- IV fluid, electrolyte, and vitamin replacement
- Lactated Ringer's solution is effective
- Large volumes of normal saline may cause hyperchloremic acidosis

Nutritional Support

Enteral: by oral or tube feeding as tolerated
Parenteral: in cases of severe depletion, and/or continued gastrointestinal dysfunction

- Assess patient's status, urgency, and impact of various routes feeding
- Consider potential complications of tube feeding (e.g. aspiration, diarrhea)
- Consider consult by nutritionist/dietician
- If deciding on enteral support, identify most appropriate formula
- Consider potential complications of parenteral nutrition (e.g. catheter insertion, line complications, septic and metabolic problems, central versus peripheral line placement); close monitoring required
- Monitor for re-feeding syndrome (e.g. hypokalemia, hypophosphatemia, hypomagnesemia, thiamin deficiency)

Enternal Nutrition

Liquid caloric and vitamin supplement, such as one of the following:

- Meal replacement formula
- Concentrated formula for fluid-restricted patients
- High-protein formula
- Elemental semi-elemental formula for patients with impaired digestion
- Modular formula for boosting select macronutrients

Parenteral Nutrition**

- With high fat content solutions, calories sufficient for short-term maintenance can be provided through a peripheral vein. If intolerance to oral feeding persists more than several days, peripheral venous nutrition cannot go on as phlebitis may develop when continued for 1 to 2 weeks.
- A representative peripheral nutrition formulation, such as 63 g of amino acids, 150 g of glucose, and 100 g of fat (total 1762 kcal) with vitamins, minerals, and required electrolytes, provides a total volume of 2000 mL/day.

Table 12.3 Nutritional support of the hyperemesis patient*—cont'd

- For patients who cannot tolerate oral feeding or for whom the vomiting appears likely to persist more than several days, high-calorie, high-glucose formulations may be required. These must be administered centrally because of the sclerosing effect of the glucose on peripheral veins.
- A representative central venous formulation can provide an adequate nutrient intake within a reasonable fluid volume for as long as necessary, such as 2400 kcal/day including 100 g amino acids, within 2000 mL.

*Adapted from [59] and incorporating recommendations from [62].
**Sample formulations given. Each formulation is patient-dependent and should be calculated individually. Once a physician determines that parenteral nutrition is required, a registered dietitian experienced in TPN and medical nutrition therapy should be actively involved in patient care.

be considered to provide nourishment and improve well-being for both mother and fetus [1, 59–61].

Current literature suggests that enteral feedings via nasogastric, gastric or jejunostomy feeding tubes can be used to either complement or replace oral feeding and has been given successfully in patients with HG [1, 59–61]. Enteral nutrition maintains gut functionality thus preventing atrophy. Importantly, it also seems to be more cost effective and associated with fewer risks than parenteral nutrition [1, 59–61]. However, parenteral nutrition through peripherally inserted central catheter (PICC) line appears to be more widely accepted by hyperemetic patients. While total parenteral nutrition (TPN) has been associated with serious complications, it has been successfully used for over 30 years [61]. Interestingly, a study found a higher rate of complications among women with centrally inserted catheters (50%) compared to women with PICC lines (9%) [61]. Physicians should assess their patients' nutritional needs on an individual basis. Due to a lower risk profile, attempts should be made to use enteral over parenteral nutrition. Of importance, while the woman is improving under IV hydration, it is critical to start effective oral antiemetic therapy, to avoid cyclic readmission due to similar presentation [1, 59–61]. The nutritional support of pregnant women with HG is addressed in Table 12.3.

Conclusion

Although NVP is the most common medical condition in pregnancy, many health care practitioners are uncertain as to how best to treat

their patients. Optimal management of NVP/HG is multidimensional and often complex. Treatment regimens should be designed on an individual basis and all women should be counseled on dietary management, non-pharmacological and pharmacological treatment options. Importantly, as studies have shown a high rate of recurrent symptoms, it is beneficial for women to receive early treatment to help reduce the severity of symptoms in future pregnancies, hopefully preventing hospitalization and improving quality of life.

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Clinical Pharmacology of Anti-Infectives During Pregnancy

13

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Serious infections can occur during pregnancy, and must be treated to prevent maternal and fetal adverse outcomes. While some antimicrobials have been studied in pregnancy, many agents have inadequate data available to evaluate safety, efficacy, and appropriate dosing, posing a challenge for drug and dose selection. Important safety data have been summarized elsewhere [1, 2]. This chapter focuses on pharmacology and pharmacokinetic studies for drugs used to treat infections in pregnancy. Drug disposition characteristics that may alter drug exposure in pregnancy should be considered in selecting a treatment regimen. For drugs that are primarily renally eliminated, clearance may increase later in pregnancy yielding lower blood concentrations of the drugs. For drugs primarily metabolized by the liver or by a combination of pathways, changes in exposure during pregnancy may or may not occur depending on the specific enzyme systems involved.

Further, drug interactions are a major concern when treating multiple infections, such as HIV and tuberculosis. For drugs that are highly protein bound, the dilutional effect on albumin in late pregnancy may increase the free or unbound drug concentration. Finally, the duration of exposure for both the mother and the fetus when a drug is given during pregnancy should be considered when selecting therapy, as about five half-lives must pass for most of the drug to be eliminated from the body. Drugs with short half-lives, whose clearance is increased during pregnancy, may need to be dosed more frequently. These alterations in disposition can be additive or antagonistic, complicating attempts to predict whether drug exposure will change significantly in pregnancy. Therefore, pharmacokinetic studies in pregnant women are necessary to fully understand changes in exposure and the implications for appropriate dose selection. In the absence of pharmacokinetic studies in pregnant women, close monitoring of drug therapy is warranted, including measurement of plasma concentrations and individual optimization of doses when possible.

13.1 Antibacterial therapy

Penicillins are the antibiotics of choice during pregnancy. They are pregnancy category B, cross the placenta and small amounts are excreted in breast milk. Penicillin G and V are 45–68% and 75–89% bound to plasma proteins, respectively, are partially metabolized (<30%) to inactive metabolites, and parent drug and metabolites are excreted in the urine via tubular secretion. One pharmacokinetic study of a dose of 1 million international units (IU) of penicillin G intravenously (IV) every 4 hours in pregnant women concluded that this produced adequate maternal penicillin concentrations for prophylaxis against Group B *Streptococcus* [3]. Current guidelines recommend an initial dose of 5 million IU, followed by 2.5–3 million IU every 4 hours [4]. Another study of a single 2.4 million IU intramuscular dose of penicillin G for prevention of congenital syphilis showed high variability and some sub-therapeutic concentrations; authors suggested that higher doses may need to be studied [5]. Current syphilis treatment guidelines in pregnancy recommend use of penicillins but state optimal doses are unknown [6]. A study of a single oral dose of penicillin V in both pregnant and non-pregnant (control) women demonstrated significantly decreased area under the concentration time curve (AUC – a measure of overall exposure), shorter half-life, and increased penicillin clearance in pregnant women.

The authors concluded shorter dose intervals (1 million IU every 6 hours instead of every 8 hours) or higher doses of penicillin V may be needed during pregnancy [7]. Studies of higher than standard doses have not been described.

Amoxicillin, ampicillin, dicloxacillin, and ticarcillin are all mainly eliminated via renal tubular filtration and secretion, with about 10% metabolized. Oxacillin is about half metabolized and half eliminated unchanged in the urine. Piperacillin is 10–20% excreted via bile into the feces, with the rest eliminated unchanged in the urine. Nafcillin, unlike all the other penicillins, is 60% metabolized, undergoes enterohepatic recirculation, and both parent and metabolites are excreted in the bile. Plasma protein binding is about 20% for amoxicillin, ampicillin, and piperacillin, is about 50% for ticarcillin, and is 70–99% for nafcillin, oxacillin, and dicloxacillin. One study of a single oral 500 mg dose of amoxicillin in pregnant women for post-exposure prophylaxis against anthrax showed increased clearance during pregnancy compared to postpartum, and concluded that anthrax preventive concentrations will not be feasible in pregnant women [8]. Studies of intravenous amoxicillin have recommended a dose during labor or during preterm premature rupture of membranes of 2 g followed by 1 g every 4 hours [9–11]. Two older reported studies of ampicillin pharmacokinetics following 500 mg doses during pregnancy found decreased exposure and suggested increased loading doses (because of the large increase in distribution volume) were likely needed [12, 13]. Finally, two studies of piperacillin-tazobactam in pregnant women found increased clearance and distribution volume during pregnancy, and suggested that higher than standard doses may be needed during pregnancy [14, 15].

Cephalosporins, pregnancy category B, can be safely used to treat various infections during pregnancy, and older agents are preferred due to more data and experience in pregnancy. Specific doses depend on the infection site and offending microbe. They are classified by antibacterial activity. Example first generation agents are: cefadroxil, cephalexin, cephradine, cephalothin, and cefazolin; second generation agents are: cefoxitin, cefatrizine, cefotetan, ceforanide, cefamandole, cefaclor, cefprozil, cefuroxime, and cefuroxime axetil; and third/fourth/fifth generation agents are: cefotaxime, ceftazidime, ceftriaxone, ceftizoxime, cefixime, cefditoren, cefdinir, cefpodoxime, ceftibuten, cefoperazone, cefepime, and ceftaroline. As a class, they all cross the placenta well [16–18], and small amounts are found in breast milk. Many are 60–90% protein bound in plasma, except for cefaclor, cephalexin, cefadroxil, cefpodoxime, cefotaxime, ceftizoxime, ceftazidime, and cefuroxime, which are less than 50% protein bound.

For first generation agents, one study of cephalothin in pregnant women concluded that pregnancy alterations in exposure were insignificant and no dose changes were warranted [19]. Cephalothin is 10–40% metabolized, with the rest excreted unchanged in urine, while the other first generation agents are not metabolized and are wholly excreted unchanged in urine. In contrast, studies of cephradine and cefazolin in pregnant women showed increased clearance and distribution volumes, decreased AUCs, and shorter half-lives, concluding that doses in pregnancy should be increased, possibly by reducing dose intervals rather than by increasing dose amounts [20, 21].

Cefuroxime, a second generation cephalosporin, has lower plasma concentrations and a shorter half-life during pregnancy compared to postpartum [18]. For cefoxitin, at 19–21 weeks' gestation, plasma concentrations were similar to those seen in non-pregnant adults [22], while at term, clearance of cefoxitin is significantly increased [23]. The second generation agents are primarily excreted unchanged in the urine.

Several later generation cephalosporins have been studied in pregnant women. Cefoperazone at term showed a larger distribution volume, lower peak concentration, and decreased protein binding (74% vs. 88%) during pregnancy compared to non-pregnant adults, but also showed that pregnancy did not greatly affect clearance, half-life or trough concentrations [24]. Of note, unlike most other cephalosporins, cefoperazone is metabolized in the liver and excreted in the bile. Ceftazidime clearance increases and concentrations decrease throughout pregnancy compared to postpartum; clearance is primarily renal excretion of unchanged drug [22, 25]. Cefotaxime is metabolized to an active metabolite, and both parent drug and metabolite are eliminated in urine. All other cephalosporins are not appreciably metabolized, and are primarily excreted unchanged in the urine. While increased dose amounts and more frequent dosing have been proposed to attain adequate drug concentrations for many cephalosporins, pharmacokinetic studies of such increased doses are lacking.

Carbapenems imipenem-cilastatin (category C) and meropenem (category B) cross the placenta, have low protein binding, and are excreted mainly unchanged in the urine. Breast milk penetration is unknown. Clearance and distribution volume of imipenem after a single 500 mg IV dose were significantly increased in early and late pregnancy compared to postpartum, and increased doses may be needed in pregnancy [26]. No pharmacokinetic studies of meropenem in pregnancy are reported. Carbacefems aztreonam and loracarbef pharmacokinetics have not been studied in pregnancy either. Loracarbef is 25% protein bound, is not

metabolized, and is excreted unchanged in the urine. Placental and breast milk penetration are unknown. Aztreonam is about 60% protein bound and is mainly eliminated unchanged in the urine, with 6–16% metabolized. It crosses the placenta well [27], and breast milk penetration is unknown. Beta-lactamase inhibitors, given in combination with penicillins or cephalosporins, include sulbactam, tazobactam, and clavulanic acid. All are pregnancy category B, and are about 30% protein bound. Sulbactam and tazobactam cross the placenta and undergo some metabolism while most of the drug is excreted unchanged in urine. Both have significantly decreased exposure during pregnancy [14, 28]. For clavulanic acid, half is metabolized, half is excreted in urine, and low amounts cross the placenta [29].

Macrolides, such as erythromycin, azithromycin, and clarithromycin, are used to treat various infections in pregnant women. Placental concentrations are less than 7% of maternal concentrations [30, 31]. Erythromycin breast milk concentrations are about 50% of maternal concentrations, and it is compatible with breastfeeding. It is 73–81% protein bound, is a substrate and inhibitor of both cytochrome P450 (CYP) 3A4 and permeability glycoprotein (Pgp), concentrates in bile and liver, and is excreted in the bile. Clarithromycin is also a substrate and inhibitor of CYP3A4 and Pgp, while azithromycin is not metabolized and has no effect on CYP enzymes. Penetration of azithromycin or clarithromycin into breast milk is unknown, and both have low protein binding. One pharmacokinetic study of azithromycin found increased distribution volume but unchanged AUC and elimination half-life in pregnant versus non-pregnant women, suggesting standard doses should be appropriate in pregnancy [32].

Vancomycin is used for Gram-positive bacterial infections. It is category B, administered intravenously, widely distributed, 55% protein bound and excreted renally. It crosses the placenta at concentrations similar to maternal concentrations [33]. It is excreted in breast milk; infants would likely not absorb vancomycin, but their gut flora may be altered. Data in pregnancy are limited, so use should be reserved for serious infections. Other polypeptides, colistin, polymyxin B, and teicoplanin, have even fewer data regarding use in pregnancy, and should only be used for compelling indications.

Chloramphenicol is well absorbed and widely distributed, is 60% bound to plasma proteins, with higher placental than maternal concentrations [34]. It is hepatically glucuronidated, and is a potent CYP3A4 and 2C19 inhibitor. Due to neonatal toxicity, “gray baby syndrome” and agranulocytosis, use during pregnancy, especially near term, should be avoided unless absolutely necessary.

Tetracyclines, including oxytetracycline, tetracycline, demeclocycline, methacycline, doxycycline, and minocycline, are pregnancy category D, and should not be used in pregnancy due to strong binding to developing teeth and bones. Tetracycline and doxycycline are enterohepatically recirculated and eliminated mainly in feces (doxycycline) or urine (tetracycline). Minocycline is partially hepatically metabolized. These agents chelate cations, cross the placenta, and penetrate into breast milk, but are considered compatible with breastfeeding. No pharmacokinetic studies in pregnancy have been reported.

Lincomycin and clindamycin, pregnancy category B, are hepatically metabolized, cross the placenta with 25–50% of maternal concentrations found in cord blood, and cross into breast milk but are considered compatible with breastfeeding. Clindamycin, given at 900 mg every 8 hours for Group B *Streptococcus*, was evaluated in pregnant women. The authors found that this standard dose may be sub-therapeutic [35]. Higher doses have not been studied in this population. These drugs should be avoided during pregnancy unless other first-line agents are ineffective or not tolerated.

Linezolid, pregnancy category C, is widely distributed, metabolized by both enzymatic (presumably CYP-mediated) and non-enzymatic processes, and about 30% is eliminated unchanged in the urine. It is used for Gram-positive infections. Data in pregnancy are very limited. Placental and breast milk penetration in humans are unknown. Dalfopristin-quinupristin, pregnancy category B, is also used for Gram-positive infections. Both agents are metabolized to several active metabolites by non-CYP processes, but these agents potently inhibit CYP3A4. The parent compounds and metabolites are mainly eliminated in the feces, with 15–20% of each parent drug eliminated unchanged in the urine. Placental and breast milk transfer are unknown, and no pharmacokinetic studies in pregnancy are available.

Aminoglycosides (pregnancy category D, except spectinomycin which is B), including streptomycin, neomycin, kanamycin, amikacin, gentamicin, tobramycin, and netilmicin, are administered intravenously and eliminated unchanged in the urine. They cross the placenta, and may accumulate in the fetus [36, 37]. Gentamicin clearance and dose requirements are increased during pregnancy, which corresponded more with increased distribution volumes than increased renal function [38]. If used, plasma concentration monitoring is necessary to individualize doses. These agents should be avoided in pregnancy unless needed for life-threatening infections because of fetal oto- and nephrotoxicity risks.

Sulfonamides, including sulfisoxazole, sulfadiazine, sulfamethoxazole, sulfapyridine, sulfasalazine, and sulfadoxine (see

malaria section), are generally used in combination with other antibiotics for various infections, and may be used in pregnancy if penicillins and cephalosporins are not effective. Near term, these drugs are pregnancy category D due to increased risk of hyperbilirubinemia in the neonate; likewise, they are contraindicated in nursing. They readily cross the placenta [39, 40], and most also penetrate into breast milk. Sulfonamides are hepatically acetylated, and are substrates and inhibitors of CYP2C9.

Trimethoprim, pregnancy category C, is used alone or in combination with sulfamethoxazole for various infections. It is extensively distributed, it inhibits CYP2C8, and is mostly eliminated unchanged in the urine. It is slowly transported in low concentrations across the placenta [39], but breast milk concentrations are higher than maternal plasma concentrations and caution should be exercised in lactating women. Trimethoprim is a second-line agent that can be used in pregnancy if first-line agents are ineffective. Folic acid supplementation (0.5 mg daily) should be used along with trimethoprim in the first trimester.

Fluoroquinolones, such as ciprofloxacin, clinafloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin, and trovafloxacin, are pregnancy category C. Absorption of fluoroquinolones is decreased with concomitant cation administration, including calcium, magnesium, iron, and zinc. Lomefloxacin, levofloxacin, norfloxacin, and ofloxacin are mainly excreted unchanged in the urine. Sparfloxacin is metabolized by CYP1A2. Grepafloxacin is glucuronidated by uridine diphosphate glucuronosyltransferase (UGT) enzymes and metabolized by CYP1A2. Moxifloxacin is glucuronidated and sulfated, but does not undergo CYP metabolism. Ciprofloxacin is partially excreted unchanged, is partially metabolized by CYP1A2, and is an inhibitor of CYP1A2. Low amounts of quinolones cross the placenta [41], while much higher amounts penetrate into breast milk [42]. No other pharmacokinetic studies in pregnancy are available. Because of arthropathy risks, quinolones should be avoided in pregnancy and lactation unless needed for complicated, resistant infections.

Metronidazole, pregnancy category B, is used in pregnancy for treatment of symptomatic bacterial vaginosis or asymptomatic disease in women at high risk for preterm delivery. It is effective for eradication of infection, but does not decrease risk of preterm birth [43, 44]. It is well absorbed, widely distributed including fetal [45] and breast milk concentrations as high as maternal concentrations [46–48], and is both oxidized and glucuronidated in the liver by unknown enzymes. Pharmacokinetic studies in early pregnancy and at term showed 15–30% reductions in AUC

compared to historical controls [49, 50], but a recent study in 20 pregnant women taking 500 mg twice daily for 3 days showed weight-corrected exposure was similar in different stages of pregnancy and to reported values in non-pregnant adults [51]. Nimorazole, tinidazole, and ornidazole do not have enough data in human pregnancy to assess appropriate use.

Nitrofurantoin has been used in pregnancy for decades for urinary tract infections. It undergoes some hepatic metabolism, but is mostly concentrated unchanged in urine. Less than 1% crosses into breast milk [52], and placental exposure is also low. It is contraindicated near term due to risk of hemolytic reactions, particularly in glucose-6-phosphatase dehydrogenase (G6PD) deficiency. Fosfomycin, pregnancy category B, is used as a single 3 g dose for uncomplicated urinary tract infections. It is not metabolized, and is excreted unchanged in urine and feces. No pharmacokinetic studies in pregnancy have been reported. Methenamine mandelate and methenamine hippurate, pregnancy category C, are antiseptics used for urinary tract infections. They cross the placenta, into breast milk, and are excreted unchanged in urine. Experience in pregnancy is very limited, and they should be avoided.

Atovaquone (see malaria section) and pentamidine, pregnancy category C, are used for *Pneumocystis jiroveci* infections. Pentamidine crosses the placenta in animals; breast milk penetration is unknown. Elimination is mainly renal, but several metabolites formed by unknown pathways are also present. The half-life is 2–4 weeks. Data in pregnancy are very limited, and no human pharmacokinetic studies are available.

13.2 Antifungal therapy

For treatment of fungal infections, topical therapy with older agents is considered safe in pregnancy. For topical and mucosal use, nystatin, clotrimazole, and miconazole are drugs of choice, with negligible systemic absorption. Other topical "-azoles" are second line, and other topical antifungals should be avoided due to lack of data in pregnancy. Systemic treatment with fluconazole, ketoconazole, itraconazole, and miconazole should be avoided unless the indication is compelling. No pregnancy pharmacokinetic studies are available. Voriconazole is pregnancy category D, can cause fetal harm, and is not recommended for use in pregnancy. For treatment of vaginal candidiasis after local treatment has failed, low-dose oral fluconazole (150 mg once daily) may be tried. For serious, disseminated fungal infections, amphotericin B is preferred.

Amphotericin B is poorly absorbed and administered intravenously for systemic fungal infections. Its metabolism is unknown, and it is eliminated slowly with a 1- to 15-day half-life. It crosses the placenta and may be retained in placental and other tissues. Pharmacokinetics of the original or the liposomal formulations in pregnancy have not been studied. Use should be limited in pregnancy to dangerous systemic mycoses.

Flucytosine, category C, is active against *Cryptococcus neoformans* and candida species. It is widely distributed, and mostly eliminated unchanged in the urine. No pregnancy studies are available. Use during pregnancy should be reserved for severe disseminated fungal infection. Griseofulvin and terbinafine should not be used orally during pregnancy because data for systemic therapy during pregnancy with these agents are limited and skin mycoses do not require urgent oral treatment.

13.3 Malaria

Pregnancy increases susceptibility to, and severity of, malaria, and maternal malaria increases risks for prematurity, low birth weight, spontaneous abortion, and stillbirth. Prophylaxis and treatment medications must be tailored to the local pattern of antimalarial drug resistance [53, 54]. The goal for prophylaxis and treatment regimens is >95% efficacy, but many regimens are associated with much lower cure rates during pregnancy; failure rates of >10 or 15% are common [55].

Chloroquine (CQ) is a drug of choice for malaria during pregnancy if the parasite is sensitive. It has not been formally assigned a pregnancy category, but is generally considered category C. It is well absorbed orally and distributes widely throughout the body. Chloroquine crosses the placenta easily and penetrates into breast milk, delivering low infant doses of ~3%, compatible with breastfeeding [56, 57]. It is partially metabolized hepatically by CYP3A4 and 2D6, and inhibits activity of 2D6. The major metabolite desethylchloroquine (DECQ) has some activity. The half-life is 1–2 months. CQ should be given with food to minimize gastrointestinal upset. Pharmacokinetic studies in Tanzania and Papua New Guinea demonstrated significantly lower exposure (25–45%) to CQ and DECQ during pregnancy, suggesting higher doses may be warranted [58, 59]. A study in Thailand showed non-significant 11–18% exposure decreases during pregnancy [60]. Above standard CQ doses in pregnancy have not been studied.

Proguanil (PG), pregnancy category C, alone or combined with CQ is a prophylaxis drug of choice in some regions. It is a prodrug, converted by CYP2C19 to the active compound, cycloguanil (CG). CYP2C19 poor metabolizers cannot make enough active metabolite for effective use. About 3% of Caucasians and 20% of Asians and Kenyans are poor metabolizers. The half-life is 12–21 hours, but longer in poor metabolizers. Four pharmacokinetic studies in pregnant women from the western border of Thailand and Zambia all demonstrate increased clearance and reduced plasma concentrations of CG by about two-fold in pregnancy [61–64]; one study recommends increasing PG dose by 50% in late pregnancy, though no data are available for this suggested dose in pregnancy [62]. One postulated mechanism for decreased CG in late pregnancy is inhibition of CYP2C19 by estrogen. Atovaquone is often combined with PG, and exposure is approximately half in pregnant versus non-pregnant women[61, 63].

Mefloquine is pregnancy category C, and is used for CQ/PG-resistant malaria. It is well absorbed and widely distributed, including penetration into breast milk. It is partially hepatically metabolized by CYP3A4, and is a substrate and inhibitor of Pgp. Elimination is very slow, mainly via bile and feces, with a half-life of 13–33 days. Two studies have reported decreased plasma mefloquine concentrations during pregnancy, suggesting higher pregnancy doses need to be evaluated [65, 66].

Sulfadoxine–pyrimethamine are pregnancy category C (sulfadoxine is category D near term due to risk of infant kernicterus), and are used in combination as a second choice antimalarial in the second and third trimesters of pregnancy. Both are widely distributed and cross the placenta and into breast milk. Both are metabolized; sulfadoxine half-life is 200 hours while pyrimethamine is 80–123 hours. Three different pharmacokinetic studies showed 30–40% decreased sulfadoxine concentrations in pregnancy, and suggested increased doses need to be studied in pregnancy [67–69]. These same three studies conflicted in respect to pyrimethamine, with one showing increased concentrations in pregnancy, one showing no change, and one showing decreased concentrations. Dapsone is also used in combination with pyrimethamine. It is well absorbed, widely distributed, and undergoes enterohepatic recirculation. It is metabolized by CYP3A4 and 2C9, with a 30-hour half-life. Large quantities are excreted in breast milk and can cause hemolytic anemia in infants with G6PD deficiency. No pharmacokinetic studies in pregnancy have been conducted.

Quinine is pregnancy category C, and may be used for CQ-resistant malaria in pregnancy. It distributes into placenta and breast milk at 10–50% of maternal concentrations [70]; the

American Academy of Pediatrics reports it as compatible with breastfeeding. It is extensively metabolized by CYP3A4 and others, may inhibit 3A4 and 2D6, and is prone to drug–drug interactions. Half-life is 8–21 hours. Large quinine doses are oxytoxic. Pregnancy does not significantly affect quinine exposure, and standard doses are recommended [71, 72].

Artemether–lumefantrine, both pregnancy category C, is a widely used potent antimalarial combination. Artemether is rapidly metabolized by CYP3A4 to the active metabolite, dihydroartemisinin (DHA), and may induce CYP3A4/5. Lumefantrine is metabolized by CYP3A4, inhibits CYP2D6 *in vitro*, and has a half-life of 3–6 days. Concentrations of both are decreased in pregnancy, and lumefantrine trough concentrations fall below threshold values associated with treatment failure [73–75]. Artemether and DHA concentrations are decreased by ~50% in pregnancy [73]. Artesunate is another artemisinin derivative rapidly metabolized to DHA. DHA clearance appears increased during pregnancy [76–78]. Increased doses of artemisinin derivatives and lumfantrine are recommended, but the optimum doses have not been determined.

Because of infant toxicity risks and limited data in pregnancy, primaquine should be avoided in pregnancy. Halofantrine may be necessary for some drug-resistant cases. Its absorption is poor and highly variable. It is metabolized by CYP3A4 to an active metabolite, and it inhibits CYP2D6. Breast milk and placental penetration are unknown, and no pharmacokinetic data during pregnancy are available. Additional agents used as drug-resistant strains become more prevalent include clindamycin (described above), doxycyline (described above), amiodaquine, and quinacrine. The latter two are category C, and are metabolized by CYP3A4/5. No pregnancy pharmacokinetic data are available.

13.4 Tuberculosis

Treatment recommendations for tuberculosis during pregnancy are the same as in non-pregnant adults. Pregnancy does not seem to alter disease course, but untreated tuberculosis poses hazards to mothers and infants. Because of increasing resistance, multidrug therapy is usually recommended; specific drugs selected depend on the resistance patterns.

Isoniazid, pregnancy category C, is used for prophylaxis and treatment during pregnancy. It is widely distributed, including into placenta and breast milk. It is compatible with breastfeeding, but the infant should be supplemented with pyridoxine. It is acetylat-

ed by the liver to inactive metabolites, with a half-life of 1–4 hours. It inhibits CYP1A2, 2A6, 2C9, 2C19, 2D6, and 3A4, yielding many clinically significant drug–drug interactions. Hepatitis from isoniazid is more common in pregnancy, so monitoring is warranted. No pharmacokinetic studies during pregnancy are available.

Rifampicin, category C, is another drug of choice for tuberculosis during pregnancy. It does cross the placenta and into breast milk, and prophylactic vitamin K should be administered to the mother and the infant. It is deacetylated in the liver to an active metabolite, and enterohepatically recycled, with 60% eliminated in feces via biliary excretion and 30% eliminated in the urine. It is a potent inducer of CYP3A4 and other CYP enzymes and causes numerous drug–drug interactions, often requiring dose increases of concomitant medications. No pharmacokinetic data are available in pregnant women.

Ethambutol, category B, is first-line treatment in combination with isoniazid and rifampicin. It crosses the placenta at about 30% of maternal concentrations, and penetrates breast milk in equal concentrations to maternal plasma; no problems with breastfeeding have been reported. It is partially metabolized in the liver, with parent and metabolite excreted in both the urine and the feces, with a half-life of ~3.5 hours. Clinically important drug–drug interactions are not common. No pharmacokinetic data are available during pregnancy.

Pyrazinamide, category C, is often reserved for use in women with documented resistance to the three aforementioned first-line agents or in women who are also HIV+. Its ability to transfer into placenta and breast milk is unknown. It is hydrolyzed in the liver to active metabolites, which are excreted in the urine, and has a 9–10-hour half-life. Clinically important drug–drug interactions are rare. Pharmacokinetic studies in pregnancy have not been reported.

Quinolones are occasionally used as second-line agents in multidrug resistance tuberculosis; ciprofloxacin is preferred. Dapsone may also be considered in specific cases. Other agents, including aminoglycosides (causing fetal ototoxicity), *para*-aminosalicylic acid (causing gastrointestinal intolerance), ethionamide, prothionamide, cycloserine, rifabutine, and rifapentine (all with no pregnancy use data available), are not recommended for use during pregnancy.

13.5 HIV

Treatment for HIV is essential during pregnancy to prevent mother-to-infant transmission of the virus. Combination therapy

throughout pregnancy is the standard of care in areas with sufficient resources; more limited treatment strategies near and during labor/delivery are used in some limited-resource settings. Current perinatal treatment guidelines can be found at http://www.aidsinfo.nih.gov/guidelines [79].

Nucleoside/nucleotide reverse transcriptase inhibitors include abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine. The nucleosides are activated intracellularly and the active triphosphate nucleosides have longer half-lives than the parent drug, have low protein binding, and all but abacavir are eliminated renally. Abacavir is metabolized, but is not a substrate for the CYP enzyme family. Lamivudine (pregnancy category B) and zidovudine (pregnancy category C) are first-line agents for HIV treatment in pregnancy. They have high placental transfer to the fetus, readily pass into breast milk (breast milk to plasma ratios of 2.56 for lamivudine and 0.4 for zidovudine), and pharmacokinetics are not significantly altered by pregnancy [80, 81]. All other nucleosides are considered alternative agents for use in pregnancy. Pregnancy does not significantly alter the pharmacokinetics of abacavir (category C), didanosine (category B), or stavudine (category C) [82–84]. Placental transfer of abacavir and stavudine are high, with moderate transfer of didanosine (cord blood to maternal plasma ratio of 0.38). Breast milk concentrations of these three agents are not known. Maternal exposure to emtricitabine and tenofovir, both pregnancy category B, is lower during the third trimester compared to postpartum, but third trimester concentrations still appear therapeutic so no dose adjustments are warranted [85, 86]. Both readily cross the placenta, but tenofovir transfer into breast milk is low while emtricitabine breast milk penetration is unknown.

First-generation non-nucleoside reverse transcriptase inhibitors include delavirdine (no longer available in the US), efavirenz and nevirapine. Efavirenz, pregnancy category D, is highly protein bound (>99%), is metabolized by CYP3A4 and 2B6, and induces CYP3A4, with a terminal half-life of 40–55 hours. A small study in 13 Rwandan women showed milk to plasma concentration ratios of 54%, and infant plasma concentrations during breastfeeding were 13% of maternal concentrations, with infant concentrations somewhat lower than concentrations targeted for treatment in adults [87]. Likewise, cord blood concentrations are about 50% of maternal concentrations at delivery [88]. Clearance is increased and trough concentrations are decreased during the third trimester compared to postpartum, but third trimester exposure is still high enough to be therapeutic using standard doses [88]. Efavirenz is teratogenic during embryogenesis, so use

should be restricted to after the first trimester of pregnancy. Nevirapine, pregnancy category B, has been used extensively and is the preferred non-nucleoside for use during pregnancy. It is 60% protein bound, has a half-life with chronic dosing of 25–30 hours, is metabolized by CYP3A4 and 2B6, and induces CYP3A4 and 2B6. It readily crosses the placenta, and breast milk concentrations are 76% of maternal concentrations. Pharmacokinetics are not significantly altered during pregnancy in studies of US women, and standard doses are recommended [89, 90]. A study in Ugandan pregnant women showed significantly decreased exposure during pregnancy compared to postpartum, including 67% of women falling below target trough concentrations, suggesting increased doses may be needed in some populations [91].

Second-generation non-nucleosides include rilpivirine and etravirine. Not enough data are available during pregnancy to recommend use of these agents. Etravirine, pregnancy category B, is 99.9% protein bound with a terminal half-life of 41 hours, is metabolized by CYP3A4, 2C9, and 2C19, induces CYP3A4, inhibits 2C9, 2C19, and Pgp, and is subject to many drug–drug interactions. Pharmacokinetics were studied in four pregnant women, and showed similar concentrations in third trimester as postpartum, preliminarily suggesting no altered dosing is necessary in pregnancy [92]. Placental transfer was approximately 33% of maternal concentrations in one woman. Rilpivirine is 99.7% protein bound, is metabolized by CYP3A4, has a half-life of 50 hours, and metabolites are excreted primarily in feces. No data regarding pharmacokinetics in pregnancy, placental or breast milk transfer are available.

Protease inhibitors include atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, and tipranavir. All are hepatically metabolized by CYP isoenzymes, including CYP3A4, and are subject to drug–drug interactions. All except nelfinavir are used with low-dose ritonavir (a potent CYP3A4 inhibitor) to boost exposure to therapeutic concentrations in pregnancy. The majority of protease inhibitors studied to date have decreased concentrations during pregnancy, with lowest exposure seen during the third trimester. Interestingly, early postpartum concentrations on standard doses of ritonavir-boosted lopinavir, fosamprenavir, and atazanavir are higher than seen in non-pregnant adults, so close monitoring for toxicity is warranted. Countries with routine access to therapeutic drug monitoring (TDM) will often draw trough concentrations throughout pregnancy and will adjust individual patient doses as needed to maintain troughs above recommended minimum concentrations.

Lopinavir (coformulated with ritonavir in 200 mg lopinavir/50 mg ritonavir tablets) is the preferred protease inhibitor

for use in pregnancy in the US [79]. It is pregnancy category C, 98–99% protein bound, metabolized by CYP3A4 with most metabolites excreted in the feces, and has a 5–6-hour half-life. Placental transfer is 20% of maternal concentrations [93], while breast milk passage is unknown. Multiple pharmacokinetic studies have shown 40–60% increased lopinavir clearance during pregnancy [93, 94]. The fraction of unbound drug increases by 18% in late pregnancy, which is not enough to overcome the decrease in total exposure [95]. Some experts recommend standard (400 mg lopinavir/100 mg ritonavir) twice daily doses during pregnancy in treatment-naive patients and increased doses (600 mg lopinavir/150 mg ritonavir twice daily) in PI-experienced patients [94], while other experts routinely increase the dose to 600 mg lopinavir/150 mg ritonavir twice daily in the third trimester (30 weeks' gestation), decreasing to standard dose just after delivery [93]. Once daily dosing of 800 mg lopinavir/200 mg ritonavir (approved in treatment-naive non-pregnant adults) is not recommended during pregnancy.

Atazanavir, pregnancy category B, is 86–89% protein bound, has a half-life of 7 hours, is extensively metabolized by CYP3A4, inhibits CYP3A4, 2C8, and UGT1A1 and is mostly excreted as metabolites in feces. Placental transfer is 10–20% of maternal concentrations, and breast milk transfer is unknown. Only when coadministered with ritonavir, is it considered an alternative agent for use in pregnant women in the US [79]. A study in 17 Italian women found no difference in pharmacokinetic parameters during pregnancy compared to postpartum with the standard dose of 300 mg atazanavir and 100 mg ritonavir once daily [96]. Three other studies found 21–45% decreased exposure in the third trimester of pregnancy compared to postpartum [97–99]. The study of mainly South African women recommended the standard dose during pregnancy despite AUC and maximum concentration decreases because minimum concentrations were still in the therapeutic range on the standard dose in pregnancy [97]. The P1026s study team investigated standard dose in second trimester and postpartum, and an increased dose of 400 mg atazanavir/100 mg ritonavir in the third trimester. The increased third trimester dose resulted in concentrations similar to those seen in non-pregnant adults [100], second trimester concentrations on standard doses were lower than typically seen in non-pregnant adults, and may be sub-therapeutic especially when coadministered with tenofovir, while postpartum concentrations on standard doses were higher than reported in non-pregnant adults. The manufacturer recommends the standard dose in pregnancy, unless the patient is also taking either tenofovir or a histamine-2 receptor antagonist,

in which case an increased dose of 400 mg atazanavir/100 mg ritonavir once daily should be used.

Saquinavir, pregnancy category B, combined with ritonavir is another alternative protease inhibitor for use in pregnancy [79]. It is 98% protein bound, has a half-life of 12 hours, and is a substrate and inhibitor of CYP3A4 and Pgp. Pharmacokinetics of older formulations showed decreased exposure to either saquinavir [101, 102] or ritonavir [103] during pregnancy compared to postpartum. A study of the newer 500 mg tablet formulation showed saquinavir concentrations were not significantly different between the second and third trimesters of pregnancy and postpartum [104]. The recommended dose is 1000 mg saquinavir/100 mg ritonavir twice daily.

Two protease inhibitors recommended in some circumstances during pregnancy are indinavir and nelfinavir [79]. Indinavir, pregnancy category C, is 60% protein bound, a substrate of CYP3A4, UGT, and Pgp, inhibits CYP3A4 and has a 2-hour half-life. Transplacental passage is minimal, while breast milk passage is unknown. The manufacturer does not recommend use in pregnancy because exposure is markedly decreased during pregnancy [105, 106]. If needed, only ritonavir-boosted indinavir should be used [107], at a dose of 800 mg indinavir/100–200 mg ritonavir twice daily [79]. For prevention of mother-to-child transmission, when treatment for the mother's infection may not be indicated yet, nelfinavir may be considered in women intolerant to the other protease inhibitors. It has been extensively used in pregnant women, and placental transfer is minimal while breast milk transfer is unknown. It is >98% protein bound, is a substrate of CYP3A4, 2C19, and Pgp, and inhibits CYP3A4 and Pgp. The half-life is 3.5–5 hours. Exposure is significantly decreased during pregnancy [108, 109], and dosing with 625 mg tablets (two tablets, 1250 mg twice daily, $n=27$) resulted in sub-therapeutic trough concentrations in 85% of patients [110], suggesting higher doses may be needed in pregnancy.

Darunavir, fosamprenavir, and tipranavir are not recommended agents in pregnancy due to insufficient data [79]. Darunavir, pregnancy category C, is 95% protein bound, is a substrate and inhibitor of CYP3A4, and has a 15-hour half-life when coadministered with ritonavir (as is required). A study in 31 pregnant women showed significantly decreased exposure during pregnancy with once or twice daily darunavir doses (800 mg darunavir/100 mg ritonavir once daily or 600 mg darunavir/100 mg ritonavir twice daily), and concluded that only twice daily doses should be used [111]. Fosamprenavir, pregnancy category C, is a phosphate ester prodrug that is rapidly converted to amprenavir *in vivo*. It

is 90% protein bound, is extensively metabolized by CYP3A4, 2C9, 2D6, is a Pgp substrate, inhibits CYP3A4, and has a half-life of 7.7 hours. Similar to other protease inhibitors, exposure is significantly decreased during pregnancy when dosed as 700 mg fosamprenavir/100 mg ritonavir twice daily [112]. However, concentrations on this dose during pregnancy are still higher than concentrations in non-pregnant adults taking one of the approved doses of 1400 mg twice daily without ritonavir, and the standard ritonavir-boosted dose should be adequate for treatment-naive patients. Tipranavir, pregnancy category C, must be coadministered with ritonavir. It is >99.9% protein bound, is a substrate for CYP3A4 and Pgp, and induces CYP3A4 and Pgp. A case report showed therapeutic concentrations in late pregnancy on the standard dose (500 mg tipranavir/200 mg ritonavir twice daily), and a cord blood to maternal concentration ratio of 0.41, higher than other protease inhibitors [113]. No other published data are available.

Raltegravir, an integrase strand transfer inhibitor classified as pregnancy category C, is 83% protein bound, is metabolized by UGT1A1 to a glucuronide conjugate, and is excreted in feces and urine, with a half-life of 9 hours. Placental transfer is variable but high, often with cord blood concentrations exceeding maternal concentrations [114, 115]. Breast milk transfer is unknown. Concentrations, while altered by pregnancy and highly variable, appear adequate with standard dosing [114]. Enfuvirtide, pregnancy category B, is an entry (fusion) inhibitor administered by subcutaneous injection. It is 92% protein bound, has a 3.8-hour half-life, and is a peptide that is hydrolyzed to an inactive metabolite, and expected to be catabolized to amino acids. It does not cross the placenta [116, 117], and transfer into breast milk is unknown. Pharmacokinetic data during pregnancy are not available. Maraviroc, another entry inhibitor classified as pregnancy category B, is 76% protein bound, a substrate of Pgp and CYP3A4, has a 14–18-hour half-life, and is subject to many drug–drug interactions. No information regarding maraviroc use in pregnancy is available.

13.6 Antivirals

Treatment for genital herpes is generally recommended during pregnancy to prevent neonatal herpes. Acyclovir is pregnancy category B, distributes widely in the body, crosses into the placenta and the breast milk at concentrations similar to or greater than maternal plasma, and is excreted unchanged in the urine

with a short half-life of 2.5–3.3 hours. Oral bioavailability is low (10–20%). A pharmacokinetic study in pregnant women concluded that 400 mg orally three times daily provided appropriate concentrations, similar to those seen in non-pregnant adults [118]. Valacyclovir, also category B, is a prodrug of acyclovir that is converted to acyclovir by first pass intestinal or hepatic metabolism, with increased bioavailability (~55% acyclovir bioavailability after valacyclovir administration). A pharmacokinetic study comparing valacyclovir 500 mg twice daily and acyclovir 400 mg three times daily found higher acyclovir exposure (approximately double) with administration of valacyclovir in pregnant women. Both were well tolerated, but insufficient safety and efficacy data (compared to acyclovir) are available to recommend use in pregnancy. Likewise, no pharmacokinetic and limited safety/efficacy data are available for famciclovir, penciclovir, ganciclovir, valganciclovir, foscarnet, cidofovir, fomivirsen, trifluridine, or vidarabine. Use of several of these agents to treat cytomegalovirus during pregnancy should be limited to serious/severe infections.

Amantadine, rimantadine, oseltamivir, and zanamivir are used for the treatment of influenza virus. Safety data are inadequate to determine risks of these medications in pregnancy, but morbidity and mortality from influenza are higher during pregnancy, so these agents may be needed in serious infections. All four are category C. Oseltamivir is hepatically metabolized (but not by the CYP P450 system) to the active form, a carboxylate metabolite, which is excreted in urine. The half-life is 1–3 hours, and penetration into breast milk yields concentrations significantly lower than considered therapeutic in infants [119]. Two studies have evaluated pharmacokinetics in pregnant women. In 30 women, carboxylate exposure did not change significantly between the three trimesters of pregnancy [120]. Concentrations were above the typical viral 50% inhibitory concentrations, and the authors concluded that standard doses should be adequate in pregnancy. Beigi and colleagues compared 16 pregnant women to 23 non-pregnant controls, and found significantly lower carboxylate metabolite exposure during pregnancy [121]. Given the wide therapeutic window of oseltamivir and the increasing prevalence of viral neuraminidase inhibitor resistance, these authors suggest increasing the treatment dose from 75 mg twice daily for 5 days to 75 mg three times daily in pregnant women to better approximate concentrations seen in non-pregnant patients. Pharmacokinetic studies on this increased dose have not been reported.

Amantadine is renally excreted unchanged, with an 11–15-hour half-life. It crosses the placenta and into breast milk, and is not recommended in breastfeeding. Rimantadine is extensively hepatically

metabolized with a half-life of 13–65 hours. Placenta and breast milk exposure are unknown. Amantadine and rimantadine are no longer first-line agents due to high resistance, but are being used in combination with oseltamivir or zanamivir as neuraminidase inhibitor resistance increases. Zanamivir is renally excreted unchanged with a 2.5–5-hour half-life. Small amounts cross into placenta; breast milk penetration is unknown. Pharmacokinetic data are not available for amantadine, rimantadine or zanamivir in pregnancy.

Ribavirin is pregnancy category X, and is teratogenic in animals. It is used for hepatitis B and C in combination with interferons (category C), and should be reserved for life-threatening infections. It is also toxic to nursing animals, and should not be used during breastfeeding.

13.7 Parasitic infections

Many parasitic infections are asymptomatic, and treatment is only indicated for severe infections during pregnancy. Mebendazole is category C, and can be used during pregnancy if indicated. It is poorly absorbed and metabolized by CYP P450, but very effective within the intestine. Flubendazole is structurally related, with limited data available in pregnancy. Albendazole is a broad-spectrum anthelmintic and is category C. It is poorly bioavailable with extensive first-pass and systemic hepatic metabolism and a 9-hour half-life. It may induce CYP1A activity and be subject to drug–drug interactions. Thiabendazole, also category C, is also extensively metabolized hepatically and is a substrate and inhibitor of CYP1A2. No data are available for use during pregnancy.

Praziquantel is category B and is a first-line agent for schistosomiasis treatment. It is metabolized hepatically, likely by CYP3A4, and subject to drug–drug interactions with a short half-life of 0.8–1.5 hours. Breast milk concentrations are about a quarter of maternal concentrations. No pharmacokinetic data in pregnancy are available. Pyrantel is another broad-spectrum anthelmintic, category C, but is not recommended in pregnancy due to very limited pregnancy use data available. Ivermectin and diethylcarbamazine are used to treat filiriasis and onchocerciasis/onchocercosis. Data for use in pregnancy are lacking; they should only be used for compelling indications. Paromomycin, category C, is used for intestinal amebiasis, and is not absorbed systemically after oral ingestion. Niclosamide, category B, is used to treat tapeworm infections, and is not significantly absorbed from the gastrointestinal tract.

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Chemotherapy in Pregnancy

14

Caroline D. Lynch, Men-Jean Lee and Giuseppe Del Priore

14.1 Introduction

Cancer is the second leading cause of death in women of reproductive age. It is diagnosed with a frequency of 1 per 1000 pregnant women; most commonly breast cancer followed by cervical, lymphoma, and melanoma [1]. Chemotherapy poses the greatest risks for the developing fetus early in pregnancy. Depending on the type of cancer and the stage of diagnosis, chemotherapy may need to be administered without delay, thus the recommendation for pregnancy termination. Neonatal risks of chemotherapy are reduced when administered in the second and third trimesters; however, longitudinal follow-up for low birth weight, intrauterine

growth restriction (IUGR), and prematurity are lacking, especially regarding the neurodevelopmental effects. The ethics of the timing of delivery must balance the risk of the health of the mother and the risk to the fetus. This chapter will review the general indications for chemotherapy in pregnancy and the data surrounding the best use of the commonly prescribed chemotherapeutic agents in pregnancy.

When the fetus is exposed to the cytotoxic effects of chemotherapy during the first trimester, the pregnancy will likely end in spontaneous abortion, major malformations, and fetal loss [2]. Organogenesis, the critical time of organ formation from 2 to 8 weeks following conception represents the time when the cardiac and central nervous system are especially susceptible to insult. However, even following organogenesis, injury may still occur to the eyes, gonads, and central nervous and hematopoietic systems as these organ systems continue to mature over the course of a pregnancy [1]. Treatment with chemotherapy in the second and third trimester is generally thought to be safer, but can be associated with intrauterine growth restriction and low birth weight infants [2]. When treatment with chemotherapy is required, whether with single or multi-agent, the clinician must have knowledge of the optimal timing of treatment, to ensure an efficacious and safe approach to therapy.

14.2 Overview of chemotherapeutic agents

14.2.1 Antimetabolites

Antimetabolites are characterized by their inhibitory activity during DNA or RNA synthesis. Examples include methotrexate, 5-fluorouracil, thioguanine, cytarabine, cladribine, cladribine, fludarabine, mercaptopurine, pemetrexed, and gemcitabine. Perhaps due to its long history in use as a chemotherapeutic agent, methotrexate has been used for many illnesses, including acute monocytic leukemia, non-Hodgkin's lymphoma, osteosarcoma, head and neck cancer, and breast cancer [4]. It is known to be an abortifacient and a teratogen. In a review of 42 cases of methotrexate exposure, 23 cases in the first trimester found no abnormalities [1]. Previous reports noted associations with mental retardation, craniodystosis, hypertelorism, micrognathia, and limb deformities [3]. It is likely that there is a critical dose above which teratogenicity or spontaneous abortion occurs. Methotrexate used in low doses in rheumatologic disease has not been demonstrated to increase rates of fetal malformation or induce spontaneous abortions [5].

5-Fluorouracil was associated with multiple fetal anomalies in a patient who received chemotherapy for colon cancer beginning at 12 weeks' gestation [3]. 5-Fluorouracil is often used in

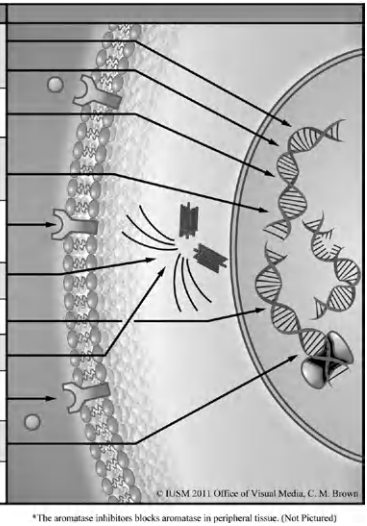
combination with cyclophosphamide and doxorubicin for the treatment of breast cancer. Generally, it is recommended to avoid its use in the first trimester (Figure 14.1).

Cytarabine is typically used in combination with other agents such as vincristine, tioguanine, or doxorubicin to treat acute leukemia. There are reports of limb malformations after first trimester exposure, either alone or in combinations for the aforementioned agents [1, 6]. In a report of 89 cases, intrauterine fetal distress (IUFD) was noted to have occurred in 6% and neonatal deaths in two [1]. Cause of death was not identified in these cases. Cytarabine and daunorubicin were used in four cases. Cytarabine and tioguanine were used in five of the six intrauterine fetal demises. The effects of underlying maternal leukemia may also have contributed to the complications [1].

A case report of 6-mercaptopurine given for treatment of acute monocytic leukemia in pregnancy during the first trimester and again in the third trimester was associated with the birth of a premature infant but no malformations were noted [1].

As with methotrexate, much of the recent data regarding the thioprine class of chemotherapeutic agents comes from the autoimmune literature where this class of medications is commonly used as immunomodulators. Mercaptopurine has been used in combination with azathiopurine in patients with inflammatory

Selected Chemotherapeutic Agents	Mechanism of Action
Alkylating agents Cyclophosphamide, chlorambucil, dacarbazine, busulfan, ifosfamide, carmustine, altretamine, melphalan	Nucleophilic Cell Substitution
Anthracyclines Doxorubicin, epirubicin, daunorubicin, idarubicin, dactinomycin, bleomycin, mitoxantrone	DNA Interposition
Antimetabolites Methotrexate, 5-fluorouracil, cytarabine, tioguanine, mercaptopurine, aminopterin, gemcitabine	Inhibit DNA Synthesis
Hormonal Agents Tamoxifen, DES, anastrozole, letrozole, vorozole, formestane, fadrozole, megestrol acetate, aminogluthethimide, testolactone	Estrogen Antagonist in breast tissue*
Plant Alkaloids Vincristine, vinblastine, vinorelbine	Inhibit DNA Synthesis
Platins Cisplatin, carboplatin, oxaliplatin	Microtubule Depolymerization
Taxanes Paclitaxel, docataxel	Inhibits Microtubule Disassembly
Targeted Therapies Trastuzumab, lapatinab, bevacizumab, rituximab, erlotinib	VEGF, HER2-neu Receptors
Topoisomerase Inhibitors Etoposide, irinotecan, tenoposide, topotecan	Topoisomerase Inhibitor
Others Allopurinol, asparaginase, mitoguazone	Various



*The aromatase inhibitors blocks aromatase in peripheral tissue. (Not Pictured)

Figure 14.1 Selected Chemotherapeutic Agents and Mechanism of Action.

bowel disease (IBD), which is estimated to affect 1.4 million Americans, with a peak onset at 15–30 years of age [7]. A retrospective cohort study by Francella identified 15 patients who remained on 6-mercaptopurine/azathiopurine for their entire pregnancy for the treatment of IBD. The authors reported that previous data showed a 3.9% congenital anomaly rate for the aforementioned agents while their study found a 2.5% rate for one case of a congenital anomaly, compared to 4% in the control group [8]. There was no difference in spontaneous abortion rates, major or minor malformations, neonatal infection rates or prematurity.

14.3 Alkylating agents

Alkylating agents are commonly used to treat breast cancer, acute leukocytic leukemia, and lymphoma. Cyclophosphamide is contraindicated in the first trimester due to significant malformations including absent toes, eye abnormalities, low-set ears, and cleft palate [1]. Again, much of the data surrounding the use of cyclophosphamide comes from the literature regarding rheumatologic diseases. A case report of a mother who was prescribed cyclophosphamide for systemic lupus erythematosis and had exposure to the agent throughout her entire first trimester resulted in an infant with multiple physical anomalies similar to those findings from animal studies, raising the question of a cyclophosphamide phenotype [9]. *In utero* exposure during the first trimester may be associated with the cyclophosphamide phenotype characterized as growth deficiency, developmental delay, craniosynostosis, blepharophimosis, flat nasal bridge, abnormal ears, and distal limb defects including hypoplastic thumbs and oligodactyly. Cyclophosphamide use has been reported as safe during the second and third trimesters.

Chlorambucil has been reported to cause cleft palate, skeletal dysplasias, and renal aplasia when administered in the first trimester [3]. A case report of a 36-year-old patient who received chlorambucil to treat her chronic lymphocytic leukemia until her pregnancy was diagnosed at 20 weeks' gestation described no associated fetal malformations, or major abnormalities [10]. In a series of 15 pregnant patients with Hodgkin's disease, one patient who received chemotherapy with chlorambucil during the latter half of her pregnancy delivered a full-term infant [11].

Dacarbazine is an alkalyting agent with little data in humans. In high doses, it is known to be teratogenic in rats [1]. Dacarbazine has emerged as an agent used in combination with tamoxifen, carmustine, and cisplatin for the treatment of metastatic melanoma

during pregnancy. It is also used as part of the ABVD regimen for lymphoma. Dipaola et al. published a case report of a patient who received two cycles of this combination therapy for melanoma prior to delivery of her healthy infant at 30 weeks' gestation [12]. No skeletal defects or cleft palate were observed as had been previously described with dacarbazine. The placental tissue was notable for invasion of malignant melanoma into the intervillous spaces; however, the fetus did not have metastatic disease.

Busulfan use in pregnancy was associated with no anomalies during the first trimester [13]. It was associated with malformations in two cases with second trimester use: in one case, unilateral renal agenesis was noted after combination of busulfan and allopurinol, and in the other case, pyloric stenosis occurred after single therapy [1].

14.4 Anthracyclines

The anthracycline agents are typically used as combination agents. A mechanism of action is by intercalating between DNA base pairs. Twenty-eight pregnancies exposed to doxorubicin and daunorubicin for treatment of acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, sarcoma, and breast cancer were summarized in a case series. One elective termination and two spontaneous abortions occurred; all fetuses were noted to be normal. Twenty-one pregnancies were delivered without complications. At birth, one infant had transient bone marrow hypoplasia, and one set of twins presented with diarrhea and sepsis at birth. Two patients expired with the fetus *in utero* prior to delivery [14]. Doxorubicin had been previously cited to be associated with limb abnormalities in the first trimester; however, it was given in combination with cytarabine [1]. A case report of a spontaneous abortion at 17 weeks occurred after exposure at 13 weeks' gestation to doxorubicin and vincristine for treatment of acute lymphoblastic leukemia (ALL). Postmortem fetal necropsy was not performed [15].

In another case, respiratory distress syndrome, neonatal sepsis, and bronchopneumonia occurred in a 31-week gestation with a birth weight of 2070 g whose mother had received doxorubicin for breast cancer at 28 weeks' gestation. Follow-up of the offspring at 6 years of age revealed normal development [15].

Of 13 women in which epirubicin was used, three fetuses were affected. One neonatal death occurred after exposure to epirubicin, vincristine, and prednisone and another to epirubicin in combination with cyclophosphamide [15, 16]. The combination of

exposure to cyclophosphamide, epirubicin, and 5-fluorouracil during the first trimester for treatment of infiltrating ductal breast cancer resulted in limb abnormalities and micrognathia [17]. The patient electively terminated the pregnancy and the fetus was examined subsequently to confirm the findings. Epirubicin has been the agent of choice for breast cancer in Europe where doxorubicin was typically used in the United States during pregnancy. There are inherent problems in comparative reviews of retrospective data; however, the conclusion of the authors was that the two agents, doxorubicin and epirubicin, show similar transplacental transfer rates and toxicity profiles [18].

Daunorubicin has most commonly been used in treatment of acute lymphocytic leukemia. Of 43 cases that were reviewed, IUGR occurred in five fetuses, four suffered from transient myelosuppression, three IUFDs occurred, two of which were notable for complications by severe preeclampsia at 29 weeks or severe maternal anemia and maternal complications from ALL [1]. The third IUFD was following combination therapy with daunorubicin, idarubicin, cytarabine, and mitoxantrone.

Though doxorubicin is typically used in advanced breast cancer in pregnancy as part of the FAC regimen (5-fluorouracil, doxorubicin, cyclophosphamide), data surrounding its use in pregnancy are limited. Unless the patient has underlying cardiac disease, this anthracycline-containing combination [2, 9] is first-line therapy [19].

Anthracyclines are known to be cardiotoxic in children and adults, but the *in utero* effects on developing fetuses are not known [20]. Meyer-Wittkopf and colleagues performed fetal echocardiograms every 2 weeks on a pregnant patient who was receiving doxorubicin and cyclophosphamide during the second and third trimesters of pregnancy for treatment of infiltrating ductal carcinoma. Measurements of ventricles of unexposed fetuses aged 20–40 weeks were used as controls. No fetal cardiac changes were noted to suggest cardiotoxicity [21]. In a European study, 20 patients were followed throughout their pregnancy, receiving weekly epirubicin at 35 mg/m^2 for treatment of breast cancer at a median gestational age of 19 weeks. No major fetal malformations were noted with the exception of one case of inheritable polycystic kidney disease. Children were reported to be developmentally normal by reports of their parents at 2 years of age [22].

14.5 Plant alkaloids

The plant alkaloids, vincristine, vinblastine, and vinorelbine, are considered to have a higher safety profile in pregnancy. One

malformation was reported in 29 patients treated during the first trimester with combination therapy of vincristine, doxorubicin, cytarabine, and prednisone; an atrial septal defect and absent fifth digit [1]. Two fetal deaths and two neonatal deaths occurred, all after combination therapy in the second and/or third trimester. Of 111 exposures to vincristine or vinblastine, nine cases of IUGR and seven cases of preterm delivery occurred [15]. Vinorelbine was administered to two subjects in combination with 5-fluorouracil and for another patient epidoxorubicin and cyclophosphamide due to disease progression of her breast cancer in pregnancy. The only fetal effect observed was anemia at 21 days of life, but no fetal malformations were noted [23].

14.5.1 Taxanes

Taxanes have been shown to be teratogenic in animal models, but their use in humans during pregnancy has been limited. Paclitaxel works by disruption of microtubule assembly. It has been shown to be toxic to chick, rat, and rabbit embryos when given during the critical organogenesis period [1]. The use of taxanes has emerged as important in patients with node positive breast cancer [24, 25]. A recent published case report from *Clinical Breast Cancer* describes a patient with invasive lobular breast cancer who received weekly paclitaxel from 19 to 33 weeks' gestation. Fetal ultrasound was performed at 6-week intervals and labor was induced at 37 weeks due to onset of preeclampsia. The fetus was of normal weight without malformations or infection at birth [25, 26].

14.5.2 Hormonal agents

Metastatic breast cancer during pregnancy poses a challenge for the practitioner in terms of treatment options. Though it had been previously held that survival was poorer for pregnant patients, when matched by stage and age with non-pregnant controls, survival is similar [27]. Research on tamoxifen in the animal literature shows epithelial changes in the neonatal period similar to those observed with diethylstilbesterol (DES). DES was used prior to tamoxifen and aromatase inhibitors for estrogen positive breast cancer. It was also used to prevent miscarriages and as estrogen replacement in estrogen-deficient states after its advent in 1938. It had significant adverse effects both on the women who took it and on exposed fetuses. Studies have shown that female fetuses exposed *in utero* show structural changes in the uterus, cervix, and upper vagina; classically, the T-shaped uteri and uterotubal anomalies that lead to repeat miscarriages [28]. There is also an increased incidence

of clear cell vaginal adenocarcinoma 1/1000 exposures. The proposed mechanism is altered embryological Mullerian duct formation due to estrogenic alterations to stromal junctions [29]. Specific structural changes and clear cell vaginal adenocarcinoma were not reported in the literature surrounding tamoxifen use in fetuses. It is not clear if DES affects fertility; certainly structural changes may affect fertility. The teratogenicity of tamoxifen has been suggested to be species specific and reports in humans are limited.

Treatment with aromatase inhibitors (AIs) improves survival for women with metastatic breast cancer by 10% [30]. In initial studies, AIs did not have a statistically significant survival benefit when compared to tamoxifen; however, the third generation AIs did demonstrate a survival benefit [31]. AIs are typically not given in pregnancy or in premenopausal women as peripheral inhibition of aromatase would not be able to overcome the estrogen produced by the growing pregnancy or the premenopausal ovary. In the postmenopausal female, aromatase inhibitor inhibits the conversion of androgen to estrogen in the adipose tissue, as it occurs on a smaller scale.

14.6 Targeted therapies

The HER-2Neu gene has been noted to be amplified in 25–50% of metastatic breast cancer patients [32]. HER-2Neu gene positivity is associated with a poor prognosis and decreased survival; however, it is an important for targeted therapies. Trastuztumab (Herceptin) is a targeted monoclonal antibody that binds the extracellular domain of the overexpressed HER-2Neu receptor in metastatic breast cancer patients. Herceptin is associated with reversible fetal oligohydramnios or anhydramnios [33]. In one case, a mother treated with Herceptin delivered a fetus with oligohydramnios, but no IUGR, and with normal lung and kidney development [33].The proposed mechanism of oligo- or anhydramnios is believed to be related to trastuztumab effects of vascular endothelial growth factor (VEGF) to inhibit amniotic fluid production in the developing fetal kidney [33]. Aside from fetal oligo- or anhydramnios, no other fetal anomalies have been associated with use to date, although human data are limited. Beyond monoclonal antibody therapy, in the near future, alternative therapies for breast cancer may include dual inhibition of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER-2) with lapatinib, HKI-272, and pertuzumab; antiangiogenesis agents, such as bevicizumab (to date, reports of bevicizumab in pregnancy are limited to intravitreal use for

neovascularization [34]); anti-mTOR effects of Temsirolimus; and anti-Hsp-90, such as 17-AAG [32].

Despite the number of new agents on the horizon, currently, standard treatment for HER-2 positive cancer consists of trastuzumab. Caution must be taken with trastuzumab in terms of maternal health. It is associated with 4% cardiotoxicity when given as single agent and 27% when given in combination with anthracyclines [35]. The cardiotoxicity is associated with a decrease in left ventricular ejection fraction and is suspected to be reversible. Memorial Sloan Kettering has adapted guidelines for monitoring cardiac dysfunction during trastuzumab use; however, these guidelines would have to be adapted for pregnancy [35].

14.7 Other agents

Cisplatin and carboplatin are typically given as combination agents. They are considered to have a relatively low toxicity profile. An infant was exposed for 2 weeks to cisplatin, etoposide, and cytarabine during the second trimester for the treatment of maternal Hodgkin's disease. Fetal jaundice, non-hemolytic anemia was observed in an otherwise normal child born at 36 weeks [15].

In another case, sensorineural hearing loss was reported in a child born with leukopenia, alopecia, and respiratory distress syndrome at 26 weeks after the child was exposed to cisplatin only 6 days prior to delivery [1]. Complicating factors include severe prematurity of the infant and postnatal treatment with gentamicin. A case report of a patient treated for stage IIIC ovarian cancer with paclitaxel and carboplatin beginning at 16 weeks' gestation resulted in no fetal anomalies or complications [36].

Few case reports and little data exist on gemcitabine, bleomycin, mitoxantrone, dactinomycin, idarubicin, allopurinol, rituximab, etoposide, asparaginase, teniposide, mitoguazone, tritinoin, irinotecan, oxaliplatin, melphalan, altretamine, and erlotinib use in pregnancy due to lack of human exposures in pregnancy; thus discussion has been limited.

14.8 Treatment of specific cancers

A summary of perinatal outcomes for 152 women who voluntarily enrolled in the national Cancer and Pregnancy Registry between the years of 1995 and 2008 allowed for significant detail

on the effects of chemotherapy. The mean gestational age at the first cycle of treatment was 20.1±6/2 weeks to the last treatment at 29.6±5.7 weeks. Overall, the rate of malformations was 3.8% (6/157 neonates exposed), equivalent to that of the general population [37]. Neonatal demise was observed in one case (0.7%), and an IUFD was observed in one case (0.7%). In 12 cases (7.6%), IUGR was observed. Nine cases delivered prematurly and transient complications of prematurity occurred in seven infants [37].

14.9 Breast cancer

In the Cancer and Pregnancy Registry, 118 women were diagnosed with a primary breast cancer, and two with a new primary during pregnancy [37]. Most tumors in pregnancy are found to be high-grade invasive ductal carcinoma, larger than their age-matched non-pregnant controls, positive for lymphovascular invasion following surgery, with 60–80% ER negative, and 28–58% reported to be HER-2Neu positive [39]. Most women were treated with Adriamycin/Cytoxan with the mean gestational age of first treatment at 20.3±5.4 weeks. The rate of congenital malformations was 3.8%, and 7.8% were small for gestational age at birth. Thirteen neonates had complications during the neonatal period involving: sepsis and anemia at birth in a prematurity infant, gastroesophageal reflux, difficulty in feeding requiring tube feeding in three, transient tachypnea in three, hyperbilirubinemia or jaundice in three, respiratory distress syndrome in two, and apnea of prematurity in two. Death occurred in a neonate who was diagnosed with a severe rheumatologic disorder, which resulted in her demise at 13 months of age. Long-term reports indicated no neurodevelopmental effects or leukemias.

Berry et al. reported there were no fetal anomalies or growth restriction in a cohort of 24 patients treated with cyclophosphamide, 5-fluorouracil, and doxorubicin after 12 weeks' gestation [39]. Current treatment options typically recommend this combination regimen of FAC (5-fluorouracil, cyclophosphamide, doxorubicin) after the first trimester [40].

14.10 Lymphoma

Lymphoma was diagnosed in 35 patients during pregnancy; 23 were diagnosed with primary Hodgkin's disease, two with recurrent Hodgkin's disease and 10 with non-Hodgkin's lymphoma. Thirty

of those 35 received chemotherapy during pregnancy, none during the first trimester. In the Cancer and Pregnancy Registry, one child was born with a congenital malformation, which consisted of syndactyly. Two children (6.6%) were small for gestational age (<10%). An IUFD occurred at 28 weeks after CHOP chemotherapy; although an autopsy was performed, the cause of death was not identified [37]. One case of speech delay was reported at 4.3 years of age.

Typical regimens for lymphoma include CHOP, CHOP-R or newer reports have included the ABVD (doxorubicin, bleomycin, vinblastine dacarbazine). Dacarbazine is the least studied agent. A case report from Japan details the use of the ABVD in the second trimester, which resulted in the birth of an infant without any malformations or infections [41].

14.11 Leukemia

Three women in the Cancer and Pregnancy Registry were diagnosed with acute leukemia in pregnancy and two received chemotherapy. Neither had low birth weights, malformations, or abnormal follow-up of the children [37].

Various combinations of chemotherapeutic agents are used. Typically, the earlier the diagnosis, the worse the prognosis for the mother and fetus; however, in these cases, treatment cannot be delayed. Fetal complications may include spontaneous abortion, prematurity, IUGR, and IUFD which have been theorized to be attributed to maternal anemia and disseminated intravascular coagulation (DIC) [1].

In the Cancer and Pregnancy Registry, three patients were diagnosed with chronic myeloid leukemia during pregnancy, although only one received chemotherapy with cytarabine. She delivered a normal infant at 42 weeks without anomalies, pregnancy complications, or long-term complications.

Aviles and colleagues followed 62 children treated for hematologic malignancies. All children were physically and neurodevelopmentally normal by school performance standardized tests and laboratory tests showing normal tolerance of infections [42].

14.12 Ovarian cancer

Eleven women were identified with ovarian cancer during pregnancy, and of those seven went on to receive chemotherapy, which

neonates in the Cancer and Pregnancy Registry to carboplatin, cisplatin, etoposide, prednisone, and bleomycin. Two infants were IUGR, one child was affected with attention deficit disorder and one child was diagnosed with genetic hearing loss (both parents were carriers of the gene) [37]. Cisplatin is commonly chosen over carboplatin for ovarian cancer during pregnancy. Carboplatin has been known to cause thrombocytopenia and is less protein bound which may lead to higher rates of placental transfer [1].

Too few cases of CNS, cervical, colorectal, melanoma, and pancreatic cancers were reported to summarize in this review.

14.13 Future fertility

Two prospective randomized controlled trials studying the use of gonadotropin-releasing hormone (GnRH) agonists during concomitant chemotherapy for premenopausal breast cancer suggest preservation of ovarian function with return of natural menstrual function [43, 44].

14.14 Pharmacokinetics in pregnancy

To date, there have not been any pharmacokinetic studies of chemotherapeutic agents in pregnant women. Animal models have contributed to research but do not provide comprehensive details. These studies have been severly critisized for methologic flaws, GnRH agonish should not be relied on to preserve fertility during chemotherapy. Much of the information regarding the chemotherapeutic agents comes from retrospective reviews and case reports. Because randomized controlled trials and pharmacokinetic studies are lacking, pregnant patients receive the same weight-based doses as non-pregnant women. Pharmacokinetic studies would further the understanding of physiologic changes of pregnancy which affect drug clearance. For example, increased renal clearance rates and increased circulating blood volume may affect active drug concentrations. Decreased plasma albumin levels, increased levels of other circulating proteins, and increased estrogen levels may decrease drug-binding levels. Changes in gastrointestinal function (which may alter absorption of oral medications) may change the active concentration of a medication as well. The volume of distribution and hepatic oxidase system may also be affected during pregnancy [1]. Elimination of a drug may also be affected by

the amniotic fluid levels with the amniotic fluid acting as a "third space" [38]. Without adequate knowledge of the pharmacokinetics, women may be underdosed; thus, more research is needed to understand the effects of antineoplastic medicines on the mother and the fetus [45].

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Substance Use Disorders

James J. Nocon

15

15.1 Introduction

Substance use in pregnancy of alcohol, tobacco, and other drugs (ATOD) is the single most preventable public health and social problem affecting women. Although accurate estimates of ATOD use in pregnancy are difficult to ascertain, a national survey in 2003 revealed the prevalence to be 15.1% among young women aged 15–17 years [1]. Unfortunately, substance use in pregnancy is significantly under reported [2]. Admitting to the use of an illegal substance may lead to prosecution, incarceration, and loss of

child custody [3]. The greater tragedy is that substance use too often goes unrecognized.

Those in the health care system often demonize pregnant addicts [4]. In one survey, 52% of physicians agreed that drug use in pregnancy constituted child abuse [5]. In another survey, obstetrical nurses had limited knowledge of substance use and over 60% demonstrated a hostile and punitive attitude [6]. The major problem is a lack of education and training, especially in the ability to screen, detect, and intervene in substance use in pregnancy. This lack of awareness gives tacit approval to the addict [7]. The American College of Obstetricians and Gynecologists addresses the ethical rationale for universal screening for at-risk drinking and illicit drug use [8]. Likewise, the American Medical Association also endorses a duty for universal screening [9].

This chapter will review the unique issues facing women and especially pregnant women involved with substance use. In addition, the chapter will include data from the treatment of over 500 patients in the Prenatal Recovery Program at Wishard Memorial Hospital, Indianapolis, Indiana (hereinafter called the Wishard data). Wishard is a public hospital for Indianapolis and a major teaching hospital for the Indiana University School of Medicine. Demographics include approximately 3000 deliveries per year of Black (40%), White (30%), and Hispanic (30%) patients. About 95% are Medicaid funded.

15.2 Substance use disorders defined

Addiction is actually an extremely difficult illness to define and the general consensus among addiction counselors is, “I know it when I see it”, paraphrasing Potter Stewart, a former US Supreme Court Justice. It is not an issue of “weak willpower”, poor character or immorality. Rejecting this notion, a more enlightened perspective has emerged as “Substance Use Disorder” (SUD) replacing the pejorative term “addiction” in the American Psychiatric Association (DSM-IV-TR) [10].

The DSM-IV distinguishes between substance dependence and substance abuse as follows [11]:

> **Substance Dependence** is a pattern of substance use, leading to clinically significant impairment or distress, with **three or more** of the following, occurring at any time in the same 12 month period:
>
> Tolerance.
> Withdrawal.

The substance is taken in larger amounts over a longer period than was intended.
A persistent desire or unsuccessful efforts to cut down or control use.
Inordinate time spent in acquiring the substance, use of the substance, or recovery from its effects.
Important social, occupational or recreational activities are given up or reduced.
The substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Substance Abuse is a separate diagnosis from substance dependence. It is a maladaptive pattern of substance use with **one or more** of the following criteria over a 1-year period:

Repeated substance use that results in an inability to fulfill obligations at home, school or work.
Repeated substance use when it could be dangerous (e.g. driving a car).
Repeated substance-related legal problems, such as arrests.
Continued substance use despite interpersonal or social problems that are caused or made worse by use.

15.3 Addiction defined as a disease of the brain

The disease model of addiction is now firmly established based on overwhelming evidence that addiction is a disease of the brain, where a substance or behavior can produce a need to use drugs or behave in a compulsive manner with known adverse consequences [12]. It manifests as a chronic relapsing process and successful treatment is comparable to, or better than, compliance with treatment plans for hypertension or diabetes [13]. And like diabetes and hypertension, addiction is an interaction between:

The substance: alcohol, tobacco and other drugs,
The host: genetics, vulnerabilities, co-morbid disorders, and
The environment: family, culture.

Continuous use of drugs changes the anatomy and physiology of brain cells, particularly in the lateral tegmental area and the nucleus accumbens [14]. PET/MRI scans have mapped the location in the brain where drugs and behaviors have their effects. Addiction depletes dopamine and the altered brain cannot manufacture sufficient dopamine to function in a normal manner [15]. This process occurs in all addictive drugs and behaviors.

The pharmacological relevance of this disease model is used in the treatment of nicotine dependence. Nicotine activates the nucleus accumbens, releases dopamine and dopamine is depleted. Antidepressants that are dopamine reuptake inhibitors are effective in stabilizing dopamine levels by blocking or blunting the effect of nicotine, decreasing the cravings, and enhancing smoking cessation. Similar antidepressants have also been used in methamphetamine treatment with good results [16].

Most recently, the American Society of Addiction Medicine (ASAM) redefined addiction consistent with the medical and neurobiological evidence [17]. The society notes that addiction is, "a primary, chronic disease of brain reward, motivation, memory and related circuitry". ASAM describes five characteristics (the ABCs) in its definition:

a. **Inability to consistently Abstain**;
b. **Impairment in Behavioral control**;
c. **Craving**, or increased "hunger" for drugs or rewarding experiences;
d. **Diminished recognition of significant problems** with one's behaviors and interpersonal relationships; and
e. **A dysfunctional Emotional response.**

Moreover, the ASAM definition holds that addiction affects emotional and cognitive behavior as well as interpersonal relationships, especially with family, community, and "to things that transcend their daily experience". This dovetails into the perspective of addiction from 12 Step fellowships in recovery. This is termed the "relationship view". Simply stated, if the substance use and associated behavior keeps the person from the physical and emotional attachments of those who love them, then they are addicted. Such behavior would trigger an intervention.

The ASAM definition creates controversy because physician's attitudes are based on physician training and current training reflects older beliefs and not the "brain disease" model [18]. Many physicians persist in holding onto the myths that treatment is not effective, it is time consuming and there are few referral services [19]. And bringing "spirituality" into treatment has often been viewed as less than objective. In fact, treatment works, brief interventions are effective, and spiritual models assist in motivating the patient in recovery [20].

15.4 The good news: the brain can recover

Current research indicates that recovery in the brain is mediated by adult stem cells, a large source of which is located by the

nucleus accumbens [21]. The stem cells can migrate relatively large distances and appear to rebuild damaged circuitry. Factors found to stimulate stem cell production include physical exercise, folic acid, and reading. It is well established that folic acid supplements are able to prevent neural tube defects and thereby be able to repair other structural damage [22]. Thus, folic acid supplementation may become a new pharmacologic strategy to enhance recovery from addiction. An interesting question is whether high dose folic acid supplements can protect against and prevent fetal alcohol syndrome and its associated brain damage.

A theory for stem cell repair would assert that alcohol damages neurons and abstinence removes the stress to the CNS. Stem cells would slowly migrate from the lateral tegmental area to rebuild the damaged circuitry. In alcohol recovery it takes 8–12 months to see distinct mental changes indicating that the stem cell process is slow and that some permanent damage may persist. Another indicator of this process is the relapse rate in alcohol recovery, which is high in the first 3 months but after 9 months of abstinence, relapse rates drop significantly.

Pharmacologic therapy in alcohol recovery is well accepted. Double blind placebo-controlled studies indicate naltrexone and acamprosate have significantly reduced relapse rates [23]. Naltrexone is an opioid antagonist and congener of oxymorphone and has a "blocking" effect on cravings. Acamprosate may act by interacting with glutamate and GABA neurotransmitter systems, with similar effects. These drugs and folic acid appear to have no harmful effects on the fetus and may be used in pregnancy.

15.5 Pregnancy enhances recovery

Call it maternal instinct, pregnancy clearly enhances recovery and makes a difference in long-term recovery. After 1 year of treatment, 65.7% of women who entered treatment while pregnant used no drugs, while only 27.7% of non-pregnant women remained drug free ($p<0.0005$) [24]. Likewise, in the Wishard study, during 2005, 23 women were enrolled in a treatment program that included prenatal care, individual and group counseling that continued for 6 months postpartum. All 23 were positive for cocaine, THC, or opiates on their first prenatal visit. Nineteen were negative for drugs at delivery (82.6%). Of the 19, 15 remained negative 6 months postpartum (65.2% of total).

Even brief interventions have proved highly effective in treating alcohol addiction in pregnancy [25]. Most importantly, prenatal substance use intervention reduces neonatal low birth weight and

preterm delivery [26]. For example, in the Wishard population, during 2003–2004, 40 patients tested positive for cocaine at the first prenatal visit. Treatment included prenatal care and brief individual counseling. Twenty-seven babies were meconium negative at delivery (67.5%) and had a mean birth weight of 3253.55 grams; s.d. 473.99, while 13 positive for cocaine had a mean weight of 2775.85; s.d. 466.68 ($p<0.01$).

It generally takes 10–14 weeks for the meconium to "clear" after cessation of cocaine use and the mechanism is unclear [27]. Thus, for a term newborn to be negative, the mother had to be drug free well before the third trimester. Early intervention clearly avoids the low birth weight effects of cocaine use in pregnancy. Brief interventions, using behavioral reinforcement plus brief motivational therapy, increases compliance with prenatal visits and results in greater abstinence, higher birth weights, and lower preterm labor [28].

15.6 Addiction in women and pregnancy

There is well-established empirical evidence supporting gender-related differences in pharmacokinetics and pharmacologic properties of psychotropic medications [29]. There is no question that males and females respond differently to many drugs. Women have much lower levels of alcohol dehydrogenase in their stomach mucosa. This results in a shorter first-pass metabolism and more rapid intoxication in women [30]. Women have increased adverse health effects from alcohol [31]. They also have a later onset of heavy use – telescoping. This leads to a more rapid progression to dependence [32].

Women also have different psychological dynamics operating in their substance use. Defense mechanisms include self-blaming and denial styles include internalizing and rationalizing while the identity components include the caretaker and selflessness [33]. Social differences reflect the "double standard" where men are expected to be able to "hold their liquor "and women who drink are "easy". And there is a special shame reserved for women who drink in pregnancy, i.e. "how can you do that to your baby?" This is sometimes called the shame-based approach [34].

In their own voices, psychological differences reflect shame as an internalized oppression in addiction. "I'm not worthy of recovery." "I'm a bad person, not sick." "I can't tolerate my emotional pain without drugs." "I can't have sex without drugs." [35] The role of shame delays diagnosis and treatment since women often use drugs and alcohol in isolation. It promotes enabling where the family often

hides the secret. Most important is the unrecognized role of trauma and PTSD. There is a strong correlation between past sexual trauma and addiction (50–80% of addicts report past sexual trauma and abuse) where women use drugs and alcohol for self-medication [36].

Hormonal differences in women may be another factor predisposing women to addiction. Women studied during the follicular phase of their menstrual cycle had peak plasma cocaine levels of 73.2 ± 9.9 ng/mL, which was significantly higher than when they were studied during their luteal phase (54.7 ± 8.7 ng/mL), but there were no differences in their subjective reports of cocaine effects [37]. However, alcohol intake is associated with a higher rate of infertility [38].

There are differences in women with regard to specific drugs. With heroin women develop dependence quicker than men [39]. Women using cocaine are more likely to use the IV route and the risk of HIV infection is greater [40]. And women are more likely to use smoking for weight control and to reduce stress [41]. Alcoholic women usually have alcoholic spouses and less spousal support [42]. Women are more likely to abuse prescription drugs, especially opioids [43]. In a related issue, women are often the only child caregivers and very few treatment programs provide child support [44].

Women are especially vulnerable to substance use. In most societies, if not all, women are disempowered, pregnant women are more disempowered, and pregnant addicts are the most disempowered. Examples would include unequal pay for equal work, unrealistic prohibitions on pregnant workers and demonizing pregnant addicts. Studies suggest that drug use is a coping strategy that some women adopt to manage this oppression [45]. In contrast, motivational empowerment is the key to successful recovery.

15.7 Psychiatric co-morbidity

A critical aspect of the effective treatment of substance use disorders is to identify and treat psychiatric co-morbid disorders. Some co-morbid psychiatric problems are more common in women [46]:

- Bipolar disorders
- Panic disorder
- PTSD
- Cluster B personality disorders
- Bulimia
- Depression

In addition, genetic markers have been identified with a number of psychiatric disorders in which there is a higher incidence of substance use [47]. They include:

- Low P3 amplitude (schizophrenia, ADHD)
- Conduct disorder (CD)
- Antisocial personality (ASPD)
- Decrease in dopamine receptor density (D2)
- Serotonin (5-HT) systems

Pharmacologic treatment of these disorders enhances recovery from substance use and also poses additional problems for the fetus including need for treatment of the neonate in special intensive care units for symptoms of withdrawal [48]. This is especially true for benzodiazepines, which have a higher rate of teratogenicity and withdrawal, especially when combined with alcohol [49]. Risks and benefits of pharmacologic treatment are most important when treating co-morbidity in pregnancy.

15.8 Substances used

The most frequently used substances in pregnancy are alcohol, tobacco, marijuana, cocaine, opioids, and the amphetamines [50]. Alcohol damages neurons, which results in the fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorders (FASD), which are the most common preventable causes of mental retardation. Alcohol is also associated with higher rates of stillbirth, spontaneous abortion, and low birth weight [51]. Nicotine is associated with a high incidence of miscarriage, low birth weight and preterm delivery. *Alcohol and nicotine cause more fetal damage than all the other drugs combined.*

Prescription opioid use has skyrocketed in the last few years [52]. The Wishard data, from 2002 to 2007, indicate that 69 of 287 patients (24%) were treated for opioid use. From 2008 through 2010, 74% of patients treated were for opioid use, especially methadone maintenance and buprenorphine maintenance. Data from the Florida Society of Addiction Medicine reveal that oxycodone in the form of oxycontin ("oxy") is responsible for 10 deaths in Florida per day and is the number one drug of abuse among 12–17-year-olds [53]. A flawed prescription-monitoring program has created an "oxy" epidemic [54].

The following sections will describe the maternal, fetal, and newborn effects of the frequently used substances. Pharmacological treatment during pregnancy involves a number of strategies

including detoxification, abstinence, maintenance, and treatment of co-morbid psychiatric disorders. Diet, nutrition, social service support, and 12 Step groups are essential adjuncts to pharmacologic therapy.

15.8.1 Alcohol

Alcohol is a known teratogen and there is no known safe level for use in pregnancy. Blood alcohol levels in women are higher than men after drinking similar amounts and women are more sensitive to its toxic effects; that is, they get drunk faster. This appears to be due to a lower percentage of body water and lower gastric alcohol dehydrogenase resulting in a reduced first-pass metabolism [55].

Alcohol readily crosses the placenta and is present in amniotic fluid well after the mother's level is metabolized to zero. Alcohol damage can occur early in pregnancy before a women realizes she is pregnant. Fetal toxicity is dose related with the greatest risk occurring early in the first trimester [56].

There are many mechanisms that result in cell death by necrosis or apoptosis including:

- Increased oxidative stress,
- Damage to mitochondria,
- Effects on glial cells,
- Impaired development and function of chemical messenger systems,
- Transport and uptake of glucose, and
- Cell adhesion [57].

In addition to cranio-facial abnormalities and mental retardation associated with FAS (average IQ is 67), for children with FASD, ADHD is more likely to be earlier onset inattention subtype. These children appear to have a disturbance in brain structure, in the corpus callosum, and the response to standard psychostimulant medication can be unpredictable [58].

15.8.1.1 Pharmacologic treatment of alcohol use in pregnancy

Treatment is predicated on detoxification and abstinence. During detoxification, benzodiazepines are the drug of choice to reduce the excitatory state of the brain during withdrawal. Carbamazepine, an antiseizure medication, has been used extensively in Europe. It is a category D drug and may be best used in the second and third trimester [59]. Folic acid supplementation is recommended with the use of carbamazepine due to an increased incidence of neural tube defects with this medication [60].

Disulferam is used to maintain abstinence. Disulferam inhibits aldehyde dehydrogenase production. Subsequent use of alcohol leads to accumulation of acetaldehyde. As a result, the patient experiences harsh symptoms including facial flushing, tachycardia, hypotension, nausea, and vomiting. This is a form of negative reinforcement and may not be well tolerated by the pregnant alcoholic in recovery. Reports of fetal anomalies are sporadic and disulferam appears to be relatively safe [61].

Naltrexone and acamprosate have also been used to support abstinence. Naltrexone is an opiate agonist. It appears to act by blocking opiate receptor activation mediated by alcohol and one effect is to reduce craving. Acamprosate has a similar outcome and the mechanism is thought to modulate NMDA receptors in the brain [62]. There are few data regarding the use of acamprosate in pregnancy. In most cases the risks of continued alcohol use far outweigh the risks of pharmacologic therapy in pregnancy.

15.8.2 Tobacco; nicotine

Nicotine in the form of tobacco smoke is a double-edged sword for fetal harm. Cigarette smoke contains cyanide, carbon monoxide, and a plethora of toxic hydrocarbons, which affect oxygen transport in the placenta. This results in spontaneous abortion, low birth weight and preterm delivery [63]. Nicotine affects umbilical blood flow, fetal cerebral artery blood flow and potentiates the effects of the smoke [64]. Smoking cessation programs are effective in reducing these effects, especially if started before or early in the pregnancy [65].

Pharmacologic therapy for nicotine use is similar to alcohol focusing on detoxification and abstinence support. Nicotine patches, lozenges, and gums are most often used in conjunction with a smoking cessation program. Nicotine replacement treatment (NRT) helps prevent relapse and removes the effects of the smoke on the fetus. It appears that minimal amounts of nicotine are excreted into breast milk and that NRT can be used while breastfeeding [66]. However, it is imperative that the patient be advised not to smoke while using these methods because the combined dose of nicotine substantially increases fetal exposure.

Selective serotonin and dopamine reuptake inhibitors have had a modicum of success. Bupropion is the most frequently prescribed antidepressant and varenicline the most recent. Bupropion is a dopamine reuptake inhibitor and creates a blocking effect of cravings. Varenicline is a partial agonist selective for $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtypes. It also reduces cravings and has a blocking effect. Both may lead to neuropsychiatric symptoms in

the mother and the physician should be aware of the black-box warnings of these agents [67].

In a survey of substance using patients in the Wishard data, about two out of every three patients continue to smoke during pregnancy. Efforts to reduce smoking have been somewhat successful. NRT is well tolerated and in selected patients, bupropion and varenicline have achieved good results. The goal is abstinence and if a patient can reduce her cigarette smoking to fewer than 10 per day, she can lower the risk of low birth weight and preterm delivery. However, even low rates of smoking are associated with some increased low birth rate [68].

15.8.3 Opiates and opioids

Opiates are alkaloids derived from the opium poppy and include morphine, codeine, and thebaine. Opioids include all opiates plus the semi-synthetics, which are derived from the alkaloids (thebaine): hydrocodone, oxycodone, and heroin, plus the synthetics: methadone, fentanyl, Nubian, and buprenorphine. Many physicians use these terms interchangeably.

There has been a major shift in the approach to opiate treatment from detoxification and abstinence to maintenance. A number of factors have contributed to this shift. Relapse is high while maintenance helps prevent relapse and diseases attributed to IV drug use. Most important is that opiate withdrawal carries an increased risk of abruption and preterm labor. However, in selected patients, detoxification has been accomplished with relative safety [69]. In one retrospective study of gradual methadone detoxification, there was no increased risk of preterm delivery [70]. However, the relapse rate in one study was 56% after detoxification [71].

Opioids bind to neuro-receptors, specifically:

- Mu: analgesia, euphoria, respiratory depression, constipation, sedation, and miosis
- Kappa: dysphoria, sedation, and psychotomimetic
- Delta: unknown

The rate of excretion is faster than withdrawal. Morphine is excreted within 72 hours while withdrawal is 3–6 days. Methadone can be excreted in 4–5 days but withdrawal is prolonged to 10–20 days. The clinical relevance is that a patient in withdrawal may have a negative urine drug screen (UDS). In addition, methadone, hydrocodone, and oxycodone are metabolized at a more rapid rate in pregnancy. Thus, the requirement for a maintenance dose will increase. In the Wishard data, 35% of the methadone

maintenance patients required an increase of 30–50% over their initial dose to prevent withdrawal.

The major maternal risk of opioid use is respiratory depression and death. Many opioid users also use benzodiazepines, which greatly increase the risk of death. In the Wishard data, 19 of 45 (42.2%) opioid chronic pain patients tested positive for benzodiazepines at their first prenatal visit. In addition, about two thirds of the patients used tobacco. The Wishard data also reveal that opioid users have a higher incidence of low birth weight and preterm labor.

Opioids were considered category B drugs with no harm noted in animal studies. Most recently, the National Birth Defects Prevention Study, a case–control study for infants born October 1, 1997 through December 31, 2005 in 10 states revealed that therapeutic opioid use was reported by 2.6% of 17,449 case mothers and 2.0% of 6701 control mothers. Treatment was statistically significantly associated with:

- Conoventricular septal defects (OR, 2.7; 95% CI, 1.1–6.3),
- Atrioventricular septal defects (OR, 2.0; 95% CI, 1.2–3.6),
- Hypoplastic left heart syndrome (OR, 2.4; 95% CI, 1.4–4.1),
- Spina bifida (OR, 2.0; 95% CI, 1.3–3.2), and
- Gastroschisis (OR, 1.8; 95% CI, 1.1–2.9) in infants [72].

In addition, methadone maintenance was also found to be associated with ophthalmologic abnormalities including:

- Reduced acuity (95%),
- Nystagmus (70%),
- Delayed visual maturation (50%),
- Strabismus (30%),
- Refractive errors (30%), and
- Cerebral visual impairment (25%) [73].

Neonatal abstinence syndrome (NAS) is the most common effect on the fetus/neonate. The incidence is as high as 90% in methadone maintenance users and varies with the opioid used, the daily dose, length of use, and concomitant use of other drugs, especially benzodiazepines [74]. In NAS, the neonate is in acute withdrawal with an onset of hours to about 4 days. Common symptoms include irritable cry, increased tone, tachypnea, sleeplessness and tremor, and treatment is based on scores from observations of psychomotor behavior [75]. Treatment consists of stabilizing the withdrawal, usually with morphine drops and then gradually decreasing the dose to detoxify the baby [76]. Pharmacologic treatment of NAS may also use clonidine, an alpha agonist used to stabilize the cardiovascular system, and phenobarbital to reduce brain activity and seizures.

There are readily observable neurobehavioral effects of opioid treatment in pregnancy. The most common observations include decreased head circumference, developmental delays, and poor fine motor coordination [77]. However, long-term effects of opioid treatment appear to be more dependent on home environment [78]. Not surprising is that methadone-exposed infants that had delayed mental development were also raised in poor environmental conditions [79].

Maternal treatment of opioid addiction involves managing acute overdose, withdrawal, maintenance, and detoxification. Most commonly, the patient presents in acute withdrawal. After she is stabilized, most are managed by maintenance with methadone or buprenorphine and only occasionally does a patient choose detoxification. As more and more opioid-dependent patients are being maintained on methadone or buprenorphine, they present for their first prenatal visit as a "methadone or buprenorphine maintenance" patient.

15.8.3.1 Opioid overdose

- Characterized by pinpoint pupils, respiratory depression, coma, and pulmonary edema.
- Establish airway.
- Inject Naloxone – repeat if long-acting opiate present, e.g. methadone.
- Naloxone will not harm fetus.
- Treatment will precipitate a severe withdrawal.
- Will need to restart and modify an opioid dose.
- For maintenance, use methadone or buprenorphine.
- Methadone: start at 20 mg bid and increase 5–10 mg per day until stable.
- Buprenorphine/naloxone: start at 2–4 mg bid; increase by 2–4 mg every 6 hours until withdrawal is abated.

15.8.3.2 Opioid withdrawal: affects major systems

- CNS – tremors, seizures.
- Metabolic – sweating, yawning.
- Vascular – hot flashes and chills.
- Respiratory – increased rate, respiratory alkalosis.
- GI – cramps, nausea, vomiting, diarrhea.
- Drug-specific effects – methadone has a prolonged withdrawal: 10–20 days.
- Restart and modify opioid dose.
- Avoid benzodiazepines; potentiates CNS and respiratory depression.
- Current recommendation is to avoid withdrawal during pregnancy.

15.8.3.3 Opiate withdrawal treatment

- Initiate methadone or buprenorphine to stabilize withdrawal: may use oxycodone 10 mg q 4–6 h for up to 72 hours to stabilize patient and then switch to methadone or buprenorphine.
- Phenergan 25 mg q 4–6 h for withdrawal symptoms – best for nausea, vomiting and GI symptoms.
- Phenobarbital, 30 mg tid for neurological withdrawal symptoms.
- Clonidine 0.1 mg tid – vascular withdrawal symptoms.
- Check acetaminophen levels in patients using opiate/acetaminophen compounds.

15.8.3.4 Opioid detoxification

- Must be closely controlled. Benefits rarely outweigh risks.
- Gradual reduction to minimize withdrawal.
- Symptomatic treatment.
- Phenergan 25 mg q 4–6 h for withdrawal symptoms – best for nausea, vomiting, and gastrointestinal symptoms.
- Phenobarbital, 30 mg tid for neurological withdrawal symptoms.
- Clonidine 0.1 mg tid – vascular withdrawal symptoms.

Preterm labor remains a major risk in overdose, withdrawal, and detoxification. Pharmacologic treatments for preterm labor, such as magnesium sulfate, may potentiate respiratory depression in the mother and neonate. Fetal monitoring is significantly affected by opioids with reduced fetal activity most common [80]. Methadone will cause a higher incidence of non-reactive non-stress tests (NST), especially if given 1–3 hours before the NST [81]. The biophysical profile is the appropriate follow-up to a non-reactive NST [82].

Intrauterine growth restriction (IUGR) is another common problem in opioid-dependent women and monitoring with ultrasound is essential to determine prenatal management. If IUGR is identified, the degree of placental dysfunction is thought to be associated with changes in diastolic blood flow through the umbilical cord. Increasing resistance of diastolic flow and reduction of amniotic fluid are markers indicating closer surveillance and earlier intervention.

15.8.3.5 Opioid maintenance strategies: methadone and buprenorphine

Methadone maintenance has been the model for maintenance of opioid-dependent pregnant patients for many years. Contrary to popular belief, it has never been approved to treat opioid dependency in pregnancy. Methadone maintenance is highly regulated and can only be dispensed for opioid dependence treatment in a

federally certified clinic. Thus, the patient must arrive early in the morning, receive her dose and its attendant side effects, and then carry on through her day.

Early reports found substantial benefits from maintenance therapy, especially reduction of infectious disease and stillbirth [83]. Originally, the dosing regimen for methadone followed the practice of using the lowest possible dose to reduce the risk of NAS. Unfortunately, doses of less than 20–40 mg often failed to achieve a blocking effect and led to increased preterm labor, low birth weight, and relapse [84]. Thus, it is most prudent to adjust the dose of methadone based on withdrawal symptoms and cravings. Up to 35% of patients will require an increase in methadone, typically in the late second and early third trimesters. Although the evidence does not support an advantage to divided doses of methadone, many patients report better tolerance and less nausea, which improves compliance with treatment and prenatal care [85]. If the patient experiences the typical postpartum diuresis, it is recommended to reduce the methadone dose by 20–40% shortly after delivery.

15.8.3.6 Opioid maintenance: methadone

- Encourage patient to remain on methadone during pregnancy.
- Expect dose to increase up to 50% during pregnancy in about 35% of patients.
- Doses range from 50–150 mg per day.
- Higher doses not associated with severity of NAS and improve maternal compliance with prenatal care [86].
- Patient should be encouraged to breastfeed [87].
- Note: Methadone is NOT FDA approved for treatment for opiate dependence in pregnancy.

Buprenorphine maintenance was first registered to treat opiate dependence in France in 1996, and practitioners were allowed to dispense buprenorphine by prescription enabling easy access to treatment [88]. Thousands of patients underwent buprenorphine treatment, among them an increasing number of pregnant women. An initial striking observation was that in the majority of newborns, the neonatal abstinence syndrome (NAS) was either absent or mild enough not to require treatment. A prospective French study of 34 buprenorphine-treated pregnancies revealed that only 13 had NAS, nine of which were confounded by other psychoactive drugs (benzodiazepines, opiates, and cannabis) [89]. Buprenorphine was approved for use in the United States in 2002 by an amendment to the Drug Treatment Act of 2000 [90]. The first United States survey of a registry of over 300 mothers treated with buprenorphine reveals that buprenorphine is safe and

effective for mothers and newborns with a qualitatively and quantitatively diminished NAS compared to methadone [91]. A comparative study between methadone and buprenorphine confirmed improved maternal and neonatal outcomes on buprenorphine [92].

Buprenorphine is an agonist/antagonist with a high binding affinity for the Mu receptor. Thus, if the patient uses another opiate while on buprenorphine, she will have a minimal euphoric experience. This effect significantly reduces the abuse potential [93]. It is metabolized by placental aromatase to norbuprenorphine resulting in low placental transfer. This may account for limited fetal exposure and its lower incidence of NAS [94].

Buprenorphine is marketed in the United States in two forms, buprenorphine (Subutex) and buprenorphine combined with naloxone (Suboxone). Initially, there was some concern that the buprenorphine/naloxone combination might cause an intrauterine withdrawal in the fetus. Hence, only buprenorphine was recommended for use in pregnancy. The evidence clearly indicates that the dose of naloxone has little to no effect on the fetus [95]. Moreover, sublingual buprenorphine has been found to be safe and effective in treating NAS [96]. Small amounts of buprenorphine are found in the breast milk. However, it has little, if any, effect on the newborn with no evidence of neonatal withdrawal when breastfeeding is discontinued [97].

15.8.3.7 Opioid maintenance: buprenorphine

- Patient must be in opioid withdrawal to start buprenorphine treatment.
- Inpatient: some recommend initiating treatment with buprenorphine, 2–4 mg sublingual by either tablet or film.
- Increase dose by 2–4 mg every 6 hours to stop withdrawal symptoms.
- Convert to buprenorphine/naloxone for outpatient use.
- Target doses range from 4 to 24 mg per day.
- Most pregnant patients are stable at 8–16 mg per day in divided doses.

15.8.3.8 Analgesia and anesthesia for opioid maintenance patients

- Epidural anesthesia for labor, delivery, and cesarean delivery is the standard.
- Spinal anesthesia for cesarean delivery.
- For acute postoperative pain, methadone and buprenorphine patients will gain relief with doses of opiates 70% over usual doses [98].
- Morphine is best tolerated by the largest group of patients.

15.8.3.9 Opioid-dependent patients: a comparison of maternal and neonatal outcomes

The Wishard data reflect a long-term observational study of opioid-dependent patients. The study includes data from the Prenatal Recovery Clinic starting in 2002 through 2010, and includes 90 patients treated with methadone compared to 46 patients treated with buprenorphine and buprenorphine/naloxone. In addition, there are data from two other groups of opioid-dependent chronic pain patients. One group ($n=31$) consists of patients whose urine drug screens revealed only opiate and opiate/acetaminophen combinations for pain control while the other group ($n=45$) had urine drug screens that revealed multiple licit and illicit substances including benzodiazepines, cocaine, and marijuana. The latter group was designated opioid "P" for poly-substance use.

The methadone group had significantly higher preterm deliveries, more low birth weight, lower birth weights, and longer length of stay (LOS) for withdrawal when compared to the buprenorphine group. Interestingly, opioid-dependent chronic pain patients who used only opioids for pain relief had the lowest maternal and neonatal morbidity. Doses of hydrocodone and oxycodone in the latter group varied from 40 to 80 mg per day.

Only nine babies of methadone-treated mothers tested positive for illicit drugs in their meconium. In a prior study in the same institution in 1999, 85% of methadone patients tested positive for an illicit substance (predominantly cocaine) in the 30 days prior to delivery [99]. It appears that a significant change in the treatment approach addressing illicit drugs resulted in substantially lower use (see Tables 15.1 and 15.2).

Opioid-dependent patients treated with buprenorphine and opioid-only-treated chronic pain patients had the lowest incidence of maternal and neonatal morbidity. In both groups, preterm delivery and birth weights were within the norm for non-opioid-dependent patients. The findings strongly suggest new strategies for managing opioid-dependent patients in pregnancy. One recommendation is to start opioid-dependent patients presenting in withdrawal on buprenorphine rather than methadone [100]. Another is to maintain the opioid-only patient on her current regimen.

15.8.3.10 Opioid-only-dependent chronic pain patient

- **Maintain current opiate regimen** – avoid withdrawal (both legal to do and meets standard of care).
- Hydrocodone 5/325 or 10/325 (up to 2 tabs q 6 h).
- Oxycodone 5/325 or 10/325 (up to 2 tabs q 6 h).
- Low rate of NAS noted with these doses.

Table 15.1 Methadone vs. buprenorphine: major pregnancy outcomes

	Bup. (46)[1]	Meth (90)[2]	*p*
Preterm delivery	5 (10.9%)	27 (30%)	0.001
Low birth weight (<2500 g)	4	26	0.01
Mean birth weight	3079 g	2718 g	0.005
Positive meconium	3 (6.9%)	9 (10.8%)	NS
Neonatal abstinence (NAS)	8	89	0.001
NAS treated	6[3]	80	0.001
Mean length of stay (days)	6.78	30.3	0.001
Failed to return PP	13 (28.8%)	28 (31.1%)	NS
PP UDS "negative"	29 (63%)	59 (65.5%)	NS
Tobacco use (>0.5 ppd)	29 (63%)	51 (56.6%)	NS

PP – postpartum.
[1]In the buprenorphine group there were 12 patients treated with buprenorphine and 34 treated with buprenorphine/naloxone with no differences within the groups.
[2]In the methadone group there were 92 babies (two sets of twins).
[3]Three of the NAS treated had concomitant use of benzodiazepines.

Table 15.2 Comparison of opioid-dependent chronic pain patients

	Opioid (31)	Opioid P (45)*	*p*
Preterm delivery	4 (12.9%)	8 (17.7%)	NS
Low birth weight (<2500 g)	3	8	NS
Mean birth weight	3085 g	2879 g	NS
Positive meconium	0	12 (26.6%)	0.001
NAS treated	1	5	NS
Mean length of stay (days)	3.3	7.8	0.01
Failed to return PP	3	13	0.01
PP UDS "negative"	23 (74.2%)	25 (55.5%)	NS
Tobacco use (>0.5 ppd)	21 (67.7%)	30 (66.6%)	NS

PP – postpartum.
*Opioid P – polysubstance use including benzodiazepines, cocaine, and marijuana.

- Requirement of opiate may increase.
- Pain moderators may be helpful.
- Amitriptyline 50–100 mg h.s.
- Gabapentin 300 mg tid.
- Physical therapy – maintain mobility.

15.8.4 Fentanyl

Fentanyl is a synthetic opioid used in anesthesia and for treating chronic pain. Chewing fentanyl patches is a common form of abuse. It has a high addictive potential and is one of the more common addictions among anesthesiologists. There is a high risk of fatal overdose among users. Maternal and neonatal effects and treatment are the same as other opioids.

15.8.5 Benzodiazepines

Benzodiazepines are gamma-amino-butyrate agonists used as muscle relaxants, anxiolytics, hypnotics, and anticonvulsants [101]. Unfortunately, they have a high addictive potential and are prescribed more often to women [102]. In the Wishard data, a very common scenario for woman dependent on opioids and benzodiazepines centers on treatment for soft tissue injuries in motor vehicle accidents. It is well established that long-term therapy leads to tolerance and dependence and should be avoided [103].

Benzodiazepines, when indicated, should be used in the lowest possible dose for the shortest time. In dependent patients, slow weaning is the treatment of choice. Maternal withdrawal can induce seizures and abrupt withdrawal can be fatal [104]. The major problem with benzodiazepines is their widespread use with other drugs, especially opioids. Although diazepam is listed as a pregnancy category D drug, it does not appear to be teratogenic, but is related to neonatal withdrawal and "floppy infant syndrome" [105]. Lethargy has been observed in breastfed babies [106].

15.8.6 Marijuana; THC

Although marijuana is usually grouped with the hallucinogens, it deserves special attention because it is one of the most commonly used illicit substances [107]. THC is the most common substance found in urine drug screens. In the Wishard data, 40% of patients tested positive for THC at the first prenatal visit. Fortunately, it is the easiest substance use disorder to treat with 95% of users testing negative at delivery.

The active substance in marijuana is delta-9-tetrahydrocannabinol, commonly abbreviated to THC. It is derived from the plant *Cannabis sativa*. Its lipophilic structure allows it to accumulate in fatty tissue and remain for days before it is metabolized in the liver. Marijuana is smoked, usually as a cigarette or in water pipes (bongs) or used in small pipes called "one hitters". Inhalation of marijuana smoke is held in the lungs for long periods and results in higher levels of carboxy hemoglobin [108].

Marijuana produces a mild hallucinogenic "high" and affects major organ systems. In high doses it may precipitate psychosis. It increases blood pressure and cardiac output, compromises respiratory function, decreases the immune response, and is not the harmless drug it is perceived to be [109]. Low birth weight is the primary fetal effect [110]. Long-term effects have been reported and include deficits in cognitive functioning, attention, analytical skills, and problems with visual integration [111]. Prenatal exposure to marijuana has been associated with increased marijuana use by age 14 [112].

Treatment of marijuana substance use is best achieved with cognitive behavioral methods and motivational enhancement. Smoking cessation programs are effective. Most patients respond to simple "coercive therapy", that is, the patient is informed if the baby tests positive for THC in the meconium, child protective services will investigate. The majority of patients test negative by the second trimester.

15.8.7 Cocaine

Cocaine is a highly addictive lipophilic alkaloid extracted from the plant *Erythroxylon coca*. It is generally "snorted", smoked and less frequently injected and is a powerful dopamine, serotonin, and norepinephrine reuptake inhibitor producing a profound "high". This effect is short lasting and users try to recapture the experience by using more of the substance more frequently. This phenomenon is called "chasing the buzz". The rapid tolerance that develops is the basis for a rapid addictive process.

Metabolism of cocaine is primarily by plasma and liver esterases. In addition, it is hydrolyzed to benzoyl ecgonine, which readily appears in the urine. Meconium drug screens have a high sensitivity for detecting cocaine use [113].

Cocaine use results in intense vasoconstriction and increase in blood pressure. It also is associated with seizures, psychosis, hyperthermia, and cerebrovascular accidents. In addition, the profound cardiovascular response markedly affects uterine blood flow and leads to abruption, low birth weight, and preterm labor [114]. The so-called "crack baby syndrome" propagated in the popular press has not been validated [115]. However, cocaine use in pregnancy has been linked to microcephaly and subtle cognitive defects [116].

Pharmacological treatment of cocaine use includes topirimate, an anticonvulsant, and baclofen, a GABA B receptor agonist. Topiramate raises cerebral GABA levels, facilitates GABA adrenergic neurotransmission, and inhibits glutamatergic activity [117]. The clinical

effect is to block the brain reward system. Topiramate is commonly used in pregnancy with few cases of reported malformations [118]. It would appear that the risk of cocaine use would outweigh the risks of topiramate use in pregnancy

Baclofen appears to act in a similar manner as topiramate in reducing cravings and substance use. However, baclofen is transferred through the placenta and long-term use is associated with a neonatal abstinence syndrome and seizures [119]. Topiramate would appear to be the safer choice for treatment in pregnancy. In the Wishard study, neither of these drugs was used. Treatment was based on cognitive behavioral methods, motivational enhancement, and the "coercive approach". At delivery, 79% of mothers testing positive for cocaine at the first prenatal visit were negative. Child protective services were far more aggressive in removing newborns from cocaine addicted mothers than from marijuana users.

15.8.8 Stimulants: amphetamine, methamphetamine; methylphenidate; ephedra; khat

The stimulants act similarly to cocaine with dopamine, serotonin, and norepinephrine release and inhibition of uptake. The effects vary from mild euphoria to profound psychosis and violent behavior. They also increase blood pressure, tachycardia, and arrhythmias, which may create obstetrical emergencies necessitating cesarean delivery [120]. A profound withdrawal is associated with amphetamines and methamphetamines producing depression, anxiety, fatigue, paranoia, and aggression [121].

Amphetamine and methamphetamine have similar adverse effects on the fetus and neonate. Growth restriction, abruption, preterm labor, and withdrawal symptoms are common [122]. The fetus has a longer elimination half-life than the mother with higher doses remaining in the fetal brain [123]. High doses of methamphetamine in the breast milk have been associated with fatal levels in the infant [124]. Long-term effects of methamphetamine revealed delays in cognitive skills and growth [125].

Pharmacologic treatment of amphetamine and methamphetamine is limited in pregnancy with only a few case reports. Randomized, placebo-controlled, double-blind trial of two GABAergic medications, baclofen (20 mg tid) and gabapentin (800 mg tid), for the treatment of methamphetamine dependence revealed limited effects [126]. Another study evaluated gamma vinyl-GABA (GVG, vigabatrin) and demonstrated a good effect on abstinence but has not been tested in pregnancy [127].

Treatment is complicated in women because of reasons for using the amphetamines. Women use it for weight control and report

these substances increase their enjoyment of sex [128]. In addition, they improve concentration and performance and may be used as a way to cope with stress. Thus, cognitive behavioral therapy and motivational enhancement are the mainstays of treatment.

Methylphenidate is pharmacologically similar to amphetamines. It is used in attention deficit disorders in children and has a high potential for addiction. Acute effects include tachycardia, irritability, and hypertension. Methylphenidate is most often obtained by diversion of a child's prescription, thus causing harm to both parent and child. Effects on the fetus are not well known. Treatment is by gradual weaning and cognitive behavioral therapy and motivational enhancement.

Ephedra is a naturally occurring stimulant used primarily as a weight loss aid. It may cause stroke, heart attacks, and death [129]. There are few data on its use in pregnancy.

Khat is related to amphetamine and is a natural stimulant. It is used primarily in East Africa and the Arabian Peninsula [130]. The leaves are slowly chewed releasing the active substance, cathionine. It may cause low birth weight [131].

15.8.9 Hallicinogens: lysergic acid diethylamide and phencyclidine

Lysergic acid diethylamide (LSD) binds to 5-hydroxytryptamine receptors and causes vivid hallucinations. It is not associated with the onset of dependence and does not cause chromosomal damage [132]. The effects on pregnancy are unknown. It does pass into breast milk and should not be used while breastfeeding.

Phencyclidine (PCP) is used as a hallucinogen. It is a dissociative anesthetic and acts as an N-methyl-D-aspartate antagonist at low doses causing methamphetamine-like effects and frequently violent behavior [133]. Newborns of users may present with irritability, poor feeding, and hypertonicity. It is readily passed into the breast milk.

15.8.10 Club drugs: MDMA; flunitrazepam; gamma-hydroxybuterate; ketamine

Methylenedioxymethamphetamine, MDMA, was patented in Germany in 1912 by E. Merck of Darmstadt. Its history is murky and it is said to have been used as an appetite suppressant. Decades later, it surfaced as "ecstasy", which often contains more volatile and toxic amphetamine-like substances [134]. Ecstasy produces highly subjective effects of stimulation, feelings of closeness, and hallucinations [135]. The drug does not appear to cause dependence. Adverse effects are life threatening. Night clubbers have suffered lethal hyperthermia and fatal hyponatremia secondary to

inappropriate secretion of antidiuretic hormone [136]. The typical side effects are similar to amphetamines. Neurotoxicity has been reported with attendant cognitive impairment [137]. *In utero* exposure may lead to an increased risk of cardiovascular and skeletal abnormalities [138].

Most people stop using ecstasy on their own. Since women who use ecstasy in pregnancy also smoke heavily, and use alcohol and other drugs, it is difficult to determine a causal role for MDMA in newborns.

Gamma-hydroxybuterate (GHB) is a dissociative anesthetic and is used to treat narcolepsy. It is used by "clubbers" for its intoxicating effects, similar to alcohol. It has a short half-life and is often used multiple times in an evening. It has a strong addictive potential and adverse effects include acute intoxication, vomiting, and respiratory depression [139]. It carries a withdrawal syndrome similar to that of benzodiazepines.

Fetal and neonatal effects are not well documented but would be expected to be similar to those of the benzodiazepines. Treatment for GHB addiction is similar to alcohol treatment and good success is seen with 12 Step Recovery support.

Flunitrazepam ("roofies") is a long-acting benzodiazepine and used outside the United States for the treatment of sleep disorders. It is implicated as a "date-rape" drug and most often used with alcohol leading to psychomotor impairment and respiratory depression [140]. Maternal and neonatal effects are typical of the benzodiazepines. It does appear in the breast milk.

Ketamine is a dissociative anesthetic. It produces changes in perception, depersonalization, and hallucination and finds it way to clubbers by diversion from legal sources [141]. There are reports of ketamine dependence.

The effects include tachycardia, vomiting, amnesia delirium, and rhabdomyolysis [142]. Although it poses a low risk of overdose, aspiration from vomitus and sedation can be profound. Some evidence suggests it can damage the developing fetal brain [143]. Treatment of ketamine dependence would include detoxification, cognitive behavioral therapy, and 12 Step Recovery support.

15.9 Screening and detection

It is not difficult to improve outcomes in pregnancy. Adequate screening and detection are essential and brief physician interventions are highly effective. The Wishard data from 2002 to 2007 enrolled 274 patients in the Prenatal Recovery Program. At

delivery, 244 tested negative for illicit drugs. In comparison, 42 patients who tested positive for illicit drugs at the first prenatal visit opted for routine prenatal care. Of those, 23 (55%) tested negative at delivery. These findings indicate that detection alone motivates many patients to abstain from substance use in pregnancy.

Universal screening means that *every obstetrical patient is asked about substance use* at the first prenatal or intake visit, and at least once per trimester thereafter. Thus, there is a clear distinction between urine drug testing and verbal screening. When identified and treated:

- The rate of abstinence increases,
- Maternal and fetal complications decrease,
- Less preterm labor,
- Less growth restriction,
- Less abruption,
- Treatment is highly cost effective, and
- Reduction in preterm labor and low birth weight account for the largest savings [144].

15.10 The role of urine and meconium testing

Both urine and meconium testing can be used to determine the prevalence in a population. In this respect, consent is not required. However, the results of urine drug screens may also carry legal jeopardy and may deter pregnant substance users from attending prenatal care. For example, in Pinellas County, Florida, prenatal urine tests were positive for alcohol or drugs in 16.3% of the medically indigent and in 13.1% in the privately insured. This was not significantly different and there were no differences in the types of substance. Florida law, at that time, required physicians to report patients with positive tests to the authorities. Discrepancies in reporting resulted in Black women being 10 times more likely to be reported than White women [145].

Urine tests of 29,494 women presenting for delivery in 202 California hospitals revealed 6.7% tested positive for alcohol and 5.2% tested for illicit drugs [146]. In another study, the prevalence of maternal drug use revealed the problem to be much greater than previously thought. Meconium testing was performed for every other newborn in one year: 3010 subjects were studied and 1333 (44%) were positive for cocaine, morphine, or cannabinoid, while only 335 (11%) mothers admitted to illicit drug use [147]. While meconium testing is more accurate, it is far more costly and not generally used for prevalence studies.

In a comprehensive drug treatment program, urine testing serves a variety of functions. It can track drug use and enhance compliance [148]. It can also serve as a tool for positive reinforcement of abstinence. Contingency management is a strategy that rewards patients with negative drug screens with vouchers to use for food, clothes, and sundry items [149]. Voucher-based programs also demonstrate better compliance with prenatal care [150].

Given the high incidence of substance use in pregnancy, urine drug screens are appropriate at the first prenatal visit, and are especially effective in revealing substance use when coupled with verbal screening [151]. Patients may be offered an "opt out" approach to the UDS:

- Inform patient that a number of routine screening tests are done in pregnancy and include blood tests, diabetes tests, genetic tests, tests for sexual infections, ultrasound, and urine tests for protein, sugar, infection, and drugs.
- Inform patient that she may "opt out" of any test.
- If patient opts out of urine drug screen, inform her that pediatricians may order drug screens after the baby is born.

State laws are very liberal about what constitutes child abuse. A patient who opts out of a urine drug screen creates a reasonable basis to suspect drug use. Thus, pediatricians may legally order urine and meconium tests on the newborn without parental consent. The patient must be informed of this if she opts out. When informed and treated in a respectful manner, our experience has been that patients rarely drop out of care.

Obstetrical indications for a urine drug screen include:

- At each prenatal visit for any patient identified as a substance user.
- Any history of drug use.
- Missing appointments.
- Late prenatal care.
- Preterm labor.
- Third trimester bleeding – abruption.
- Growth restriction.

The major limiting factor of urine drug screens is that, with few exceptions, they only reveal recent drug use. Table 15.3 indicates how long a particular drug may be detectable in the urine after typical use.

Urine drug screens must be congruent with the drug use in the area. Department of Health and Human Services guidelines for the workplace require testing of amphetamines, cannabinoids, cocaine, opiates, and phencyclidine [153]. In a prenatal treatment

Table 15.3 Length of time substance is detectable in urine [152]

Substance		Time
Alcohol		24 h
Amphetamines		48 h
Barbiturates	Short acting	48 h
	Long acting	7 days
Benzodiazepines		72 h
Cocaine		72 h
Marijuana	Single use	72 h
	Chronic use	30–40 days
Opiates	Morphine/Heroin	72 h
	Methadone	96 h
	Codeine	Up to 10 days
Nicotine		3–5 days from last use

clinic, the drugs of choice may be different and preferences vary markedly from region to region.

Urine screens can be quantified for specific drugs and this may be of significant value in monitoring behavior (see Table 15.4). Most urine screens only test for the free drug while many drugs are conjugated. For example, most opioids are conjugated with glucuronide in order to be eliminated from the kidney. In addition, urine tests are very sensitive and will almost always bring up metabolites and even trace metabolites. Benzodiazepines break down to many metabolites, which may cause confusion in interpretation.

15.11 Brief office screening strategies

Every health care provider has an obligation to screen each of their pregnant and postpartum patients for substance use.

A simple "Two Item Screen" for substance use takes less than a minute and has good sensitivity and specificity. It consists of two questions [154]:

- "In the last year have you ever smoked cigarettes, drunk alcohol or used any drugs more than you meant to?"
- "Have you felt you wanted or needed to cut down on your smoking or drinking or drug use in the last year?"

Table 15.4 Metabolites of common drugs in urine drug screens

Drug	Major metabolite	Trace metabolite	Negative cut-off in nanograms; comments
Hydrocodone	Hydrocodone	Hydromorphone	600 ng
Oxycodone	Oxycodone	Oxymorphone	1500–2000 ng; order opiate confirmation to detect levels less than 2000 ng
Morphine	Hydromorphone	Hydrocodone	300 ng
Codeine	Codeine; morphine	Nor-codeine;	300 ng
Heroin	6-mono-acety-morphine (6MAM)	Morphine; codeine	Metabolized rapidly
Methadone	Methadone		300 ng. Requires separate screen
Buprenorphine	Nor-buprenorphine		Separate screen; does not cross react
Marijuana	Carboxy THC	DihydroxyTHC; Hydroxyl THC	Federal cut-off is 15 ng (accounts for passive inhalation). Cut-off is 50 ng for positive test
Clonazepam	Clonazepam Oxazepam*	Many metabolites	3000 ng; not well detected, need separate screen to determine use
Aprazolam	Aprazolam; many metabolites	Many metabolites	75 ng
Diazepam	Nordiazepam Oxazepam Temazepam	Many metabolites	
Restoril	Temazepan		

*Almost all benzodiazepines metabolize to oxazepam.

In this study, two random samples of primary care patients (434 and 702 participants) aged 18 to 59 had the following results:

- "No" to each question: 7.3% chance of a current substance use disorder.
- One yes answer: 36.5% chance.
- **Two positive responses had a 72.4% chance.**
- Likelihood ratios were 0.27, 1.93, and 8.77, respectively.

Another practical and validated screening approach is the "4Ps Plus" method [155]. In this verbal screen, five questions are asked:

- "Did either of your **PARENTS** have a problem with alcohol or drugs?"
- "Do any of your **PEERS** have a problem with alcohol or drugs?"
- "Does your **PARTNER** have a problem with alcohol or drugs?"
- "Have you ever drunk beer, wine or liquor to excess in the **PAST**?"
- (Plus) "Have you smoked any cigarettes, used any alcohol or any drug at any time in this **PREGNANCY**?"

The overall reliability for the five-item measure was 0.62. Seventy-four (32.5%) of the women had a positive screen. Sensitivity and specificity were very good, at 87 and 76%, respectively. Positive predictive validity was low (36%), but negative predictive validity was quite high (97%). Of the 31 women who had a positive clinical assessment, 45% were using less than 1 day per week [156].

Numerous screening approaches have been developed for alcohol use in women.

The T-ACE screening tool is adapted from the classic CAGE questions for alcohol use. It can be used alone or in combination with the 4Ps Plus questions. If there was a positive answer to questions about Past and Current Pregnancy in the 4Ps Plus, then follow up with the T-ACE. A score of 2 or more points indicates at-risk drinking in pregnancy [157]:

- **T: Tolerance**: "How many drinks does it take you to feel high?" (More than 2 drinks is a positive response – score 2 points)
- **A: Annoyed**: "Have people annoyed you by criticizing your drinking?" (Yes – score 1 point)
- **C: Cut down**: "Have you ever felt you ought to cut down on your drinking?" (Yes – score 1 point)
- **E: Eye opener**: "Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?" (Yes – score 1 point)

TWEAK is used for alcohol screening in the current pregnancy [158]:

- **T: Tolerance**: "How many drinks does it take you to feel high?" (More than 2 drinks is a positive response – score 2 points)
- **W: Worried:** "Have close friends or relatives worried or complained about your drinking?" (Yes – score 1 point)
- **E: Eye opener**: "Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?" (Yes – score 1 point)
- **A: Amnesia:** "Has a friend or family member ever told you about things you said or did while drinking that you could not remember?" (Yes – score 1 point)

- **K: Cut down**: "Have you ever felt you ought to cut down on your drinking?" (Yes – score 1 point)

With positive answers to the alcohol screens, it is imperative to ask questions about consumption:

- Consumption – "Do you have more than 1 drink a day?"
- Consumption – "Do you have more than 3 drinks per social occasion?"
- At risk consumption:
- Consumption is >14/drinks/week or >4 drinks per occasion (men)
- Consumption is >7/drinks/week or >3 drinks per occasion (women)
- Document the consumption

NOTE: A positive answer to any question on any screen for substance use in pregnancy should trigger a urine drug test. Combined verbal screening and urine testing will yield the best results.

15.12 Brief office interventions

When the patient admits to drug use or a screen is positive, a urine drug screen is indicated. Showing the patient the laboratory report of a positive urine drug test is the most effective way to break through the denial that often accompanies substance use. A brief office intervention is immediately indicated. Brief office interventions have proven to be powerful therapeutic approaches with results comparable to more prolonged therapies [159]. If a patient does not change behavior after a brief intervention, she should be referred.

FRAMES was used in a World Health Organization study to assess brief interventions. The study evaluated heavy male drinkers from 12 countries with obvious cultural differences in alcohol use. A brief intervention resulted in a decrease in alcohol use of 27%, compared to 7% among controls, still present 9 months after the intervention [160]. FRAMES also works well with other drug use [161].

- **F – Feedback** about the adverse effects of drugs or alcohol. This allows for patient education.
- **R – Responsibility** for a change in behavior: "Only you can decide that you want to stop using. If you do, how will your life be better?"

- **A – Advise** to reduce or stop use: "For the next two weeks, stop using, and let's see how you feel."
- **M – Menu** of options: treatment; medications: "If you find that not using for the next 2 weeks is impossible, then we should consider other options."
- **E – Empathy** is central to the intervention. "I know this may be hard to do."
- **S – Self-empowerment**: You can change. "I am impressed that you are considering making this change. Your strong determination is going to help you succeed."

In the FRAMES intervention, feedback follows a specific formula that has universal applications. The interviewer uses four issues to clarify the situation: data, feelings, judgments, and what the interviewer wants to happen. For example, the interviewer would say the following:

- The data in your urine screen was positive for cocaine.
- I'm afraid (feeling) that if you are positive at delivery, CPS will investigate and may put the baby in foster care.
- My opinion (judgment) is that you can stop using.
- I want you to stop using now.

This four-point approach is designed to:

- Clarify the issues.
- Share feelings to enhance empathy in the relationship.
- Empower the listener to act.
- Make the listener less likely to resist.

15.13 Long-term care and maintenance

Screening and detection are critical for the treatment of substance use in pregnancy. By identifying the patient, the physician can determine the appropriate path to recovery, which may include detoxification, pharmacologic treatment, and maintenance. Short-term interventions are designed to educate the patient and empower her to change her behavior. A number of strategies have evolved to enhance long-term abstinence or maintenance.

Motivational Enhancement Therapy (MET) is the foundation for supporting the substance user as she moves through the stages of recovery. Developed by Miller, its premise is that the responsibility for change rests squarely on the shoulders of the patient [162]. The approach is easy to learn and apply in prenatal care. Basic interviewing skills include the ability to express empathy,

to roll with the resistance, and to empower the patient to move through the changes occurring in her life. This approach has improved maternal and neonatal outcome in pregnancy [163].

Integrating MET with the Stages of Change approach, developed by Prochaska, creates a powerful therapeutic alliance leading to maintenance of recovery [164]. Prochaska describes six stages of change and it measures progress over time. The goal is to motivate the patient to move from one stage to the next, only when the patient is ready to move forward [165]. Psychosocial support for the recovering addict is critical in maintaining abstinence and preventing relapse. They also improve retention in prenatal care and substance treatment programs [166].

Conclusion

The identification and treatment of substance use in pregnancy is most challenging. It requires a thorough evidence-based command of the pharmacologic effects of a plethora of drugs on the mother, fetus, and neonate. Most important is the ability of the physician to form a close and supportive therapeutic relationship with the patient. This relationship has a tremendous potential to convert a patient's lifestyle into a positive and healthy life. Moreover, it can influence the well-being of her children and future generations.

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Diabetes in Pregnancy

16

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16.1 Introduction

Pregnancy imposes unique metabolic demands to provide sustained and sufficient transfer of nutrients to the growing fetus during fasting periods by ensuring adequate nutrient storage during feeding. Hormones produced by the feto-placental unit play a pivotal role in adjusting metabolic features to benefit both mother and fetus. However, in pregnancies complicated by diabetes mellitus (DM), its metabolic consequences for both mother and fetus can be exacerbated by the otherwise-adaptive effects of pregnancy *per se* [1]. The effect of DM on the fetus is determined by two factors: the intrauterine environment provided by the mother and the fetal response to it. Tight glycemic control with exogenous insulins led to markedly improved maternal and perinatal outcomes; more recently, oral hypoglycemics have similarly improved outcomes in women with gestational DM (GDM). Recent evidence

that directly relates even mild maternal hyperglycemia with poor perinatal outcomes highlights the importance of maternal treatment [2]. This chapter reviews the clinical diagnosis and effects of diabetic pregnancy with a focus on therapeutics.

16.2 Epidemiology

Pregestational DM complicates approximately 1.3% of pregnancies; with increasing prevalence, due principally to type 2 diabetes [3], associated with obesity and with increasing maternal age [3]. As well, new guidelines will further increase the recognition of GDM and pregestational DM by using lower glycemic thresholds (GDM: fasting ≥ 92mg/dL or 1-hour postprandial ≥180mg/dL or 2-hour postprandial ≥ 153mg/dL; Type 2 (pregestational) DM: fasting ≥126mg/dL or random glucose ≥200mg/dL or HbA1c ≥6.5%) [4]. The incidence of GDM is even greater, complicating approximately 5 to 10% of pregnancies [5] with higher rates in younger, obese women [6].

16.3 Classification

Outside of pregnancy, diabetes is classified according to its pathophysiology [7]. Broadly, type 1 DM is due to absolute insulin lack, most commonly due to immune destruction of β-cells, while type 2 DM is characterized by progressive insulin resistance, which leads initially to compensatory hyperinsulinemia, and then to defective insulin secretion as well. While treatment of type 1 DM requires insulin replacement, many type 2 DM patients will also be treated with insulin as adjunctive or primary therapy; thus, the terms insulin dependent [8] and non-insulin dependent DM [8] should no longer be used. During pregnancy, women can be categorized as those who were known to have DM prior to pregnancy – *pregestational* or *overt* – and those diagnosed during pregnancy – *gestational*. As noted briefly above, some women who have been classified as having GDM must actually have had pregestational DM that had not come to clinical recognition before the more attentive medical evaluation that accompanies antenatal care; evolving definitions will reclassify these women accordingly. The American Congress of Obstetrics and Gynecology [9] has recently shifted toward a focus on differentiating between gestational and pregestational DM, as advocated by the Expert Committee on the

Diagnosis and Classification of Diabetes [7] and away from the White classification [10], which focused on classifying women by the type and severity of diabetic target organ damage.

Pregnancy is associated with resistance to the glucose-lowering effects of insulin resulting in relative postprandial hyperglycemia. It is thought that the endocrine effects of the feto-placental unit play an important role in the development of insulin resistance during pregnancy [11, 12]. In fact, pregnant women experience less hypoglycemia in response to exogenous insulin but more fasting hypoglycemia than non-pregnant women [13], and normal pregnant women have exaggerated insulin responses to glucose ingestion compared to non-pregnant women [14]. It is estimated that in healthy pregnant women insulin sensitivity decreases by 40–56% during the third trimester [15].

To compensate, pregnancy is characterized by an adaptive increase in pancreatic β-cell function [16] that also leads to maternal pancreatic hypertrophy and hyperplasia [17]. GDM results when insulin resistance exceeds the capacity to increase insulin secretion.

The absolute or relative insulin deficiency which characterizes type 1 and type 2 DM, respectively, precludes normal pancreatic β-cell compensation during pregnancy, resulting in maternal hyperglycemia sufficient to impact fetal development unless adequate exogenous insulin is provided. Although patients with type 1 DM usually have normal insulin sensitivity when non-pregnant, the insulin resistance of pregnancy leads to a substantial (1.5- to 3-fold) increase in their insulin requirements [18]. Patients with type 2 DM have striking pregestational insulin resistance, leading to insulin requirements higher than women with type 1 DM [19]. Insulin requirements increase throughout gestation, paralleling the rise in insulin resistance; following delivery, they are decreased markedly [18].

16.4 Gestational diabetes

GDM may be mild or may present with more severe hyperglycemia that suggests previously unrecognized overt DM. Women with GDM but without fasting hyperglycemia usually revert to euglycemia following delivery. However, they carry an ~50% risk of developing DM [20] during the first 5 to 10 years following an affected pregnancy [21, 22]. Women with GDM appear to have underlying (though unrecognized) insulin resistance that is exacerbated by the additive insulin resistance due to pregnancy [23]. The origin of the underlying insulin resistance has been linked,

in some women with GDM, to abnormal glucose transporters in adipocytes [24], or to polymorphisms in the region of the insulin receptor and the insulin-like growth factor 2 genes [25]; surely other specific predisposing molecular mechanisms will be discovered. Obesity further increases insulin resistance in many women whose pregnancies are complicated by GDM [26]. Since both insulin resistance and impaired compensatory β-cell function are usually required to manifest either type 2 DM or GDM, it is not surprising that maternal hyperglycemia is associated with insufficient insulin secretion in gestational diabetics [27].

16.5 Diabetes management in pregnancy

16.5.1 Nutritional goals and exercise

Lifestyle modifications, including both diet and exercise, remain the first-line therapy for newly diagnosed GDM. All pregnant women with diabetes should follow a carbohydrate-restricted diet based on their ideal pre-pregnancy body weights. A diet restricted to 2000–2400 kcal/day with 35% of calories from complex and high-fiber carbohydrates has been shown to delay the need for hypoglycemic therapy with insulin [28, 41]. Unless otherwise contraindicated, diet should be combined with regular exercise, such as walking 1–2 miles three times a week. A major concern is that a 2-week trial of lifestyle intervention may delay glycemic control and increase fetal risk; therefore close monitoring to enable rapid initiation of drug therapy for persisting hyperglycemia is essential.

16.5.2 Glucose monitoring and glycemic control

Monitoring of capillary blood glucose 4–6 times/day, including fasting, preprandial, and postprandial values, is central to tight management of DM during pregnancy. Treatment goals for blood glucose control are: fasting 90–99 mg/dL, 1 h postprandial <140 mg/dL, and 2 h postprandial <120–127 mg/dL [5]. Women treated only with lifestyle modifications or with stable and optimal glycemic control can monitor less frequently (2–4 times/day). HbA1c can aid in assessing the risk of congenital anomalies in overt diabetes if measured in the first trimester while repeated measures each trimester may aid in assessment of longer-term glycemic control. In 2011 the American Diabetes Association recommended that women with HbA1c ≥6.5% be diagnosed with type 2 DM rather than GDM [29]. In euglycemic women, intermediate (5.3–6%) and high (>6%) HbA1c during the first trimester are associated with

higher GDM risk later in pregnancy. Studies have determined that HbA1c >6% during early pregnancy is associated with increased odds of insulin use for the treatment of GDM independent of oral glucose tolerance test (OGTT) results and gestational age at the time of GDM diagnosis [30]. These results suggest that HbA1c may be used to identify women in early pregnancy who are at high risk for GDM and who develop the poorer glycemic control. The association of HbA1c and birth weight is strongest when it is measured after GDM diagnosis compared to at the time of diagnosis [31, 32]. The later measurement may be a more accurate reflection of poor glycemic control during the third trimester. Tight glycemic control is essential to improve outcomes in all women, whether with severe DM, mild DM or GDM [33, 34]. Despite the variety of effective therapies for DM during pregnancy, treatment barriers persist. There are particular challenges to instituting insulin therapy in pregnant women with DM, in that it is important to control hyperglycemia quickly, yet opportunities for patient education and insulin titration are limited. Further, many women are reluctant to administer multiple insulin injections daily, resulting in limited adherence to treatment with poor glucose control. In addition, treatment-associated hypoglycemia often limits the ability to achieve tight glucose control. Oral hypoglycemics have gained only limited popularity in clinical practice, due in part to inadequate glucose control in a significant fraction of women with GDM. Poor control may be due, in many cases, to irrationally slow dose titration. For example, while glyburide dose is most commonly adjusted weekly, pharmacokinetic data in pregnancy suggest that its $t_{\{1/2\}}$ is decreased; steady state is therefore achieved faster and dose titrations should occur nearly daily if optimal glycemic control and reduction of morbidity is desired. The next section will review the pharmacology of treatment options for diabetes during pregnancy.

16.5.3 Insulin therapy

Exogenous insulin therapy attempts to use glucose monitoring-guided dose adjustment of long and short acting insulin analogs to mimic the normal profile of insulin in response to diet and metabolic demands in order to maintain euglycemia. Insulin therapy is currently recommended for nearly all women with pregestational diabetes during pregnancy and for women with GDM who fail to achieve glycemic control with diet and oral hypoglycemic therapy. Insulin therapy will usually require separate insulin analogs and dosing strategies to mimic the normal basal secretion of insulin as well as the rapid and transient β-cell response to meals. In most women, essentially all nutrients are absorbed within 90 min after

a meal and both plasma glucose and insulin return to pre-meal values within 2 h [10]. Endogenous insulin is secreted largely from the pancreas into the portal circulation with hepatic extraction of ~50% [35]. Insulin concentrations in the portal vein exceed those in arterial plasma by approximately three-fold. In healthy adults, the rate of basal insulin secretion into the portal system is ~1 unit/h. With the intake of food, the rate increases by 5–10-fold [35]. Insulin acts in the liver by prompt and efficient inhibition of glycogenolysis [35], beginning within minutes and reaching full effect within hours [36]. Secondarily and subsequently, insulin inhibits hepatic gluconeogenesis, principally by decreasing release and transport of free fatty acids and precursors from fat and skeletal muscle to the liver. The effect on gluconeogenesis is usually delayed and requires more insulin than the effect on glycogenolysis, due to its peripheral sites of action [35, 37].

Insulin metabolism is, itself, altered during pregnancy, with 24 and 30% reductions in hepatic insulin extraction noted in women with type 1 DM and GDM, respectively, perhaps due to changes in hepatic blood flow [38, 39]. Placental perfusion studies show that only 1–5% of maternal insulin is transferred into fetal circulation, likely due to its molecular weight of ~5800 Da [40]. Maternal insulin–antibody complexes facilitate placental transfer of insulin. Since the risk of fetal macrosomia has been linked to high levels of insulin in cord blood and amniotic fluid [41], strategies to minimize maternal anti-insulin antibody production may improve fetal morbidity. Use of human insulins minimizes but may not eliminate anti-insulin antibodies [42].

Regular human insulin needs to be administered 30–45 minutes prior to meals to control postprandial hyperglycemia, though its peak effect occurs 2–4 h after injection, likely due to delayed absorption and leading, in some cases to inadequate control followed by late postprandial hypoglycemia. The delayed absorption may be due to formation of insulin molecular clusters (hexamers) that dissociate slowly, limiting the rate of absorption of active insulin from the subcutaneous space into the systemic circulation [43]. The inconvenience associated with injecting human insulin half an hour prior to a meal often leads to poor compliance and suboptimal glycemic control [44]. These limitations of regular insulin led to the development of analogs with improved characteristics, including short acting (SA) insulins with faster onset and clearance of long acting (LA) insulins with delayed and prolonged distribution resulting in low sustained levels. The different types of insulin used currently in pregnancy are listed in Table 16.1.

Short acting (SA) analogs attempt to mimic the rapid onset and disappearance of endogenous insulin around a meal. Lispro and

Table 16.1 Insulin analogs and pharmacokinetics

Type	Onset of action	Peak of action (hours)	Duration of action (hours)
Humalog (lispro)	1–15 minutes	1	2
Novolog (aspart)	1–15 minutes	1	2
Regular insulin	30–60 minutes	2	4
Humulin N (NPH)	1–3 hours	8	8
Lantus (glargine)	1 hour	No peak	<24
Levemir (detemir)	3–4 hours	No peak	12–24 hours (dose dependent)

Aspart form hexamers that dissociate more rapidly so they can be administered immediately before or up to 15 minutes after starting meals. Their effect peaks after 1–2 h with peak concentrations twice that of regular insulin [45]. Severe hypoglycemic episodes are less common with SA insulins. Circulating levels of SA insulins mirror the rise and fall in serum glucose following an oral load, leading both to better control of postprandial glucose excursion and to fewer episodes of late postprandial hypoglycemia.

Longer acting agents are needed to complement SA agents in order to mimic basal pancreatic insulin secretion, and maintain euglycemia without hypoglycemic episodes between meals and overnight. NPH (Neutral Protamine Hagedorn), an intermediate acting insulin, is usually administered twice daily in pregnancy to provide 24 h glycemic control in concert with prandial SA insulin. However, recent data from studies of two LA insulin analogs, glargine and detemir, may alter practice [36, 46]. The LA agents contain stabilized hexamers that dissociate slowly, resulting in a stable monotonous basal profile decreasing the risk of fasting hypoglycemia. LA agents are associated with decreased fasting glucose, HbA1c, and nocturnal hypoglycemia [47]. When compared to NPH insulin, LA agents had similar or lower rates of maternal microvascular morbidity, macrosomia, and neonatal hypoglycemia [48–50]. Recent placental perfusion studies using glargine and detemir demonstrated negligible placental transfer and animal studies showed rates of teratogenicity and embryotoxicity similar to human insulin [51, 52].

Besides influencing glucose metabolism, insulin acts to alter cellular proliferation, differentiation, and cell apoptosis. At higher concentrations it promotes growth and proliferation via activation of receptors for insulin-like growth factor type I (IGF-I) [53]. Structural changes in the design of insulin analogs appear to alter its affinity

for IGF-1 receptors [54]. Indeed, glargine has a 6–8-fold increased affinity for IGF-1 receptors when compared to insulin in an osteosarcoma cell line [54]. Lispro has also been shown to have some increase in IGF-1 binding [55]. This interaction could potentially lead to increased fetal growth and other mitogenic effects, though there are no *in vivo* or clinical data to support these concerns. IGF-1 binding appears not to be increased for other insulin analogs.

Insulin pumps deliver insulin in a pattern that closely resembles physiologic insulin secretion and may be used safely in pregnancy. Studies have described similar safety and efficiency as multiple injection therapy with use during pregnancy [56]. A short acting insulin (either regular or lispro) is used, with 50–60% of the total daily dose (which may be calculated as described in Table 16.2) given as the basal rate and the remaining 40–50% given as pre-meal/snack boluses. Insulin pump therapy requires high patient compliance and the ability to calculate insulin requirement throughout the day.

Insulin requirements vary across trimesters and are illustrated in Table 16.2. Early in pregnancy (9–13 weeks), a decrease in insulin may be needed to adjust for decreased oral intake and vomiting. After 14 weeks of gestation, insulin requirements increase steadily (Table 16.2). Maternal obesity increases the insulin requirement by 0.1 to 0.2 units/kg. Figure 16.1 illustrates a suggested protocol for insulin dosing during pregnancy and Figure 16.2 a protocol for insulin adjustment.

16.5.4 Oral hypoglycemics

Oral agents are first-line therapy for type 2 DM outside of pregnancy [57]. They are indicated during pregnancy when diet and exercise fail to achieve treatment goals and are favored over insulin in cases with mild hyperglycemia because of quicker patient learning, lower risk for hypoglycemia, and higher compliance. In addition, since both defective β-cell insulin secretion and insulin resistance are characteristics

Table 16.2 Daily insulin dose across trimesters

Gestational period (weeks)	Total daily dose (units/kg*)
1–18	0.7
18–26	0.8
26–36	0.9
36–40	1
0–6 (postpartum)	0.4

*Based on actual weight.

not only of type 2 DM but of GDM as well, oral agents targeting either of these pathophysiologies may benefit gravidas with DM.

Glyburide, a third generation sulfonylurea oral hypoglycemic agent, acts primarily through specific receptors on the β-cell surface. Drug-receptor binding acts to close adenosine triphosphate-dependent potassium channels, resulting in cellular depolarization, calcium influx, and translocation of insulin secretory granules to the β-cell surface. The resulting release of insulin into the portal vein rapidly suppresses hepatic glucose production and later facilitates peripheral glucose use [58, 59]. Insulin resistance commonly diminishes as a secondary result of the reversal of hyperglycemia

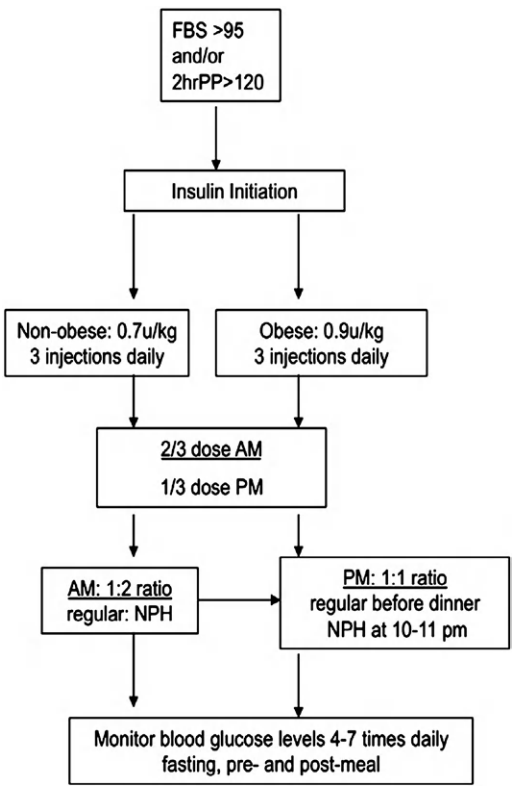

Figure 16.1 Insulin protocol during pregnancy. FBS: fasting fingerstick glucose; 2hrPP: 2 h postprandial fingerstick glucose.

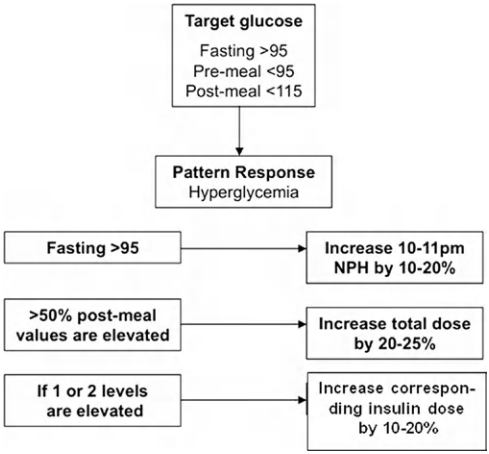

Figure 16.2 Insulin adjustment protocol.

[59, 60]. Because sulfonylureas rely on a preserved β-cell response, they are ineffective in patients with absent or severely diminished β-cell function, as in type 1 DM or advanced type 2 DM. Sulfonylureas increase insulin secretion in direct proportion to plasma glucose levels from 60 to 180 mg/dL, with no effect if glucose is less that 60 mg/dL [61, 62]. Despite these data, sulfonylureas, including glyburide, can still lead to symptomatic and severe hypoglycemia, most commonly in the setting of unrecognized renal insufficiency. There is then a minimal lag time between the changes in plasma glucose and the change in insulin secretion rate [63, 64]. When given as a single agent, peak plasma glyburide concentrations are achieved within 4 h and absorption is not affected by food. Its elimination $t_{\{1/2\}}$ is approximately 10 h in non-pregnant adults and shorter in pregnancy due to increased clearance. While many practitioners remain concerned that glyburide could lead to neonatal hypoglycemia, data do not support this concern [65].

A recent pharmacokinetic–pharmacodynamic (PK–PD) [66] study of glyburide in 40 women with GDM receiving glyburide monotherapy, and controlled for fasting glucose concentration <95 mg/dL, described 50% lower dose-adjusted plasma drug concentrations in pregnancy, likely due to an increase in hepatic metabolism [67]. One might expect, therefore, that dose increases, perhaps beyond those in non-pregnant labeling might overcome increased glyburide clearance, resulting in better glycemic control. However, the glyburide dose–response relationship is uncertain

and a ceiling effect may limit benefits due to higher doses. Indeed, studies in non-pregnant patients with type 2 DM suggest little incremental benefit following increased doses [68, 69]. While glyburide normalized insulin secretion in women with GDM following a mixed meal in the glyburide PK–PD study, this was inadequate to compensate fully for their insulin resistance, manifest as imperfect control of postprandial hyperglycemia in those women [67]. A prior study had similarly demonstrated the challenges due to insulin resistance in women with GDM during insulin infusion [70]. Taken together, these results suggest that although some women with GDM may benefit from more aggressive glyburide dose titration, treatment in others may be improved by the use of additional or alternative agents to improve insulin resistance.

Studies of glyburide in pregnancy describe glycemic control and pregnancy outcomes similar to those of insulin in eligible women when dosing was adjusted frequently [52, 71], starting at 2.5 mg in the morning titrating to a maximum dose, based on non-pregnant package labeling, of 10 mg twice a day [71]. However, almost 20% of women with GDM treated with glyburide will eventually require insulin therapy; granted this may have been due to poor dose titration and switching to insulin prior to reaching maximal doses [72].

There are accepted guidelines for fasting and postprandial glucose levels in pregnancy that are associated with a decrease in neonatal morbidity [73]. However, these glycemic targets are not purely based on normalization of diabetic physiology. The discrepancy between physiology and outcome may be explained by recent data demonstrating a continuous relationship between maternal glycemic levels and neonatal outcomes [2].

It remains unclear whether the benefits of tighter glycemic control in women with GDM exceed those due to potential hypoglycemia. Still, primary or combined therapy with agents that target insulin resistance may be especially useful in improved glycemic control in GDM.

Metformin is primarily an insulin sensitizer that reduces hepatic glucose production by suppressing gluconeogenesis [74, 75]. It may also augment peripheral glucose uptake, though this may be secondary to reversal of hyperglycemia. Since it does not increase insulin secretion, the risk for hypoglycemia is minimal. Peak metformin plasma concentrations are achieved within 4 h of oral administration and administration with meals decreases drug-induced gastrointestinal discomfort, though it decreases absorption. Metfomin's elimination $t_{\{1/2\}}$ in non-pregnant adults is approximately 6 h. Its renal clearance increases significantly in mid- and late gestation, in parallel with gestational increases in creatinine clearance [76]. Metformin crosses the placenta, resulting in variable fetal drug

levels [76]. A study assessing 126 infants at age 18 months born to 109 mothers who conceived and continued metformin during pregnancy found similar size and motor-social development in infants exposed to metformin compared to a non-exposed group [77].

Studies comparing metformin to insulin or glyburide describe lower rates of achieving euglycemia with metformin [78, 79]. Yet, once euglycemia was achieved, neonatal outcomes were similar to those in subjects receiving glyburide [78]. The higher rates of failure in women receiving metformin may have been due to inadequate dose adjustment to account for increased renal and total body drug clearance drug during pregnancy [76]. Metformin and insulin treatment each resulted in similar rates of perinatal morbidity, including metabolic abnormalities, premature birth, and birth trauma in a recent randomized trial for the treatment of GDM unresponsive to lifestyle interventions between 28 and 32 weeks' gestation [79]. The starting dose was 500 mg once or twice daily with dose titration every 1 to 2 weeks to meet glycemic targets [79]. Women receiving both metformin and insulin had lower insulin requirements and gained less weight during pregnancy and during postpartum follow-up than those receiving insulin only [79]. In study subjects, metformin was highly accepted and preferred over insulin [79]. These findings highlight the potential benefits of combination therapy with metformin, either with glyburide or insulin, and suggest that outcomes could be improved with more aggressive dose titration.

16.5.5 Postpartum metabolic management

Insulin requirements decrease immediately after delivery, when women with overt diabetes can either have their insulin dose empirically decreased by 50% or be returned to their pre-pregnancy hypoglycemic regimen. Women with GDM should be reminded about their increased risk for diabetes and the need for screening by OGTT starting at 6 to 8 weeks after delivery. Breastfeeding may improve maternal glucose levels [80]. Despite observations that support the use of combination hormonal contraceptives in women with diabetes, the American Congress of Obstetricians and Gynecologists (ACOG) recommends that their use be limited to nonsmoking, healthy women with diabetes who are younger than 35 years with no evidence of hypertension, nephropathy, retinopathy, or other vascular disease [9].

Conclusion

The number of pregnancies complicated by DM is increasing. Yet, the current screening and diagnostic strategies are not well aligned

with birth complications. New evidence suggests that tighter glycemic criteria may improve neonatal outcomes but would result in a higher rate of GDM diagnoses. The current treatment strategies for DM during pregnancy are limited and have not been adjusted to account for pregnancy-induced metabolic changes. Further research is needed to investigate alternative therapies and develop pregnancy-specific treatment strategies.

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Cardiovascular Medications in Pregnancy

17

Thomas R. Easterling

17.1 Introduction

Women with known and unknown cardiovascular disease may experience destabilization in their condition due to physiological adaptations to pregnancy. In becoming pregnant, women accept a burden of risk to their life and health. For healthy women in the developed world, these risks are modest where maternal mortality ranges from 10 to 20 per 100,000 live births. In some parts of the developing world such as Haiti, Afghanistan, and Somalia, the lifetime risk of dying in pregnancy ranges from 1:10 to 1:20 due to high maternal mortality rates and high

rates of parity. Medical complications such a severe pulmonary hypertension and advanced Marfan's syndrome may confer a risk of death as high as 1:10. The maternal risk of hypertensive disease is most commonly managed by delivery of the fetus. When delivery is preterm, the burden of disease risk is transferred to the neonate. By carrying a pregnancy, an individual woman affirms the inherent value of that pregnancy in her life that serves to balance the risks that she encounters in carrying the pregnancy.

Appropriate pharmacological management of maternal complications serves to reestablish the physiological homeostasis of a normal pregnancy with the goal of improving maternal and neonatal outcomes. Treatment is frequently associated with perceived and occasionally real risk to the fetus for the advantage of the mother. Errors of omission are frequently made due to perceived risk or due to a failure to balance risk. Just as maternal benefit is usually dose dependent, risks to the fetus are often dose dependent rather than absolute. Drugs with cardiovascular activity operate in a physiological environment that is altered in pregnancy. These changes are dynamic over the course of pregnancy with different trajectories depending on the point in gestation. The pharmacodynamic effect of drugs in pregnancy operates in the context of these changes and with potential impact on utero-placental perfusion impacting fetal well-being. Metabolic pathways of drug clearance and transport operate to limit our exposure to xenobiotics. Many of these mechanisms are significantly upregulated in pregnancy presumably limiting fetal exposure. In some cases, the placenta itself will operate through these mechanisms to further limit fetal exposure. After birth, neonates can potentially be exposed to maternal medications through breast milk. Appropriate pharmacological care of pregnant women with cardiovascular conditions requires an understanding of the physiological environment of pregnancy and the impact of these changes on disease states; an understanding of the pharmacodynamic impact of drugs on this environment and the fetal environment; and an understanding of changes in the pharmacokinetics of drugs in pregnancy. The intent of this chapter is to offer a framework of understanding about the impact of cardiovascular medications in pregnancy. In some limited cases, there are clear data regarding specific drugs to effectively inform the clinician. In many cases, however, drug-specific data are lacking. In these cases, a framework of pharmacodynamic and pharmacokinetic effects is developed to offer clinical guidance and a basis for ongoing investigation.

17.2 Cardiovascular changes in pregnancy

Pharmacological treatment of women with cardiovascular disease will usually involve drugs that are hemodynamically active impacting the relationship between mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR) described by: MAP=(CO•TPR)/80. MAP is calculated from diastolic blood pressure (dBP) and systolic blood pressure (sBP): MAP=(2dBP+sBP)/3. Cardiac output is the product of stroke volume (SV) and heart rate (HR): CO=SV•HR.

Pregnancy is associated with dramatic, usually predictable, changes in maternal hemodynamics [1]. These are described in Figure 17.1. Early in the first trimester, TPR falls which is associated with a decrease in MAP and an increase in CO. As pregnancy advances CO continues to rise due to volume loading reflected in an increase in SV and an increasing HR. Near term, CO is maintained increasingly due to an increased HR. Throughout most of pregnancy, a reduction in blood pressure is maintained despite an elevated CO by a proportionately larger reduction in TPR. Near term, BP rises to near non-pregnant levels due to an increase in TPR. These hemodynamic changes are described graphically in Figure 17.2 where CO is displayed on the x-axis and MAP on the y-axis. Isometric lines of vascular resistance allow all three variables to be simultaneously displayed. Hemodynamic changes that are due to changes in TPR result in vectors of change perpendicular to isometric lines. Those due to changes in CO result in vectors parallel to isometric lines. In early pregnancy, hemodynamic changes are characterized by a line perpendicular to lines of resistance followed by a vector parallel to lines of resistance through mid-pregnancy and then followed by a vector perpendicular but due to rising TPR. Data from nulliparus women who subsequently developed preeclampsia result in a similar "fishhook" pattern which starts with higher MAP and CO [1]. With advancing preeclampsia, these women experience a dramatic increase in resistance with worsening hypertension [2].

During labor CO is increased due to elevated HR due to discomfort and due to increased SV due to volume loading associated with centralization of uterine blood volume due to uterine contractions [3]. Postpartum, pregnant women volume load as they mobilize extravascular volume; they remain tachycardic; TPR rises returning to non-pregnant norms [4]. These hemodynamic changes represent a "perfect storm" for women with vulnerable conditions such as mitral stenosis, cardiomyopathy, and pulmonary hypertension [5]. Compounding these hemodynamic changes, the normal hemodilution of pregnancy results in

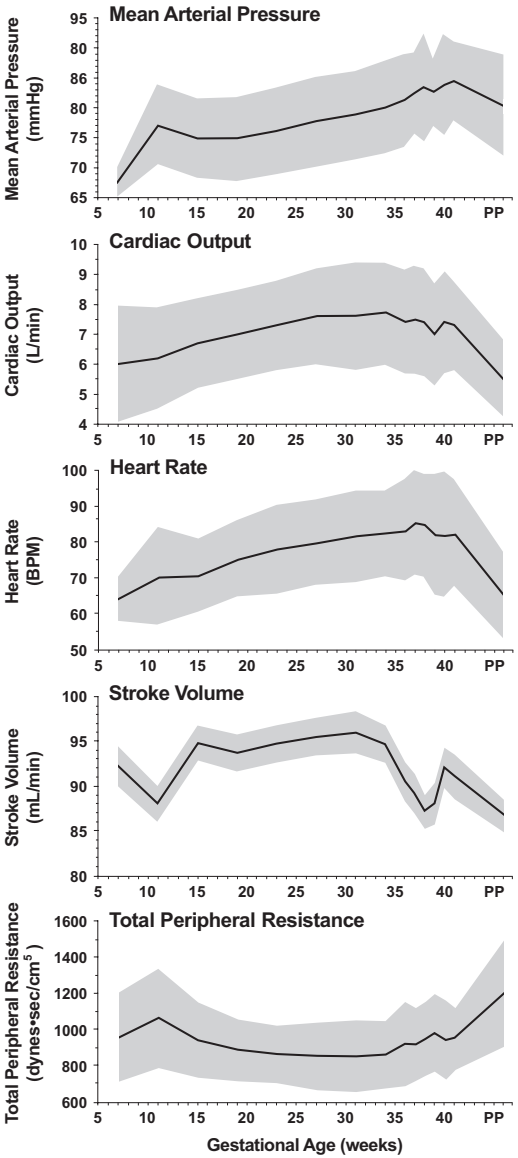


Figure 17.1 Cardiac output, mean arterial pressure, total peripheral resistance, stroke volume and heart rate derived from serial measurements in normotensive nulliparous pregnancies: mean ± sd.

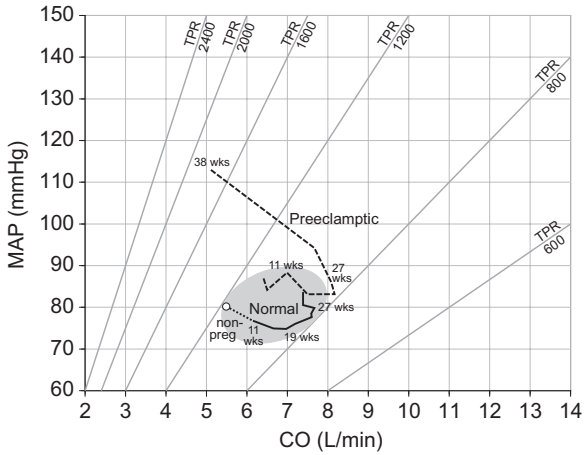


Figure 17.2 Cardiac output vs. mean arterial pressure with total peripheral resistance represented by diagonal isometric lines. Hemodynamic changes in normotensive pregnancy are represented by a "fishhook" shaped curve lower and to the left of a second curve that describes hemodynamic changes in preeclamptic pregnancies.

reduced serum albumen concentration, reduced colloid osmotic pressure and an increased tendency towards pulmonary edema [6]. Pharmacological management of pregnant women with hemodynamically active medications requires an understanding of these fundamental cardiovascular changes and the timing of these changes in pregnancy integrated into the desired pharmacodynamic effect.

17.3 Cardiovascular diseases in pregnancy

Hypertension is the most common cardiovascular complication in pregnancy. The spectrum of disease ranges from women with a preexisting diagnosis of chronic hypertension to preeclampsia defined by new onset hypertension or acutely worsening chronic hypertension accompanied by proteinuria. Preeclampsia can be a life-threatening condition contributing to significant maternal mortality in the developing world. It can result in a broad spectrum of maternal end-organ diseases including seizures, cerebral edema, cerebral hemorrhage, renal failure, elevated liver function

tests, hepatic rupture, hemolysis, thrombocytopenia, heart failure, and pulmonary edema. Definitive treatment requires delivery of the fetus which, when preterm, may result in significant neonatal morbidity and mortality. The risk of maternal seizures is substantially reduced by treatment with magnesium sulfate [7].

The threshold and timing for treatment of blood pressure in pregnancy remains controversial. Clearly, blood pressures above 160–170/105–110 should be treated to avoid acute cerebrovascular complications. Earlier, more aggressive initiation of pharmacological management decreases the risk of hypertensive crisis, but may also result in a slowing of fetal growth [8]. Early and aggressive treatment of hypertension in high-risk pregnancies such as those complicated by diabetic nephropathy may reduce maternal complications and the need for preterm delivery due to hypertension [9]. Based on meta-analysis of available antihypertensive trials, each 10 mmHg reduction in MAP results in approximately 180 g of decreased fetal growth [10]. The decision to treat is generally a balance of the risk of uncontrolled maternal health, the risk of the potential need for preterm birth due to uncontrolled hypertension, and the risk of reduced fetal growth.

The specific hemodynamic conditions associated with maternal hypertension may be varied and change over the course of pregnancy. Maternal hemodynamics prior to the onset of clinical preeclampsia are best characterized by elevated CO and reduced TPR [1, 2]. Some women with chronic hypertension will have an elevated CO; others will be characterized by increased TPR. As preeclampsia becomes severe, TPR may dramatically increase over the course of days [2]. The hemodynamic characteristics of acute hypertension in pregnancy are associated with a differential impact on fetal growth. Increased TPR at presentation is associated with infants smaller for gestational age than those presenting with elevated cardiac output [11]. The hemodynamic effect of treatment can also impact fetal growth. If CO falls below the mean for gestational age or resistance rises above 1150 dyne•sec/cm^5, reduced fetal growth can be expected [12]. In most clinical settings, measurements of maternal CO and TPR are not available to direct therapy. Nevertheless, an understanding of the maternal hemodynamics, the potential impact on the fetus, and the pharmacodynamic activities of specific drugs should serve to guide empiric therapy.

Increasing numbers of young women with surgically corrected congenital heart disease are surviving to young adulthood and are choosing to have children. Mitral stenosis due to rheumatic heart disease remains common among children who grew up in conditions of crowding and poverty. With increased surveillance, more young women are diagnosed with hypertrophic cardiomyopathy

that is becoming one of the most common cardiac conditions seen in pregnant women. Improved medical management of dilated cardiomyopathy and pulmonary hypertension offers the potential for improved outcomes in pregnancy. The hemodynamic changes associated with normal pregnancy may hemodynamically destabilize a pregnant woman with cardiac disease. Volume loading will adversely affect women with mitral stenosis, dilated and hypertrophic cardiomyopathy, and repaired congenital heart disease where the right heart is now the systemic ventricle such as a Fontan or Mustard repair. They may require diuresis to remain compensated. The acute volume loading associated with the postpartum period may be acutely destabilizing [5]. This may contribute to the high mortality rate seen postpartum in women with pulmonary hypertension and a failing right heart. Tachycardia results in decreased time in diastole for flow across a stenotic mitral valve.

Pharmacological control of tachycardia improves outcomes [13]. Many young women with congenital heart disease will have a tendency towards tachyarrythmia. This will worsen during pregnancy. In some series, tachyarrythmia is the most common serious complication among pregnant women with congenital heart disease. Tachyarrythmia associated with hypertrophic cardiomyopathy predictably worsens during pregnancy. Many of these women will benefit from pharmacological control of heart rate. Afterload reduction associated with a decrease in TPR may initially benefit women with dilated cardiomyopathy, systemic right hearts, and aortic and mitral regurgitation. However, the rise in TPR seen in the late third trimester and the acute increase in afterload experienced postpartum may result in decompensation. An understanding of the hemodynamic changes in pregnancy, the specific vulnerabilities of individual conditions, and the pharmacodynamic impact of specific medications will help a provider to treat preemptively to prevent decompensation rather than reacting to an acutely deteriorating maternal condition.

17.4 Pharmacodynamics of hemodynamically active drugs in pregnancy

Hemodynamically active drugs generally have primary effects on TPR, HR or SV. Changes in each of these parameters will affect CO. A reduction in vascular resistance can be induced through a number of pathways: direct action on vascular smooth muscle (e.g. hydralazine), inhibition of calcium channels (e.g. nifedipine), inhibition of central adrenergic output through central

alpha stimulation (e.g. clonidine), or inhibition of the angiotensin system (e.g. angiotensin converting enzyme inhibitors). A reduction in CO can be achieved through either a reduction in heart rate or a reduction in stroke volume. The hemodynamic action of vasodilators can be represented as a vector in Figure 17.3 that runs perpendicular to the isometric lines of vascular resistance. A reduction in TPR results in a reduction in MAP and an increase in CO. In the upper left of the chart, changes in TPR result in relatively small changes in MAP and disproportionately large changes in CO. In the upper right portion of the chart, similar changes in TPR result in relatively small changes in CO and large changes in MAP and potentially hypotension. A reduction in CO will result in a vector of change parallel to isometric lines of resistance and an associated fall in MAP. On the upper left portion of the chart, lines of TPR are steep resulting in substantial changes in MAP with small changes in CO. In the upper right portion of the chart, large changes in CO are needed to lower MAP. Adding vectors, head to tail, can be used to predict the potential effects of combined drug therapy.

The pharmacodynamic effects of several individual drugs in pregnancy are plotted in Figure 17.4. Hydralazine [14] and captopril [15] demonstrate clear vasodilatory effects as described above.

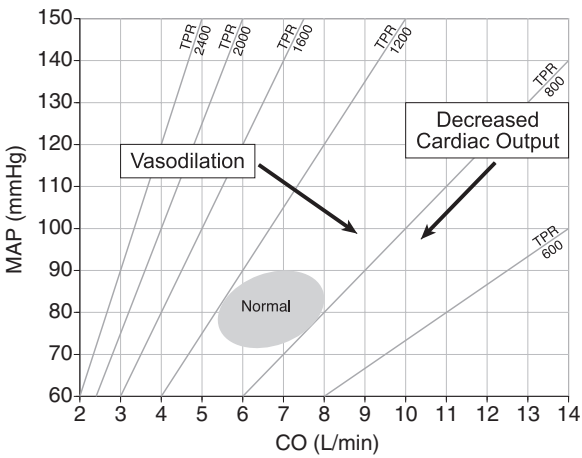
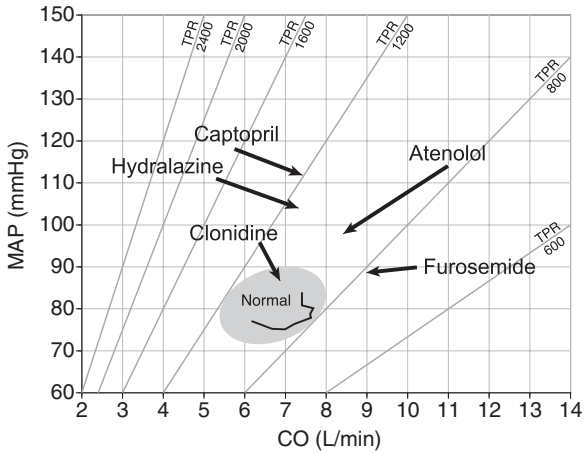


Figure 17.3 Cardiac output vs. mean arterial pressure with total peripheral resistance represented by diagonal isometric lines. Vectors of change associated with treatment with atenolol, furosemide, hydralazine, clonidine and captopril are represented.

The direction of the hemodynamic vector of change of individual patients in these studies was fairly consistent as represented by the mean vector. The magnitude of effect varied. The pharmacodynamic effect of nifedipine has been reported in severely hypertensive patients. As would be expected, a reduction in MAP was associated with a fall in TPR and a rise in CO [16]. The data are not reported in a manner to permit plotting a vector. Nifedipine has been reported to significantly induce cerebral vasodilation that would be expected to increase cerebral perfusion pressure which is associated with adverse outcome in women with preeclampsia [17].

The vector for atenolol, a β-blocker, runs roughly parallel to lines of resistance but with a tendency towards increasing TPR [14]. The primary effect of a reduction in CO achieved by a reduction in heart rate is blunted by a rise in stroke volume. The effect on MAP is countered to some degree by a rise in TPR. As with hydralazine and captopril, the direction of individual vectors was fairly consistent while the magnitude of the vectors varied among patients. Pharmacodynamic data in pregnancy is not available for metoprolol or propranolol, other commonly used β-blockers. One could infer similar actions from class effects from these drugs.



Figuer 17.4 Cardiac output vs. mean arterial pressure with total peripheral resistance represented by diagonal isometric lines. Vectors representing a reduction in TPR generally run perpendicular to liners of resistance. Vectors representing a reduction in CO generally run parallel with some tendency towards increasing resistance.

The vector for furosemide, a diuretic, also runs generally parallel to lines of resistance and with a tendency towards increasing resistance [18]. The primary impact on reducing CO is achieved through a reduction in SV with some associated blunting of effect from a rise in HR. The pharmacodynamic effects of other diuretics have not been reported. Inference from class effect may again be considered.

The pharmacodynamic effects of clonidine, a central alpha agonist, and labetalol, a combined α- and β-blocker, are more complex [19]. Clonidine has been studied and the reported vector of change is displayed in Figure 17.4. The vector is vertical, intermediate between that expected from a vasodilator and a β-blocker. Unlike other drugs reported, a large variability of effect was observed across patients; some exhibited changes consistent with vasodilator action; others with changes consistent with beta blockade. Given its mechanism of action, the final effect may be dependent on the character of individual patient's central adrenergic tone. As will be discussed below, the differences in hemodynamic effect may be relevant to the fetus. Labetalol is a combined α- and β-blocker. It is a chiral drug with two diastereomeric pairs of racemates. Two are pharmacologically inactive; (RR)-labetalol is a nonselective beta antagonist; (SR)-labetalol is an alpha adrenergic antagonist and operates as a vasodilator [20]. The intravenous use of the drug has a 7:1 ratio of beta:alpha effect compared to a 3:1 effect as an oral agent [21] due to differential clearance of isomers. While intravenous use usually results in a reduction in HR, oral use frequently does not.

The hemodynamic effects of some drugs in pregnancy are well described. Some generalizations of effect by class of drug are reasonable. An understanding of the individual effects of single drugs in the paradigm of vectors described above can assist the clinician in achieving a desired effect, particularly in the context when more than a single drug is required. In most clinical settings, pharmacodynamic response cannot be assessed with bedside measurements of hemodynamics. However, pharmacodynamic response to β-blockers can be assessed by change in heart rate, and response to diuretic can be assessed by change in serum beta naturetic peptide.

17.5 Fetal pharmacodynamic response to hemodynamically active drugs

The fetus can be affected directly by drugs that cross the placenta and then act in the fetus. Alternatively, hemodynamically active drugs can, through their actions on the mother, change

the environment of utero-placental blood flow and, in doing so, impact the fetus. Most information regarding impact on the fetus has been derived from hypertensive pregnancies.

Baseline maternal hemodynamic conditions during hypertensive pregnancies impact fetal growth. In a cohort of 79 women with hypertension prior to 29 weeks, those with a TPR ≥1150 dyne•sec/cm^5 had, at delivery, a mean birth weight percentile of 18.7 compared to 38.8 among women with a TPR <1150 dyne•sec/cm^5 ($p=0.003$) [11]. The observed reduction in growth may be the result of less favorable conditions of utero-placental perfusion associated with elevated TPR. Alternatively, reduction in growth may be the result of placental injury that in turn results in destabilization and dysregulation of maternal vascular function and vasoconstriction. Superimposed on maternal baseline conditions, hemodynamically active drugs may further impact fetal growth. In a meta-analysis of antihypertensive trials, von Dadelszen et al. reported that every 10 mmHg reduction in MAP resulted in a 145 g reduction in birth weight [10]. The results were not influenced by duration of therapy or antihypertensive agent.

Reports of the impact of specific medications are limited. Atenolol has been the drug most broadly reported regarding the impact of fetal growth. In a small randomized trial of chronic hypertension, Butters et al. reported a reduction in birth weight associated with treatment with atenolol [22]. Of particular concern were two infants that were quite small. This study was small and women were treated with doses up to 200 mg per day. Patients not controlled with placebo were removed from the trial, 12.5% of the cohort. Follow-up after 1 year found no significant differences in birth weight. In a randomized trial of prehypertension characterized by elevated CO, the atenolol arm was associated with a reduction in birth weight compared to the placebo arm [23]. The reduction was characterized by fewer babies >4000 g and more babies <3000 g. The incidence of IUGR, <10th percentile, was 4.8% in the atenolol arm and 5.2% in the placebo arm. Neither group was different from a low risk, untreated control group. The smallest babies in the atenolol group had CO lowered below the mean for gestational age. In a report of 235 women with risk factors for preeclampsia treated with atenolol, the incidence of IUGR, <10th percentile, was 19.8% [12]. IUGR was strongly associated with a history of IUGR in a prior pregnancy ($p<0.001$) and treatment that permitted CO to fall below the mean for gestational age or TPR to rise above 1150 dyne•sec/cm^5.

The impact of clonidine on fetal growth has also been evaluated [19]. As reported above, the pharmacodynamic effects of clonidine are varied and probably dependent on the character of

an individual patient's central adrenergic output. In this report, one-third of women experienced a primary reduction in CO when treated with clonidine. Their initial hemodynamics and demographics were similar to the others. The gestational age at birth was also comparable. Nevertheless, the average birth weight was 2555 ± 726 compared to 2938 ± 784 among the women who experienced a vasodilatory effect ($p = 0.02$).

While there is no extensive data over a breadth of drugs on the impact of fetal growth, medications that impact maternal hemodynamics do seem to affect fetal growth. The work of von Dadelszen [10] suggests a broad but modest effect of lowering blood pressure on fetal growth. The experience with atenolol suggests that the impact is mediated by an associated reduction in CO, generally below pregnancy norms, or an elevation in TPR above pregnancy norms. This effect would be expected to be common to all β-blockers and potentially to diuretics that also reduce CO. The experience with clonidine suggests that the observations made with atenolol are neither specific to the drug itself nor specific to action at the beta receptor. The impact on fetal growth seems fundamentally related to changes in maternal hemodynamics that are reflected in changes in utero-placental perfusion. While these observations are preliminary, they offer a frame of reference regarding drug therapy.

17.6 Direct fetal effects of hemodynamically active drugs

A full review of the potential teratogenicity of hemodynamically active drugs is beyond the scope of this chapter. Frequently updated evaluations can be found in online databases such as Teris and Reprotox. For most medications, modest or limited data exist. That which exists is generally reassuring.

Angiotensin converting enzyme (ACE) inhibitors deserve special consideration. Substantial data suggest that the use of ACE inhibitors in the second and third trimesters is associated with a syndrome of oligohydramnios, pulmonary hypoplasia associated with oligohydramnios when severe and prolonged, neonatal oliguria and renal failure [24]. In addition fetuses have been reported with underdeveloped skull bone, presumably due to hypotension. These effects are seen most commonly with higher doses and longer administration. Small studies of low dose therapy have been reported without complications [24]. The renal effects are consistent with adverse impact in adults with excessive

dosing particularly in the face of renal insufficiency. These reports have been reviewed and summarized [24]. While fewer data exist regarding risk associated with angiotensin receptor blockers, the similar mechanisms of action and complications in adults would suggest similar concerns.

Conflicting reports have been published on the risks associated with ACE inhibitors in the first trimester. A report from the Tennessee Medicaid data suggests a risk ratio of 2.71 (95% CI 1.72 to 4.27) associated with use in the first trimester for major malformations and a risk ratio of 3.72 (95% CI 1.89 to 7.30) for cardiovascular malformations [25]. This study has been criticized for the potential for serious confounders and for potential ascertainment bias in the diagnosis of fetal anomalies. A subsequent report from the Swedish national database suggests an adjusted odds ratio of 2.59 (95% CI 1.92 to 3.51) for cardiovascular defects for women taking any antihypertensive without drug specificity and no incremental risk associated with ACE inhibitors [26]. The authors suggest that the underlying disease, chronic hypertension and the association with obesity, insulin resistance, and diabetes represent the true risks. Given the clear benefits of ACE inhibitors to the cardiovascular health of women outside pregnancy and the importance of entering pregnancy with optimal endovascular health, withholding these medications during the preconceptional period may be harmful and result in a worse outcome in pregnancy. While a clear recommendation cannot be made, the risks associated with exposure in the first weeks of pregnancy seem to be quite small. Risk–benefit counseling with individual patients is appropriate.

17.7 Pharmacokinetic changes in hemodynamically active drugs in pregnancy

Pregnancy is associated with clinically important changes in drug metabolism that are summarized in Chapter 3. These changes include an increase in GFR and upregulation of CYP3A, CYP2D6, and P-glycoprotein. Some drugs such as atenolol and digoxin have been specifically studied. For others, changes in clearance can be suggested from the known mechanism of drug clearance and knowledge regarding the impact of pregnancy on that mechanism. Knowledge regarding the precise timing of changes in clearance is frequently lacking, including when, at or around conception, they begin, when the changes reach a maximum, and when they completely resolve postpartum. For some drugs, a minor pathway of clearance outside pregnancy may

become the predominant pathway in pregnancy. In some cases, the inducible minor pathways that are relevant have not been described. Examination of specific drugs whose mechanisms of clearance are known can serve to elucidate the issues.

Digoxin may be prescribed in pregnancy to blunt a rapid ventricular response in women at risk for the development of atrial fibrillation such as those with mitral stenosis and left atrial enlargement. Digoxin has also been prescribed to treated fetuses with supraventricular tachycardia and associated fetal hydrops. To be effective in both cases, high serum levels are required. Renal clearance is increased in pregnancy 61% due in part to an increase in glomerular filtration rate. Renal secretion clearance, clearance in excess of filtration, increases by 120% attributed to an increase in P-glycoprotein activity (and possibly organic anion transporter polypeptides) [27]. To achieve therapeutic levels in the mother, digoxin must be dosed aggressively and drug levels monitored. P-glycoprotein is also expressed in the placenta operating as a reverse transporter limiting fetal exposure. Thus, digoxin monotherapy has had limited success in controlling fetal supraventricular tachycardia (see Chapter 5).

Atenolol is a selective β_1 receptor antagonist prescribed in pregnancy as an antihypertensive and for maternal heart rate control. Between 85 and 100% of atenolol is excreted unchanged. In pregnancy, atenolol renal clearance is strongly correlated with creatinine clearance. In the third trimester, renal clearance is increased by 31.5% compared with the clearance postpartum, and apparent oral clearance is increased by 37.5% [28]. Increased clearance usually requires an increase in total dose and the frequency of dosing to twice a day to achieve an equivalent and consistent effect. As discussed above, hemodynamic changes in pregnancy increase the tendency to tachycardia usually requiring an increase in dosing independent of pharmacokinetics to achieve an equivalent pharmacodynamic effect. Drug efficacy can be monitored effectively by monitoring maternal heart rate. Maternal responses to needed adjustments in atenolol dosing are therefore reasonably predictable. Drug exposure to infants through breast milk from mothers taking atenolol has been studied [29]. Weight adjusted dose to the fetus ranged from 5.9 to 14.6%; serum levels in the infants were below the detection limit of the assay (10 ng/mL); no reduction in heart rate was observed compared to infants whose mothers were not taking atenolol. Information from a prior case report had been used to suggest that breastfeeding on atenolol was potentially dangerous [30]. The drug levels reported in the case report are inconsistent with levels that could be achieved through drug delivered through breast milk.

Metoprolol is also a selective β_1 receptor antagonist prescribed for similar indications as atenolol. Outside pregnancy, metoprolol is used more commonly in cardiology practice. Therefore, pregnant patients with medical complications may enter pregnancy treated with metoprolol. Metoprolol is metabolized by CYP2D6 that is not known to be induced by pharmacological agents. In pregnancy, CYP2D6 activity is increased by 25.6% at mid-pregnancy and by 47.8% at term with considerable variability between patients presumably due to genetic polymorphisms with different activity [31]. Metoprolol apparent oral clearance is increased by 292% in the third trimester of pregnancy with significant variability between patients [32]. Metoprolol therefore becomes a challenging drug to use in pregnancy. Not only is clearance increased, but maximal change in clearance is not achieved until near term and considerable variability between patients in clearance and change in clearance is observed. By monitoring heart rate, appropriate changes in dosing can be made. Total dose may need to be increased 3–4-fold to achieve an equivalent pharmacodynamic effect. Dosing frequency must be increased.

Labetalol is a combined α–β receptor antagonist. It is a chiral drug with two diastereomeric pairs of racemates. The (RR)-labetalol is responsible for β-blocking activity; the (SR)-labetalol is responsible for α-blocking activity. Labetalol is eliminated by glucuronidation by UDP-glucuronosyltransferase. In a small study of hypertensive pregnant women the terminal elimination half-life after oral administration for the total drug has been reported to be 1.7 ± 0.27 hours compared to 6–8 hours in non-pregnant subjects [33]. In a larger study of clearance of stereoisomers, differences were observed depending on the route of administration [19]. With intravenous treatment, the clearance of (RR)-labetalol (β-blocking activity) and (SR)-labetalol (α-blocking activity) were equivalent (0.8 vs. 0.9 L/h/kg). When administered orally, the apparent oral clearance for (RR)-labetalol (β-blocking activity) was 1.7 times greater than clearance for the (SR)-labetalol (α-blocking activity) (2.9 vs. 4.4 L/h/kg). The increased clearance of labetalol in pregnancy requires an upward dose adjustment and more frequent dosing. This difference in clearance of stereoisomers suggests a difference in pharmacodynamic effect based on route of administration. Oral administration would be expected to have less β-blocking activity than intravenous administration. The pharmacodynamic effect can be assessed by monitoring heart rate. If a β effect is needed, oral labetalol may not be an optimal choice.

Nifedipine is a dihydropyridine calcium channel blocker. It is prescribed in pregnancy as an antihypertensive with pure

vasodilator properties. It is also used to inhibit uterine contractions. Nifedipine is metabolized by CYP3A whose activity is increased in pregnancy [27]. The apparent oral clearance of midazolam, a marker for CYP3A activity, is increased by 108% in pregnancy compared to postpartum. In a small study comparing pregnant hypertensive women, the apparent oral clearance in pregnancy was four-fold higher than non-pregnant controls [34]. Again, the increased clearance in pregnancy requires an upward dose adjustment and more frequent dosing. Data on CYP3A and nifedipine can probably be generalized to other calcium channel blockers as substrates for CYP3A.

Sildenifil is a cGMP-specific phosphidiesterase inhibitor used in the treatment of pulmonary hypertension. It achieves its vasodilatory pharmacological effect by increasing nitric oxide levels in the pulmonary arterioles. Pulmonary hypertension is a rare but lethal complication of pregnancy. Reports of maternal mortality range from 20 to 50%. Appropriate, steady-state dosing of sildenafil is of critical importance. Unlike β-blockers where pharmacodynamic effects can be monitored by heart rate, the effect of sildenafil cannot be monitored at the bedside. Given the rarity and acuity of the disease in pregnancy, informative pharmacokinetic studies are unlikely to be performed. Sildenafil metabolism is principally mediated by CYP3A. Based on knowledge from studies of midazolam, increased clearance of sildenafil would be expected in pregnancy. Empiric upward total dose adjustment and more frequent dosing would be appropriate.

Clonidine is prescribed as an antihypertensive in pregnancy. It is a central α agonist that achieves its antihypertensive effect by decreasing central adrenergic output similar to methyldopa. As discussed above, its hemodynamic effects are variable. Outside pregnancy, 50 to 60% of the drug is excreted unchanged in the urine. In pregnant women, apparent oral clearance is increased by approximately 83% with only 36% excreted unchanged in the urine [35]. Due to these observations, human microsome studies were performed which demonstrated that clonidine was a CYP2D6 substrate that accounts for its increased clearance in pregnancy [35]. Again, increased clearance in pregnancy requires an upward dose adjustment and more frequent dosing. In the case of clonidine, increased CYP2D6 activity in pregnancy changed the predominant pathway of clearance in a previously undescribed pathway. Other drugs, particularly older drugs, may have previously undescribed metabolic pathways that are relevant to pregnancy.

Pregnancy is associated with important hemodynamic changes that, while well tolerated by healthy women, can result in clinical decompensation in the context of medical complications.

Pregnancy is also associated with clinically significant changes in pathways of drug clearance that impact the dosing of medications used to manage cardiovascular disease and maintain cardiovascular homeostasis. To achieve the desired therapeutic effect, the clinician must establish treatment goals and recognize changes in drug metabolism that will impact the desired pharmacodynamic effects. Since maternal hemodynamics and drug metabolism change dynamically over the course of pregnancy, the treatment strategy must also be dynamic over the course of pregnancy anticipating these changes. Dosages may need to be increased; the timing of doses may need to be more frequent. In some circumstances, therapy can be based on data specific to the circumstances. In many other cases, an understanding of classes of hemodynamic action and mechanism of drug metabolism will be needed to make more empiric decisions which then must be reevaluated for desired effect.

Key points

- Substantial changes in cardiovascular physiology occur during pregnancy that may require management through initiation of medications or changes in existing dosing.
- The pharmacodynamic changes associated with hemodynamically active drugs occur in the context of changing baseline conditions throughout the course of pregnancy and postpartum period.
- The pharmacodynamic changes associated with hemodynamically active drugs can impact utero-placental perfusion and therefore the welfare of the fetus.
- The pharmacokinetics of medications used in pregnancy are impacted by increased maternal GFR, upregulation of pathways of drug metabolism such as CYP3A and CYP2D6, and upregulation of transporters such as P-glycoprotein.
- Upregulation of minor pathways of drug metabolism in pregnancy may substantially alter primary mechanisms of drug disposition.
- Specific information regarding pharmacokinetics and dynamics of specific drugs in pregnancy may be lacking. General assumptions regarding these drugs can be made from mechanism of action and disposition that can then be used to guide

therapy. The effectiveness of treatment must then be confirmed clinically.

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Antidepressants in Pregnancy

18

Elizabeth M. LaRusso and Marlene P. Freeman

18.1 Introduction

Depression is common among women during pregnancy, with prevalence estimates indicating that 14–23% of pregnant women will experience a depressive disorder during pregnancy [1]. Although pregnancy is a time of increased health care utilization, pregnant women are less likely than non-pregnant women to receive psychiatric care, and a significant amount of women suffering from psychiatric illness during pregnancy are neither identified nor treated [2]. The size, complexity, and frequently inconsistent nature of the literature regarding the safety of psychotropic medications in pregnancy is daunting; consequently, many physicians are reluctant to manage psychiatric illness during pregnancy. Untreated maternal depression may be associated with

significant morbidity or even mortality for mother–infant pairs, and both psychiatric illness and psychotropic medication must be conceptualized as agents of fetal exposure. Prescribing psychiatric medication to pregnant women requires a complex risk–benefit calculus that balances the risks of untreated psychiatric illness to mother and fetus with the potential risks of medication use during pregnancy; ideally this process includes shared decision making between the patient and psychiatric, obstetric, and/or primary care providers. The goal of this chapter is to provide an overview of the management of depression during pregnancy and to summarize the most relevant issues impacting clinical decision making.

Symptoms of depression include depressed mood or anhedonia for at least a 2-week period, accompanied by symptoms that include changes in sleep, appetite, energy, concentration, psychomotor activity, feelings of guilt or worthlessness, and/or suicidal ideation [3]. Diagnosing depression in pregnant women can be complicated by the fact that many symptoms of depression overlap with normal symptoms of pregnancy; consequently, the presence of affective symptoms such as feelings of guilt or worthlessness, anhedonia, and thoughts of suicide may more strongly support the diagnosis of depression in pregnant women. Risk factors for developing perinatal depression encompass elements of a woman's genetics, hormonal/reproductive history, current stressors, and life experiences; biologic factors that have consistently been associated with increased risk include a past history of depression or premenstrual dysphoric disorder and a family history of depression. Psychosocial factors, including stressful life events and lack of perceived social support, have also consistently been found to predict perinatal depression [4].

18.2 Effects of untreated perinatal depression on women and children

Untreated perinatal depression is associated with significant morbidity for mother–infant pairs via association with adverse obstetric outcomes and as a risk factor for poor maternal health, inadequate prenatal care, and postpartum depression [5, 6]. Poor nutrition, increased number of exposures to medications or herbal remedies, increased alcohol and tobacco use, and decreased compliance with prenatal care have been consistently associated with untreated psychiatric illness during pregnancy [7]. Increased rates of hypertension, preeclampsia, and gestational diabetes have also been associated with untreated maternal depression [8]. Data regarding

specific adverse obstetric outcomes resulting from untreated depression during pregnancy are inconsistent. Miscarriage, fetal growth effects (low birth weight and intrauterine growth restriction), and preterm delivery have all been associated with untreated maternal depression. The strongest association appears to be with preterm birth; however, because of methodological limitations of the available data, it is not currently possible to draw definitive conclusions regarding associations between untreated maternal depression and these adverse reproductive outcomes [7–9].

In addition to the potential negative impact on pregnancy outcomes, perinatal depression is associated with disrupted maternal–infant bonding, increased irritability, decreased attentiveness, and decreased facial expressions in neonates [1, 10, 11]. Children and adolescents born to depressed mothers are at risk for delayed cognitive and language development, lower IQ, and increased prevalence of psychiatric and emotional problems [1, 7, 11, 12]. Depression that begins during pregnancy frequently continues or worsens after delivery.

18.3 Approach to treatment

Current guidelines created by a joint task force of the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG) recommend individual or group therapy as an initial treatment approach for pregnant women with mild to moderate depression [1]. For women who are unable to access or have not responded to evidence-based psychotherapies, who are experiencing an episode of moderate to severe depression during pregnancy, and/or who have a history of recurrent severe depression or suicidality, initiation or maintenance of psychiatric medications is likely indicated [1].

It is ideal to evaluate women with a history of psychiatric illness prior to pregnancy in order to generate an individualized treatment plan. However, since 50% of pregnancies in the United States are unplanned, preconception evaluation is often not feasible in practice [13]. Discontinuation of antidepressants during pregnancy is common and is associated with significant increase in relapse. In one large study, women who stopped antidepressants had a 68% recurrence rate of depressive symptoms as compared to 26% for women who continued their medications [14]. Frequently, patient and physician concerns about potential teratogenesis or other negative neonatal outcomes overshadow consideration of the risks associated with untreated maternal

psychiatric illness. This decision-making process is complicated by several factors, including varying fetal risks at different stages of gestation, inadequacy of the US Food and Drug Administration (FDA) medication categorization system, and limitations of currently available data regarding the safety of antidepressants in pregnancy [1, 7].

The approach to prescribing antidepressants in pregnancy can be guided by several general principles. The goal of treatment is remission of depressive symptoms, as inadequately treated depression subjects the fetus to risks associated both with maternal illness and with medication exposure. Choosing a medication with an established safety profile and a proven history of efficacy in the patient maximizes the potential for symptom response and minimizes potential risks to the fetus. One medication at higher dose is preferred to multiple medications at lower doses in order to decrease the total number of fetal exposures; pregnant women should receive the minimal *effective* dose of a single antidepressant [1, 7].

Antidepressant dose requirements may increase across gestation as a consequence of induction of cytochrome enzymes 3A4 and 2D6 that increase drug metabolism in the second half of pregnancy [1, 15]. Although there is a limited literature revealing lowered levels of both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in many women in late pregnancy, there is wide interpersonal variability in the pharmacokinetic changes of these medications across gestation. Currently, there are no evidence-based guidelines for altered dosing or therapeutic monitoring of antidepressants during pregnancy [16].

Considering the possibility of increased antidepressant metabolism during pregnancy, women must be monitored closely for the reemergence of depressive symptoms, especially during the third trimester. The possibility that some women may require higher doses of antidepressants in late pregnancy contradicts the clinical approach that advocates tapering antidepressants prior to delivery in hopes of mitigating potential adverse neonatal effects of medication use. Tapering antidepressants proximal to delivery has not been shown to decrease the potential risk of neonatal complications associated with medication use in late pregnancy [17]. Discontinuing antidepressants has been associated with significant increase in relapse of depressive symptoms, and currently neither the APA nor ACOG recommend tapering antidepressants prior to delivery [1, 7, 14].

In addition to possible changes in antidepressant dose requirements across gestation, optimal management of perinatal mood and anxiety disorders includes recognizing the potential for

postpartum illness. Women who are not already engaged in psychotherapy should be provided with referrals to begin depression-focused psychotherapy, specifically cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT), both of which have been well studied for perinatal depression [16]. Supportive dynamic psychotherapy has been less well studied in pregnancy but is a reasonable approach if CBT and IPT are not available [1].

In addition to specific considerations regarding antidepressant use in pregnancy, prescribers should be familiar with current practice guidelines for the treatment of depression in general. There is no specific antidepressant that is better than another, and the choice of medication should be based on side effect profile, safety, tolerability, and previous response to medication in the individual patient [16]. Antidepressants should be started at low dose and titrated over time to effectiveness; the speed of the titration depends upon the severity of associated side effects. Frequently, patients require 4 to 8 weeks of antidepressant treatment prior to experiencing moderate symptom reduction. Once remission of depression has been achieved, patients with less than three prior depressive episodes should be continued on antidepressants for a *minimum* of 4 to 9 months prior to considering discontinuation while patients with three or more episodes of major depression may require maintenance antidepressant treatment indefinitely [16]. Tapering antidepressants slowly over at least 2 weeks decreases both the risk of relapse of depressive illness and the severity of antidepressant discontinuation syndrome (flu-like symptoms, paresthesias, insomnia) which is associated more strongly with SSRIs with short half-lives [16, 18]. Decisions regarding tapering and discontinuation should be made in consultation with prescribing clinicians and patients should be monitored to assess for reemergence of depressive symptoms.

18.4 Potential risks of selective serotonin reuptake inhibitor (SSRI) use during pregnancy

Due to their efficacy, tolerability, and safety profile, SSRIs are currently among the first-line pharmacologic treatments of major depression, and recent data suggest that up to 13% of US pregnancies have antidepressant exposure [19]. All SSRIs, indeed all psychotropic medications, cross the placenta and are excreted in breast milk [7]. The reproductive safety of SSRIs in pregnancy has been extensively studied. However, the data are often

contradictory and limited by several factors, including the lack of randomized controlled trials, small sample sizes and limited power of many studies, the absence of information about disease state of the mother, and the failure to control for multiple confounding variables that impact reproductive outcomes [1]. Currently available data in the major domains of reproductive toxicity will be summarized here.

18.4.1 Obstetric outcomes

Similar to untreated depression during pregnancy, miscarriage, fetal growth effects, and preterm delivery have all been inconsistently associated with SSRI use during pregnancy [1, 9]. The APA and ACOG treatment guideline report states that currently there is not enough evidence to establish an association between SSRI use in early pregnancy and miscarriage [1]. There appears to be adequate evidence to support a true association between low birth weight and SSRI use in pregnancy; however, there is currently not enough evidence to support causality, and the impact of the underlying disorder and other confounders must be considered [1, 6]. Finally, a growing literature supporting an association between preterm delivery and SSRI use in pregnancy is emerging, including at least one study that attempts to control for maternal depression [1, 9]. Studies that do identify an association between preterm delivery and SSRI use in pregnancy tend to find a small effect size, with decrease in gestational age of less than or equal to 1 week [1]. Currently it remains difficult to differentiate whether observed adverse obstetric outcomes are related to antidepressant treatment or to depressive illness itself, and research that adequately controls for underlying disease state is necessary to either support or refute these associations.

18.4.2 Congenital malformations

There is a large amount of evidence supporting the conclusion that SSRIs as a group are not associated with increased risk of major congenital anomalies [1, 6, 7, 9]. There is some evidence that individual SSRIs may be associated with very low risk of minor malformations; however, this finding is not widely replicated [1, 6, 11, 20]. Specific concern over paroxetine use and increased risk of congenital cardiac malformations emerged in 2005 when GlaxoSmithKline reported a 1.5–2-fold increase in atrial and ventricular septal defects in infants exposed to paroxetine in the first trimester. This finding prompted a change in the medication's FDA pregnancy rating from C to D and generated the current recommendation that, if possible, paroxetine should be avoided during the first

trimester of pregnancy and in women contemplating pregnancy. Since 2005, other studies have not supported the association between paroxetine and cardiac malformations; however, enough uncertainty exists that avoiding first-trimester fetal exposure to paroxetine and considering fetal echocardiography in exposed cases continues to be recommended [1, 7]. In summary, the overwhelming convergence of data suggests that the absolute risk of congenital malformations associated with SSRI use during early pregnancy, if indeed there is a risk at all, is small; consequently SSRIs are not considered to be teratogenic [1, 6, 7, 9].

18.4.3 Persistent pulmonary hypertension of the newborn (PPHN)

PPHN is a clinical syndrome characterized by failure of the normal fetal-to-neonatal circulatory transition causing right-to-left shunting of blood through the ductus arteriosus and foramen ovale and subsequent neonatal hypoxia. PPHN is a rare condition: baseline population rates are 1–2 infants/1000 live births, or 0.1–0.2%. A 2006 case–control study noted an association between maternal use of SSRIs after 20 weeks of pregnancy and increased risk of PPHN, with adjusted odds ratio of approximately 6, raising the absolute risk to 6–12/1000 births [20]. Subsequent studies have revealed either lower absolute risk or no association, and no studies to date have established a causal link between SSRI use in late pregnancy and PPHN [1, 7]. In December 2011, the FDA released a drug safety communication concluding that there is currently insufficient evidence to support a potential link between SSRI use in pregnancy and PPHN and recommending that prescribers continue to treat depression in pregnancy according to their current clinical practice. In summary, most of the evidence suggests that there is not an association between PPHN and use of SSRIs in late pregnancy, although it has been reported. However, even if this association proves to be true, the absolute risk remains quite low and there is currently no evidence that tapering SSRIs proximal to delivery decreases this potential risk.

18.4.4 Poor neonatal adaptation

Exposure to SSRIs in late pregnancy has also been associated with transient neonatal distress, including tachypnea, jitteriness, poor muscle tone, weak cry, and irritability. This symptom constellation is often termed “poor neonatal adaptation” or “withdrawal” and lasts from several hours to 2 weeks post-delivery. Poor neonatal adaptation occurs in roughly 15–30% of infants of mothers who used SSRIs in late pregnancy and symptoms are generally mild, transient, and managed by supportive care in special care nurseries.

Symptoms have been reported with all SSRIs but the highest reported rates for this syndrome occur with fluoxetine and paroxetine [1, 7, 10]. It is unclear if these symptoms represent neonatal serotonin toxicity, a discontinuation phenomenon, or are the result of some as yet undiscovered mechanism, and tapering antidepressants towards the end of pregnancy has not been shown to decrease neonatal symptoms [17]. Future studies examining potential impact of SSRI exposure on neonates must control for the impact of maternal psychiatric illness, as behavioral symptoms such as irritability and decreased attentiveness have also been strongly associated with poorly treated maternal depression [1, 10, 11].

18.4.5 Neurodevelopmental outcomes

The impact of prenatal antidepressant exposure on long-term cognitive, behavioral, and motor outcomes in exposed children has not been extensively investigated. Despite a general paucity of information, the available data are largely reassuring. The majority of studies show no difference in measures of intelligence, language development, or behavior between children exposed to antidepressants *in utero* and unexposed controls. Two studies showed subtle delays in psychomotor development; however, these studies had significant methodological problems. Larger, well-designed studies with increased length of follow-up are required to either support or refute associations between *in utero* exposure to SSRIs and negative neurodevelopmental outcomes [11].

18.5 Potential risks of non-SSRI antidepressant use during pregnancy

Non-SSRI antidepressants include bupropion, duloxetine, mirtazepine, nefazodone, trazodone, and venlafaxine, and as a group they have been much less well studied than the SSRIs. Currently available data do not suggest increased risk of adverse obstetric outcomes, major congenital malformations, or PPHN with non-SSRI antidepressants in pregnancy. A syndrome of poor neonatal adaptation similar to that attributed to SSRIs has been consistently documented in infants born to mothers who have used non-SSRI antidepressants in late pregnancy, and virtually no information exists on long-term neurocognitive outcomes in exposed children [1, 7, 11, 20]. This general lack of negative findings should be interpreted with caution as it currently reflects a paucity of data as opposed to a true absence of risk. In general,

non-SSRI antidepressants should not be considered first-line agents for treatment of depression during pregnancy unless there is a compelling clinical reason to use them instead of medications with more established safety profiles. Such indications may include established history of efficacy in an individual patient, lack of response or inability to tolerate SSRIs, fetal exposure to non-SSRI antidepressant in early pregnancy, or patient preference.

18.6 Potential risks of older antidepressant use during pregnancy

Tricyclic antidepressants (TCAs), the mainstay of treatment for depression prior to the introduction of SSRIs in the late 1980s, have been well studied in pregnancy; due to their side effect profile and lethality potential in overdose they are no longer considered a first-line treatment for depression. Similar to the SSRIs, there is conflicting data regarding potential association with obstetric complications like low birth weight and preterm delivery, while most studies reveal no association with increased rates of congenital malformations [1, 7]. The use of TCAs in late pregnancy has been associated with transient neonatal toxicity and withdrawal symptoms including jitteriness, tachycardia, mild respiratory distress, hypertonia, and irritability; currently there is no evidence of negative long-term neurobehavioral sequelae [1, 7, 12]. Monoamine oxidase inhibitors (MAOIs) are infrequently used in modern clinical practice due to their severe side effect profile; they are essentially contraindicated during pregnancy due to increased rate of congenital anomalies in animal studies and the possibility of precipitating a hypertensive crisis if tocolytic medications are required to postpone labor.

18.7 Anxiety

Anxiety disorders such as generalized anxiety, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder may exist independently of, or co-morbid with, depressive illness. A detailed discussion of anxiety disorders during pregnancy is beyond the scope of this chapter; however, the approach to management of anxiety during pregnancy is similar to that of depression and SSRIs are currently considered a first-line treatment for anxiety spectrum illness.

18.8 Summary

Depression during pregnancy is associated with significant risks for women and infants, and the goal of treatment should be remission. Ideal management of depressed pregnant women includes maximization of non-psychopharmacologic treatments such as psychotherapy and utilization of antidepressant medication for pregnant women with moderate to severe depressive symptoms. Optimal patient care includes an individualized treatment approach that balances the potential maternal and fetal risks of untreated depression with the potential risks of antidepressant exposure. Avoiding polypharmacy, using the lowest effective dose of a medication with a history of efficacy in the individual patient, and monitoring patient response over time are strategies that may mitigate potential risks.

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Uterine Contraction Agents and Tocolytics

19

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19.1 Introduction

Human parturition is a complicated process that is not yet completely understood. There are several pathways through which parturition can be initiated. The process itself begins long before "labor" can be clinically detected. Both biochemical and hormonal factors prepare the uterus and cervix for delivery of the fetus. Physicians have long sought to identify drugs that could be used to both induce and arrest labor. Medications currently used for these purposes are referred to as uterotonics and tocolytics, respectively. Some of these medications have additional indications such as the treatment of uterine atony or cervical ripening. Most are not FDA approved and their use in obstetrics is considered off-label. This chapter will serve to review the indications, mechanism of action, dosing, and evidence to support the use of the most common uterotonics and tocolytics prescribed in modern obstetric practice.

19.2 Uterine contraction agents (uterotonics)

Uterotonics are by far the most common drugs administered on any labor and delivery suite. Clinically, they are used primarily for labor induction/augmentation and to control postpartum

hemorrhage. All agents in this category cause uterine contraction, but each does so through a different pathway. It is important to have a working knowledge of each medication, as each can cause as much harm as good.

19.2.1 Pitocin (oxytocin)

Pitocin is one of the most potent uterotonic agents available. It is currently approved for medically indicated labor induction (i.e. premature rupture of membranes, diabetes, hypertension, preeclampsia, etc.), labor augmentation, and as an adjunctive therapy in the management of an incomplete or inevitable abortion. Additionally, Pitocin is a first-line agent for the treatment of postpartum hemorrhage secondary to uterine atony or subinvolution [1].

Pitocin is a polypeptide composed of nine amino acids. It is identical in structure to its endogenous counterpart, oxytocin. Pitocin stimulates uterine contractions by increasing intracellular calcium. Pitocin binds to the oxytocin receptor located on the myometrial cell membrane and stimulates phospholipase C (Figure 19.1). This

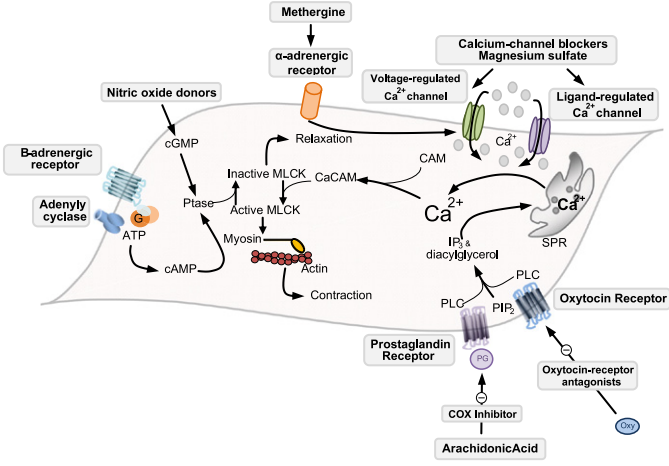

Figure 19.1 Contractant and relaxant pathways of a myometrial cell. Ptase – Phosphate kinase; MLCK – Myosin light-chain kinase; CaCAM – Calcium–calmodulin complex; CAM – Calmodulin; PLC – Phospholipase C; PIP_2 – Phosphatidylinositol 4,5-biphosphate IP_3 – Inositol triphosphate; Pg – Prostaglandin; Oxy – Oxytocin; SPR – Sarcoplasmic reticulum

leads to increased production of inositol triphosphate which acts to mobilize intracellular calcium by promoting release from the sarcoplasmic reticulum [2]. Binding to the oxytocin receptor also induces an influx of extracellular calcium through nonselective, cation channels on the myometrial cell membrane [2]. Intracellular calcium then binds with calmodulin to form the calcium–calmodulin complex. This complex activates myosin light-chain kinase (MLCK), the key regulator of smooth muscle contractility [3]. MLCK phosphorylates myosin which in turn binds actin, initiating myometrial smooth muscle contraction.

Pitocin is widely distributed throughout the extracellular fluid, and has a half-life of 3–10 minutes [4–7]. Pitocin is primarily metabolized by the kidney, and it is rapidly removed from plasma. This rapid metabolism can in part be attributed to the 50% increase in glomerular filtration rate observed during pregnancy. Additionally, the half-life is further reduced in late pregnancy and during lactation secondary to inactivation by oxytocinase [7].

At least 4–5 half-lives are necessary for a drug administered intravenously as a continuous infusion to achieve steady state [8, 9]. Steady state is the point where the plasma concentration is stable such that the full effect of that concentration of the medication will be observed. This is the basis for the recommendation to increase a Pitocin infusion every 40 minutes (10 minute half-life × 4 half-lives). However, when infusion protocols start at 1 mU/min, a great deal of time is required to achieve a clinical response. Thus, Pitocin is typically increased at more frequent intervals with close maternal and fetal monitoring.

Currently, there is no consensus regarding the optimal dosing regimen for Pitocin for labor induction or augmentation. Both low and high dose protocols have been shown to be safe and effective [10]. Both meta-analysis and a randomized controlled trial report that high dose protocols with infusion increases at shorter intervals are associated with shorter labor, decreased chorioamnionitis, decreased need for cesarean section secondary to labor dystocia, and less neonatal sepsis [11, 12]. However, these protocols are also associated with tachysystole with associated fetal heart rate changes [11, 12].

Suggested Pitocin regimens start at 0.5–6 mU/min, with increases of 1–6 mU/min every 15–40 minutes. Studies have shown that infusion rates up to 6 mU/min result in plasma concentrations of Pitocin similar to concentrations achieved during spontaneous labor [13]. The maximum dose of Pitocin has not been established, but most protocols do not exceed 42 mU/min [14].

Pitocin is also used as an adjunctive therapy for incomplete, inevitable, and elective abortions in the first and second trimester. It can be administered after delivery of the placenta to aid with

uterine contraction and hemostasis. This can usually be achieved with standard postpartum Pitocin protocols (10 units in a 500 cc bag of normal saline administered over 3–4 hours). High dose Pitocin protocols have been described and shown to be as effective as other methods of midtrimester labor induction. One can refer to Ramsey and Owen's review entitled "Midtrimester cervical ripening and labor induction" for specific protocols [15].

In the postpartum setting, Pitocin is considered a first-line agent for the treatment of uterine atony. It can be administered as a bolus of 3–6 units intravenous (IV), as a continuous infusion of 10–40 units in 1 liter of normal saline (NS) infused at a rate adjusted to control uterine atony (range 10–80 IU/1L NS, with higher doses considered safe), or as an intramuscular injection of 10 units directly into the thigh, gluteal muscle, or myometrium [16].

Pitocin is considered a pregnancy category C drug because of the potential for fetal hypoxia in the setting of uterine tachysystole. Appropriate precautions (i.e. administration via an infusion pump, continuous fetal and uterine monitoring, and immediate availability of obstetrician) should always be taken to ensure patient safety. Additional maternal side effects include nausea, vomiting, and hyper- or hypotension. A rare but serious maternal side effect is water intoxication secondary to the antidiuretic properties of Pitocin. This condition has been reported in women who received Pitocin in D5 water and/or high dose protocols (>20 mU/min) for prolonged periods of time. To avoid this, it is recommended that Pitocin be administered with an isotonic saline solution, strict intake and output should be monitored, and, per product labeling, the total Pitocin dose should not exceed 30 units in a 12 hour period [1].

19.2.2 Methergine (methylergonovine)

Methergine, a semi-synthetic ergot alkaloid, is a potent uterotonic that increases the force and frequency of uterine contractions at low doses. At higher doses, methergine can increase basal uterine tone and cause uterine tetany. In obstetrics, methergine is indicated for the treatment of postpartum hemorrhage secondary to uterine atony or subinvolution [17].

The uterotonic properties of ergot alkaloids have been known for centuries. Their use as a labor stimulant was first described by Adam Louicer in 1582 [18]. Although the uterine effects of ergots were discovered hundreds of years ago, the exact mechanism by which methergine causes myometrial contraction is not known. Ergot alkaloids are known to cause vasoconstriction, uterine contractions, and stimulation of central dopamine receptors [18].

Ergots have been shown to bind alpha adrenergic, serotonin (5-HT), and dopamine D1 receptors [19]. Based on several studies, it is likely that methergine specifically interacts with alpha adrenergic receptors on the myometrial cell (Figure 19.1). This interaction alters transmembrane calcium channel activity, causing an influx of calcium into the myometrial cell and activation of the contraction cascade [18, 20, 21].

After oral administration or intramuscular injection, methergine is rapidly absorbed and distributed throughout the plasma and extracellular fluid. Approximately 25% more medication is absorbed via the intramuscular route compared to oral [17]. Methergine is metabolized by the liver and excreted in the urine. The half-life of methergine is 3.4 hours (1.5–12.7 hours) when administered intramuscularly [17].

In the setting of postpartum hemorrhage, the preferred dose and route of methergine administration is 0.2 mg intramuscularly every 2–4 hours, for a maximum of five doses. It can also be directly injected into the uterus; however, one should be careful to avoid intravascular administration as this has been reported to result in acute coronary vasospasm and/or myocardial infarction [22–24]. Alternatively, the medication can be administered orally at a dose of 0.2 mg every 6–8 hours for 2–3 days (maximum of 7 days).

Methergine should be avoided by those who are pregnant, those with uncontrolled hypertension, and those with a sensitivity to the drug. Methergine use in postpartum women with preeclampsia should only be considered if the benefits outweigh the risks. Common side effects include nausea, vomiting, hyper- or hypotension, and headache. Patients should be monitored closely for any adverse side effects after administration of the drug [17].

19.2.3 Prostaglandins

Prostaglandins are potent uterotonics with utility in several circumstances in obstetrics including facilitation of second trimester abortion, cervical ripening, labor induction, and the treatment of postpartum hemorrhage. For the purposes of this chapter we will focus on their effect on the uterus in the setting of postpartum hemorrhage. The prostaglandins used to treat postpartum hemorrhage include 15-methyl $PGF_{2\alpha}$ (Carboprost, Hemabate), Prostin E_2 (dinoprostone), and Prostaglandin E_1 (Misoprostol, Cytotec).

The prostaglandins used in obstetric practice are synthetic analogs of endogenous prostaglandins which are cyclic, unsaturated

C_{20} fatty acids [25]. Prostaglandins are grouped into subtypes (A,B,C,D,E,F,G,H,I,J,K) according to the chemical substitution on the pentane ring. Specific to obstetrics, the F subtype has two hydroxyl groups on the pentane ring and the E subtype has one keto and one hydroxyl group [25] (Figure 19.2).

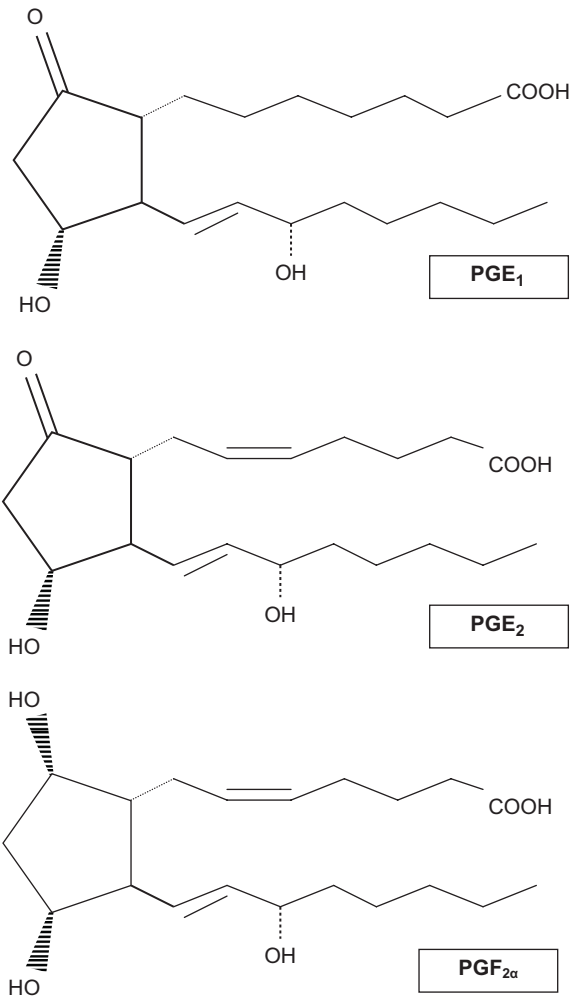

Figure 19.2 Prostaglandin E_1, Prostaglandin E_2, and Prostaglandin $F_{2\alpha}$.

Prostaglandins cause uterine contractions by altering membrane permeability and increasing intracellular calcium [25–27]. They promote the formation of gap junctions, facilitating transmission of signals throughout the myometrium [28]. Additionally, they upregulate the expression of oxytocin receptors in the uterus which in turn promotes contractility [28] (Figure 19.1).

The synthetic prostaglandins are rapidly absorbed and distributed systemically in the plasma. The half-life of endogenous prostaglandins ranges from a few seconds to minutes as they are rapidly metabolized in the lungs and liver. The synthetic prostaglandins have much longer half-lives ranging from 2.5 to 5 minutes for Prostin E_2 (dinoprostone), approximately 35 to 40 minutes for $PGF_{2\alpha}$ (Hemabate, Carboprost), and 20 to 40 minutes for PGE_1 (Misoprostol, Cytotec) [29–31]. All are excreted via the kidneys.

For the treatment of postpartum hemorrhage, prostaglandins are either second- or third-line agents depending on patient comorbidities. For instance, in patients with hypertension, after oxytocin a prostaglandin would be a more appropriate second-line agent than would an ergot alkaloid. Among the various prostaglandins, the second and third generation formulations (15-methyl $PGF_{2\alpha}$ and PGE_1) are preferred over first generation formulations (PGE_2), as the side effect profile is somewhat improved.

15-Methyl $PGF_{2\alpha}$ (Hemabate, Carboprost) is administered at a dose of 0.25 mg IM (or intramyometrial) every 15–90 minutes with an eight dose (or 2 mg) maximum. PGE_1 (Misoprostol, Cytotec) is administered at a dose of 800–1000 mcg and placed rectally. Prostin E_2 (dinoprostone) can be used as a 20 mg rectal or vaginal suppository (Table 19.1).

Two studies have shown rectal Misoprostol to be as effective as oxytocin for the management of the third stage of labor in the prevention of hemorrhage [32, 33]. However, because of the better side effect profile and cost, Pitocin is the preferred first-line agent.

15-Methyl $PGF_{2\alpha}$ (Hemabate, Carboprost) should be avoided in patients with asthma or pulmonary disease as it can cause acute bronchoconstriction. Prostin E_2 (dinoprostone) should be avoided in women with hypotension as it can acutely drop the diastolic blood pressure. There are no absolute contraindications to PGE_1 (Misoprostol, Cytotec) for the treatment of postpartum hemorrhage other than sensitivity to the drug.

Common side effects of all the prostaglandins above include abdominal pain, diarrhea, nausea, vomiting, headache, paresthesias, fever, and shivering. The side effect profile improves with second and third generation formulations ($PGF_{2\alpha}$ and PGE_1). All patients should be monitored for the development of side effects after administration of the medication.

Table 19.1 Uterotonics

Drug	Clinical indication	Route	Dose	Frequency	Considerations
Pitocin (oxytocin)	Induction/ augmentation of labor	Intravenous	Low dose regimen: start at 0.5–1 mU/ min	Increase by 1–2 mU/ min every 15–40 min, maximum dose 42 mU/ min	Titrate to maternal response and fetal tolerance
			High dose regimen: start at 4–6 mU/ min	Increase by 4–6 mU/ min every 15–40 min, maximum dose 42 mU/ min	Titrate to maternal response and fetal tolerance
	Postpartum hemorrhage	Intravenous	3–6 IU as bolus	Once	Monitor for hypotension, especially with IV administration
		Intravenous	10–80 IU in 1L of normal saline	Continuous	
		Intramuscular	10 IU (thigh, gluteal, or myometrial)	Once	

Methergine (methylergonovine)	Postpartum hemorrhage	Intramuscular	0.2 mg	Can repeat dose every 2–4 hours, maximum 5 doses	Avoid in women with uncontrolled HTN. Use in women with preeclampsia or HTN should only be considered if benefits outweigh risk
		Oral	0.2 mg	Can repeat dose every 6–8 hours for 2–3 days (maximum 7 days)	
		Intravenous	–	–	Avoid, can cause severe HTN, CNS and coronary artery vasospasm, and hemorrhage
Hemabate (15-methyl $PGF_{2\alpha}$)	Postpartum hemorrhage	Intramuscular	0.25 mg	Can repeat dose every 15–90 minutes (maximum 8 doses or 2 mg)	Avoid in patients with asthma or pulmonary disease, can cause bronchoconstriction
		Intramyometrial	0.25 mg		
Cytotec (Misoprostol, PGE_1)	Postpartum hemorrhage	Rectal	800–1000 mcg	Single dose	No absolute contraindications other than sensitivity to the drug
Dinoprostone (Prostin E_2)	Postpartum hemorrhage	Rectal or vaginal suppository	20 mg	Once	Avoid in hypotensive patients

HTN – Hypertension; CNS – Central nervous system.

19.2.4 Uterotonics summary

- These medications are powerful tools in an obstetrician's armamentarium that can be used for both labor induction/augmentation and control of postpartum hemorrhage.
- All of these medications have extensive side effect profiles and the potential for maternal and/or fetal toxicity. Thus, a good understanding of their administration and dosing is essential for safe and effective use.

Uterotonics: Pitocin, methergine, and prostaglandins:

- In general, this class of medications works to promote myometrial contraction by increasing intracellular calcium concentrations.
- Pitocin increases intracellular calcium via the phospholipase C/IP_3 pathway.
- Methergine is thought to bind to alpha adrenergic receptors on the myometrial cell and alter transmembrane calcium channel activity, resulting in calcium influx.
- Prostaglandins not only increase intracellular calcium by altering transmembrane permeability, but they also promote gap junction formation and upregulate expression of oxytocin receptors.

19.3 Uterine relaxation agents (tocolytics)

Preterm birth is a leading cause of neonatal morbidity and mortality worldwide. There are several pathogenic processes that can trigger uterine contractions and cervical dilation with subsequent delivery of the preterm neonate. The goal of tocolysis is to arrest uterine contractions and prolong pregnancy to allow for administration of steroids and possibly transport to a tertiary care center. Available treatments are intended to arrest uterine contractility and are not necessarily geared toward the underlying pathogenic process initiating labor. It is important to acknowledge that studies evaluating tocolytics are limited and difficult to analyze secondary to significant bias and inherent design flaws. Additionally, there is a paucity of placebo-controlled trials assessing the efficacy of these medications. Thus, the literature is somewhat limited regarding optimal tocolytic therapy and current protocols are based on the best available evidence. Presently, no agent is FDA approved for this indication and all are used off-label (Table 19.2).

Table 19.2 Tocolytics

Drug	Indication*	Route	Dose	Frequency	Considerations
Nifedipine	Acute tocolysis (48–72 hours)	Oral (short acting only)	Loading dose: 10–20 mg every 15–30 min (max 40 mg in first hour)	10–20 mg every 6–8 hours for 48–72 hours	Monitor for maternal side effects including hypotension, flushing, nausea, headache, dizziness, anxiety, cough, and dyspnea
		Sublingual/oral (short and long acting)	Loading dose: 10–40 mg short acting medication sublingual	60–160 mg long acting medication daily	
Terbutaline	Acute tocolysis (48–72 hours)	Subcutaneous	250 mcg every 20–30 min until contractions arrest (4 dose maximum)	Once tocolysis achieved, can repeat dose every 3–4 hours for 24–48 hours	Monitor for maternal side effects including tachycardia, flushing, dizziness, hyperglycemia, hypo-/hypertension, pulmonary edema/ARDS, and myocardial ischemia/infarction. Maternal heart rate should not exceed 120 bpm
	Acute tocolysis (48–72 hours)	Intravenous	2.5–5 mcg/min continuous infusion	Increase 2.5–5 mcg/min every 20–30 min, maximum 25 mcg/min	Titrate infusion to uterine quiescence or maternal side effects. Maternal heart rate should not exceed 120 bpm
	Tachysystole	Subcutaneous	250 mcg	Usually single dose	
	Tachysystole	Intravenous	125 mcg	Usually single dose	

(Continued)

Table 19.2 Tocolytics—cont'd

Drug	Indication*	Route	Dose	Frequency	Considerations
Indomethacin	Acute tocolysis (48–72 hours)	Oral/rectal	50–100 mg loading dose	25 mg every 4–6 hours	May cause significant maternal GI upset. Fetal surveillance with use >48 hours
Nitroglycerin	Acute uterine or cervical relaxation	Intravenous	50–200 mcg	Can consider repeating dose after 1–4 min if inadequate response	Monitor for hypotension and uterine atony
Atosiban†	Acute tocolysis (48–72 hours)	Intravenous	6.75 mg bolus followed by 300 mcg/min infusion for 3 hours	100 mcg/hour for up to 45 hours	Medication not approved for use in United States
Magnesium sulfate‡	Acute tocolysis (48–72 hours)	Intravenous	4–6 g loading dose	2–4 g/hour titrated to uterine response and maternal toxicity	Avoid in patients taking other calcium channel blockers and in patients with myasthenia gravis. Mentioned for historical purposes only, medication is not effective for tocolysis

*None of the medications are FDA approved, all are used off-label.
†Medication is not approved for use in United States.
‡Medication has not been shown to be effective for tocolysis.

19.3.1 Magnesium sulfate ($MgSO_4$)

Magnesium sulfate was first used as a tocolytic in the 1960s after it was shown to reduce uterine contractility both *in vitro* and *in vivo* [34]. Magnesium acts via extracellular and intracellular mechanisms to decrease intracellular calcium concentrations, thereby preventing the contractile response [35]. However, a large randomized controlled trial and a meta-analysis have shown it to be no better than placebo for preterm birth prevention [36, 37]. Additionally, compared to other tocolytic agents that affect intracellular calcium, magnesium has similar efficacy but a much higher rate of drug discontinuation secondary to maternal side effects. Thus, we are mentioning this drug for historical purposes only and do not recommend its use as a tocolytic.

19.3.2 β-Adrenergic-receptor agonists

β-Adrenergic-receptor agonists have been studied extensively in several randomized controlled trials with comparisons to both placebo and other tocolytics. A meta-analysis of these studies comparing β-adrenergic-receptor agonists to placebo indicate that β-adrenergic-receptor agonists significantly delay delivery and reduce the incidence of preterm birth and low birth weight [38]. No significant decrease in perinatal/neonatal death or respiratory distress syndrome was observed. Among women who received a β-adrenergic-receptor agonist, there was a 37% reduction of preterm birth within 48 hours (RR 0.63; 95% CI 0.53–0.75). However, there was no significant decrease in the number of births within 7 days.

β-Adrenergic-receptor agonists work to arrest uterine contractions by binding β2-adrenergic receptors on the myometrial cell (Figure 19.1). This interaction leads to increased levels of cyclic AMP which activates protein kinase. Protein kinase inactivates myosin light-chain kinase thus preventing uterine contractility [39].

Among the β-adrenergic-receptor agonists, ritodrine and terbutaline have been the two medications most commonly used for labor inhibition. Historically, ritodrine was the only medication ever to receive FDA approval for uterine tocolysis. However, this medication was voluntarily removed from the US market by the manufacturer after cases of maternal death were reported in the setting of ritodrine-induced pulmonary edema [40, 41]. Currently, the only β-adrenergic-receptor agonist used in the United States for uterine tocolysis is terbutaline. Recently, the FDA issued a black box warning regarding the use of terbutaline for tocolysis. The warning states that oral terbutaline

should not be used for the prevention or treatment of preterm labor because it has not been shown to be effective and has the potential for serious maternal heart problems and death. Injectable terbutaline should not be used for the prevention or prolonged treatment (>48–72 hours) of preterm labor because of similar safety concerns [42].

Typically, terbutaline is administered for acute tocolysis intrapartum in the setting uterine tachysystole with associated fetal distress. Additionally, it can be used for uterine relaxation prior to external cephalic version and/or maternal/fetal surgery.

For preterm labor tocolysis, 250 mcg of terbutaline can be administered subcutaneously every 20–30 minutes up to four doses or until tocolysis is achieved. A dose of 250 mcg may then be repeated every 3–4 hours for 24–48 hours depending on uterine activity and maternal hemodynamic response [43]. For acute tocolysis in the setting of uterine tachysystole with associated fetal heart rate changes, a dose of 250 mcg subcutaneous or 125 mcg intravenous can be administered. The medication should be held if the maternal heart rate is >120 beats per minute [44]. The medication is rapidly absorbed, the onset of action typically occurs within 5–15 minutes after subcutaneous dosing. It is faster with intravenous administration. The half-life of the medication in pregnancy is 3.7 hours [45]. The majority of the medication is eliminated unchanged via the kidney [46].

The drug can also be administered as a constant intravenous infusion with escalating doses. The infusion is generally started at 2.5–5 mcg/min; this can be increased every 20–30 minutes by 2.5–5 mcg/min to a maximum dose of 25 mcg/min [44, 47]. The infusion can be titrated until uterine quiescence or maternal side effects occur. Once uterine quiescence is achieved, the infusion can be reduced by 2.5–5 mcg/min to the lowest dose that maintains quiescence. Again, the maternal heart rate should not exceed 120 beats per minute.

This medication has an extensive side effect profile including: tachycardia, flushing, nervousness, dizziness, hyperglycemia, hypokalemia, and hyperthyroidism. More serious side effects including cardiac arrhythmia, hypo-/hypertension, pulmonary edema/acute respiratory distress syndrome, and myocardial ischemia/infarction have been reported with an incidence of 0.3–5%. Maternal death has been reported in the setting of long-term use (injectable or oral use) [40, 41]. Care should be taken when administering terbutaline to women with diabetes; terbutaline should be avoided in pregnant women with either preexisting or pregnancy-related cardiac disease.

19.3.3 Nitric oxide donors

Nitric oxide is a potent vasodilator and smooth muscle relaxant produced by a variety of cells. Nitric oxide relaxes smooth muscle via interaction with guanylyl cyclase (Figure 19.1). This interaction increases guanosine monophosphate (cGMP), which in turn inactivates myosin light-chain kinase leading to smooth muscle relaxation [48, 49].

Nitroglycerin (NG) is more commonly used for acute uterine relaxation in the setting of uterine inversion, or to facilitate external cephalic version, fetal delivery at the time of c-section, uterine relaxation for fetal surgery, and/or to relieve fetal head entrapment with vaginal breech delivery. It has been shown to be an effective uterine/cervical relaxant when administered at a dose of 100–200 mcg IV [50]. The half-life of NG is very short at 1–4 minutes [51]. Common side effects include hypotension, flushing, and headache. One may encounter uterine atony after administration, thus, uterotonics should be readily available.

Nitroglycerin has been studied in randomized controlled trials as a tocolytic. Intravenous nitroglycerin was shown to be inferior to magnesium sulfate as a tocolytic [52]. Transdermal nitroglycerin was found to be superior to placebo and similar to ritodrine with respect to delaying delivery for 48 hours [53, 54]. Although nitroglycerin has been shown to delay delivery, its use as a tocolytic is limited secondary to the potential for significant maternal hypotension [55].

19.3.4 Calcium channel blockers

Calcium channel blockers are commonly used as first-line agents for acute tocolysis. Calcium channel blockers work to relax smooth muscle by directly blocking entry of calcium ions into the myometrial cell and through prevention of intracellular calcium release from the sarcoplasmic reticulum (Figure 19.1). Calcium is necessary for myosin light-chain kinase (MLCK)-mediated phosphorylation. In the absence of calcium, MLCK is inactivated resulting in myometrial relaxation [56, 57].

Nifedipine is the most common calcium channel blocker used for acute tocolysis. A systematic review of 26 randomized controlled trials involving 2179 women compared nifedipine to other tocolytics [58]. Compared to β-adrenergic-receptor agonists, nifedipine reduced the risk of delivery within 7 days of initiation and before 34 weeks' gestation, and reduced the risk of respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, and admission to the neonatal intensive care unit. There was no difference in tocolytic efficacy

between nifedipine and magnesium sulfate; however, there were fewer maternal adverse events associated with nifedipine. Maintenance tocolysis with nifedipine (>48 hours) was ineffective in prolonging gestation or improving neonatal outcomes when compared with placebo or no treatment. To date, there have been no placebo-controlled trials studying the efficacy and safety of nifedipine for acute tocolysis.

The optimal dosing regimen of nifedipine for tocolysis has not been established. Numerous studies have reported that the peak serum concentration and half-life of nifedipine are significantly reduced, while the clearance rate is increased during pregnancy [59]. Concentrations peak in 30–60 minutes and the half-life is 1–2 hours in pregnant women (compared to 2–4 hours in nonpregnant state). Approximately 40% of the drug is inactivated by first pass metabolism in the liver (CYP3A4); 70–80% of the metabolites are excreted renally [59]. These alterations in the pharmacokinetics of nifedipine observed during pregnancy limit the duration of action to 6 hours and necessitate more frequent dosing [59].

Common dosing regimens for tocolysis include a 10–20 mg loading dose of nifedipine administered orally every 15–30 minutes for the first hour of treatment (maximum dose of 40 mg in the first hour). An alternate loading dose is 20 mg administered orally followed by an additional 20 mg dose 90 minutes later. Maintenance treatment (for 48–72 hours) can be dosed at 10–20 mg every 4–8 hours. The dose or frequency can be adjusted to lessen maternal side effects and achieve tocolysis. Alternatively, a combination of sublingual and long acting nifedipine has also been studied and shown to have similar efficacy to intravenous ritodrine [60, 61]. This regimen consists of 10–40 mg of sublingual nifedipine followed by 60–160 mg of long acting nifedipine daily. With either strategy, we recommend limiting the maximum daily dose to 120 mg per day, although others have reported using higher daily doses [62].

Common side effects include hypotension, flushing, nausea, headache, dizziness, anxiety, cough, and dyspnea. Thus, patients should be counseled and advised to monitor for symptoms. Additionally, maternal blood pressure should be monitored closely as acute hypotension can result in fetal heart rate changes and lead to maternal syncope.

19.3.5 Cyclooxygenase inhibitors (COX inhibitors)

Cyclooxygenase inhibitors are commonly used in obstetrics for acute tocolysis and as an intervention for preterm cervical shortening. COX inhibitors prevent the conversion of arachidonic acid

to prostaglandin. Prostaglandins have a significant role in the labor process by stimulating myometrial gap junction formation and by increasing the intracellular calcium levels [63]. Thus, COX inhibitors work to inhibit labor through the prevention of prostaglandin formation (Figure 19.1).

The most common COX inhibitor used for tocolysis is indomethacin. Indomethacin is typically administered as a loading dose of 50–100 mg orally or rectally, followed by 25 mg orally every 4–6 hours [64–66]. Oral indomethacin is rapidly absorbed and distributed systemically in the plasma with 99% being protein bound [67]. The half-life of the medication is approximately 4.5 hours [67]. It is eliminated via metabolism, renal and biliary excretion [67].

Two randomized controlled trials have compared indomethacin tocolysis to placebo [68, 69]. In the first, 30 patients were randomized to receive either indomethacin or placebo for the treatment of preterm labor [68]. This study reported that indomethacin was significantly more effective than placebo for preventing preterm labor during a 24-hour course of treatment (1/15 treatment failures in indomethacin group compared to 9/15 in placebo group). Although indomethacin was more effective for acute preterm labor prevention, there was no significant difference in gestational age at delivery or neonatal outcomes between the groups. A second trial randomized 34 women to receive either indomethacin or placebo for preterm labor treatment [69]. The primary outcome of this study was perinatal mortality and neonatal morbidity. Indomethacin was found to be more effective than placebo for prolonging gestation for >48 hours (81% in indomethacin group compared to 56% in placebo group). Additionally, there was no difference in perinatal mortality or neonatal morbidity between the two groups. Additional trials have shown indomethacin to be as effective as magnesium sulfate and β-adrenergic-receptor agonists for acute tocolysis (delay delivery by 48 hours) [66, 70–72]. In all of these trials, indomethacin was better tolerated by the patient. Recently, a comparative effectiveness trial showed indomethacin to be inferior to nifedipine for immediate tocolysis (relief of symptoms within 2 hours), but equivalent to nifedipine for delaying delivery for up to 48 hours or for 7 days [73]. Indomethacin may also be effective in prolonging pregnancy in women with a short cervix. However, data supporting this use are limited and mostly retrospective.

Long-term indomethacin use requires close fetal surveillance. Indomethacin can cause premature closure of the fetal ductus arteriosus and oligohydramnios. Neither of these complications

has been reported in the setting of short-term tocolysis (≤48 hours) prior to 34 weeks' gestation; however, they have been reported with long-term use [74–76]. A recent retrospective cohort study looking at 124 women who received prolonged antenatal indomethacin reported a 6.5% rate of ductal constriction and a 7.3% rate of oligohydramnios [77].

Indomethacin is known to be a potent vasoconstrictor of fetal vessels. Indomethacin blocks the production of prostaglandins, which are necessary to maintain a patent ductus arteriosus. This can result in ductus arteriosus constriction or closure. The mechanism by which indomethacin causes oligohydramnios is through reduced perfusion of the fetal kidney with a subsequent decrease in fetal urine production. The reduction in perfusion is thought to be caused by suppression of renin activity and/or vasoconstriction of the renal arteries [78]. Both fetal ductus arteriosus constriction and oligohydramnios will typically resolve with cessation of indomethacin.

Thus, women treated with indomethacin for longer than 48 hours should have weekly fetal echocardiograms to monitor for ductal constriction/closure (between 24 and 32 weeks) and weekly ultrasound evaluation for oligohydramnios. The medication should be discontinued with abnormal testing or at 30–32 weeks' gestation, whichever occurs first. Although early observational studies also reported an increased risk of necrotizing enterocolitis and intraventricular hemorrhage with antenatal indomethacin administration, a recent meta-analysis by Loe et al. of 1621 neonates exposed to antenatal indomethacin found no increased risk of intraventricular hemorrhage, ductus arteriosus closure, necrotizing enterocolitis, or mortality [79]. The study cautiously endorsed indomethacin use for tocolysis, but called for additional, adequately powered randomized controlled trials to further clarify the controversy.

Gastrointestinal upset is a common maternal side effect of indomethacin. Thus, we recommend an H_2 blocker or proton pump inhibitor for gastrointestinal prophylaxis with long-term maternal use.

19.3.6 Oxytocin receptor antagonists (atosiban)

Atosiban is not available for use in the United States. It is currently used throughout Europe for acute tocolysis. The drug itself is a selective oxytocin–vasopressin receptor antagonist that competitively inhibits oxytocin from binding to its receptors in the myometrium and decidua (Figure 19.1).

Several trials have compared atosiban to placebo or other tocolytics. A meta-analysis of 1695 women found that compared to placebo, atosiban did not reduce the incidence of preterm birth or improve neonatal outcome [80]. One randomized controlled trial carried out in the United States reported a trend toward higher rates of fetal death in women treated with atosiban [81]. These results may have been confounded by infection and extreme prematurity; however, an association with atosiban could not be excluded. Thus, the United States FDA denied approval of atosiban for tocolysis secondary to safety concerns [82].

19.3.7 Tocolytics summary

- There is an overwhelming abundance of data regarding tocolytics; however, the studies are often flawed and their results are difficult to interpret and implement in clinical practice.
- It is important to choose a tocolytic based on efficacy and safety, and the choice at times will be patient and situation specific (i.e. not administering indomethacin to a patient greater than 32 weeks' gestation or adjusting the nifedipine dose for a patient with mild hypotension).
- It is important to remember appropriate fetal surveillance when indicated, especially with indomethacin administration.

Tocolytics: Magnesium sulfate, β-adrenergic-receptor agonists, nitric oxide donors, calcium channel blockers, COX inhibitors, and oxytocin receptor antagonists:

- Magnesium is thought to function as a calcium channel blocker, thereby reducing intracellular calcium and preventing myometrial contraction.
- β-Adrenergic-receptor agonists bind β2-adrenergic receptors on the myometrial cell. This interaction leads to increased cAMP and activation of protein kinase. Protein kinase inactivates MLCK and prevents contraction.
- Nitric oxide donors relax smooth muscle via interaction with guanylyl cyclase. This leads to increase cGMP and inactivation of MLCK.
- Calcium channel blockers both directly block the entry of calcium ions into the myometrial cell and prevent intracellular calcium release from the sarcoplasmic reticulum.
- COX inhibitors prevent prostaglandin formation and thus block their contractile effects on the myometrium.
- Oxytocin receptor antagonists competitively inhibit oxytocin from binding oxytocin receptors.

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Antenatal Thyroid Disease and Pharmacotherapy in Pregnancy

20

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20.1 Thyroid function and physiology in pregnancy

In pregnancy, abnormalities of thyroid gland can be easily overlooked due to the normal physiologic changes of pregnancy often mimicking disturbances of thyroid gland function. As a result, basic knowledge of thyroid gland function and the changes the thyroid gland undergoes during the course of pregnancy are essential. Regulation of the thyroid gland and its hormones is controlled through an endocrine feedback loop that includes the hypothalamus and anterior pituitary [1]. The hypothalamus initiates this feedback loop with the release of thyrotropin-releasing hormone (TRH), which in turn regulates the release of thyroid-stimulating hormone (TSH) from thyrotrope cells in the anterior pituitary. TSH then prompts the release of thyroid hormones T4 and T3 from the thyroid gland. Abnormal production of T4 and T3 occurs with hyperthyroidism and hypothyroidism in the pregnant patient, with various etiologies accounting for the observed abnormal levels.

Table 20.1 Maternal thyroid function testing and associated physiologic alterations in normal pregnancy

Increased	Decreased	No change
TBG	TSH	FT3
TT3	Plasma iodide	FT4
TT4	Hepatic clearance	
Thyroid gland size		
hCG		
Albumin		

The physiologic changes of pregnancy affect thyroid function in numerous ways. The thyroid gland itself increases in size and can be newly palpable on physical examination. This increase in size is due to an increase in thyroid volume, the formation of new thyroid nodules, and/or increased iodine turnover [2, 3]. These changes normally occur without any significant change in thyroid hormone levels. Although the formation of thyroid nodules can occur during pregnancy, any palpable nodule should be evaluated with an ultrasound of the thyroid gland [1]. The observed increase in iodine turnover and subsequent depletion of the maternal iodine pool is predominantly a result of a reduction in serum iodine due to fetal use of maternal iodine and increased maternal renal clearance of iodine, resulting in an increase in thyroid gland size in 15% of pregnant women [4–6]. As pregnancy progresses maternal renal clearance of iodine increases due to an increase in renal blood flow and glomerular filtration rate, which further increases iodine clearance [7]. Physical examination of the thyroid gland during pregnancy is important on entry to care, especially if the patient is exhibiting potential signs or symptoms of thyroid gland dysfunction. (See Table 20.1.)

The physiologic changes of thyroid gland function particularly during the first trimester of pregnancy are well documented. TSH and human chorionic gonadotropin (hCG) are glycoproteins that share similar alpha subunits. This similarity between the alpha subunits results in negative feedback on the pituitary by hCG and decreased TSH production [5, 8]. As hCG levels continue to rise during the first trimester, TSH levels decline by approximately 20–50% reaching a maximal decrease at 8–14 weeks' gestation [5, 9, 10]. In fact, TSH levels may decrease below the lower limit of normal in up to 20% of women with little clinical consequence [8]. As a result of this decrease in TSH, FT4, and FT3 levels may slightly increase and even

Table 20.2 Maternal thyroid disease and relation to TSH and FT4

	TSH	FT4
Subclinical hyperthyroidism (or GTT)	Decreased	Normal to high-normal
Hyperthyroidism	Decreased	Increased
Subclinical hypothyroidism	Increased	Normal to low-normal
Hypothyroidism	Increased	Decreased

reach high-normal levels. The observed changes in TSH, FT4, and FT3 levels is referred to as transient subclinical hyperthyroidism or gestational transient thyrotoxicosis (GTT). It occurs in 10 to 20% of pregnant women and typically does not require treatment [1, 11]. In the second and third trimester TSH levels will start to rise due to the increased renal clearance of iodine and placental degradation of thyroid hormone, and FT4 and FT3 levels will then start to decrease back into normal range [1]. (See Tables 20.1 and 20.2.)

Although circulating T4 and T3 are predominantly bound (>99%) to the carrier proteins thyroid binding globulin (TBG) and albumin, it is the free hormone (<1%) that is biologically active. During pregnancy, serum TBG levels increase two- to three-fold due to increased TBG synthesis through the effects of increased estrogen and by decreased hepatic clearance [5, 8, 12]. Increased TBG leads to a rise in total T4 (TT4) and T3 (TT3) concentrations by approximately 50% starting at 6 weeks of gestation without significantly altering free T4 (FT4) and T3 (FT3) concentrations [1, 6, 13, 14]. In addition, the thyrotrophic effect of hCG likely further contributes to the increase in TT4 and TT3 concentrations [15]. Since FT4 and FT3 are the biologically active hormones, unaltered levels of FT4 and FT3 ideally allow the pregnant patient to remain euthyroid. Although there can be a transient rise in FT4 during the first trimester due to increasing levels of hCG and its interaction with TSH, TSH will start to increase in the latter trimesters resulting in a fall in FT4 [16]. Overall, the FT4 levels should remain within normal range, and FT3 levels will parallel that of FT4 and remain in the normal reference range as well [16]. (See Table 20.1.)

20.2 Hyperthyroidism in pregnancy

Hyperthyroidism occurs in 0.2% of pregnant women, or 1 in every 1000–2000 pregnancies [13, 17, 18]. The causes of hyperthyroidism are multiple and include nodular goiter, solitary toxic adenoma,

gestational trophoblastic disease, subacute and lymphocytic thyroiditis and tumors of the pituitary gland or ovary [8]. Graves' disease is the most common cause in pregnancy and occurs in 85–95% of all pregnant patients with hyperthyroidism [8, 19]. It is an autoimmune disease caused by autoantibodies, or stimulatory TSH-receptor antibodies (TRAb), that activate the TSH-receptor and stimulate the thyroid to produce an excessive amount of thyroid hormone [1]. These TRAb cause thyroid hyperfunction and thyroid gland hypertrophy, although there is no correlation between levels of antibody activity and disease severity [8]. The diagnosis may be particularly difficult if the patient presents in the first trimester, but the symptoms specific to hyperthyroidism should help to confirm the diagnosis. Symptoms include tachycardia, nervousness, tremors, heat intolerance, weight loss, goiter, frequent stools, excessive sweating, insomnia, palpitations, hypertension, ophthalmopathy, and dermopathy [8, 20]. Any combination of these symptoms in concert with abnormal laboratory testing (TSH, FT4) and the presence of TRAb should confirm the diagnosis.

As previously discussed, GTT can occur in the first trimester of pregnancy due to the cross-reactivity of the alpha subunits of TSH and hCG. During this period of gestation, differentiating between GTT and true Graves' disease is important as the former is expected to resolve spontaneously without intervention and the latter requires therapeutic intervention. If the TSH is suppressed and the FT4 is elevated, the diagnosis is overt hyperthyroidism, and laboratory assays of TRAb, thyroid stimulatory immunoglobulins (TSI) or thyroid-stimulating hormone-binding immunoglobulins (TBII) will likely be abnormal. If the TSH is suppressed and the FT4 is normal to high-normal, laboratory assays of TRAb should be considered, especially if the diagnosis of hyperthyroidism versus GTT cannot be readily made [21]. If TRAb are normal, the diagnosis is GTT or subclinical thyrotoxicosis. If elevated levels of TRAb exist, the diagnosis is hyperthyroidism. Furthermore, elevated TRAb levels carry a prognostic value for fetal and neonatal thyrotoxicosis as TRAb can cross the placenta resulting in neonatal thyrotoxicosis in 1–5% of neonates of mothers with Graves' disease [10, 21]. If high titers persist in the third trimester, fetal or neonatal hyperthyroidism is more likely to develop [22]. Such a complication is more likely if maternal Graves' disease has been difficult to control or there has been a delay in diagnosis [6]. Once the diagnosis of hyperthyroidism is established, consideration for evaluation of TRAb levels in early pregnancy and again in the third trimester to assess for the potential of neonatal disease is recommended by some [21]. (See Tables 20.2 and 20.3.)

Table 20.3 Maternal thyroid disease, thyroid antibodies, and neonatal effects

Hyperthyroidism	Hypothyroidism
TSH receptor antibodies (TRAb) – thyroid stimulatory immunoglobulins (TSI): can cause neonatal thyrotoxicosis – thyroid-stimulating hormone-binding immunoglobulins (TBII): can cause hypothyroidism or transient neonatal hypothyroidism	Thyroglobulin antibodies (TgAb) Thyroid peroxidase antibodies (TPOAb) –neither affect fetal thyroid gland function

GTT (suppressed TSH and normal-high normal FT4) is the diagnosis if there are no TRAb, thyroid nodules, goiter, or orbitopathy present, and there is no maternal history of Graves' disease [15, 21]. Once the diagnosis of GTT is confirmed, the patient can be reassured that symptoms and laboratory abnormalities will be resolved without intervention. Of note, the increase in hCG that is associated with GTT is also a contributor to the development of hyperemesis gravidarum (HG). However, GTT more specifically refers to the transient elevation of FT4 and FT3 associated with the decrease in TSH in the first trimester, whereas HG is the more severe form of nausea and vomiting in pregnancy (NVP) seen in the first trimester [21]. Abnormal thyroid function tests similar to that observed in GTT, consisting of elevated FT4 and suppressed or undetectable TSH, are found in about 60% of women with HG with levels typically normalizing after 16–20 weeks [23]. Finally, newly diagnosed cases of overt hyperthyroidism can present with HG or NVP, making thyroid function testing essential. In this scenario, once therapy is initiated, symptoms resolve with successful treatment of the disease [6].

Uncontrolled or poorly controlled hyperthyroidism in pregnancy has significant maternal and fetal/neonatal effects. Maternal complications include heart failure, preeclampsia, and thyroid storm, which can be precipitated by labor and delivery, infection, or preeclampsia. When considering the fetus, there is an increase in fetal loss, low birth weight, preterm labor, and congenital malformation [24, 25]. As stated earlier, the neonate can be affected by the transplacental transfer of TRAb [26, 27]. Furthermore, the fetus may also develop tachycardia and goiter *in utero* due to the presence of these antibodies, and in severe cases cardiac failure and fetal hydrops can occur. There is not a general consensus on whether to routinely follow TRAb in a patient with Graves' disease. However, if the patient is poorly controlled, continues to be symptomatic, or is noncompliant, evaluation of TRAb should be strongly considered.

20.3 Pharmacotherapy with thionamides in pregnancy

Once the diagnosis of hyperthyroidism is made, prompt initiation of treatment with thionamides is recommended. Thionamides inhibit thyroid hormone synthesis by interfering with thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin, an important step in the synthesis of T4 and T3 [28]. Propylthiouracil (PTU) and methimazole (MMI) are the mainstays of treatment in pregnancy. PTU has historically been used more commonly in the US because it was believed that PTU crossed the placenta to a lesser degree than MMI due to the increased protein binding of PTU, therefore decreasing the chance of inducing fetal hypothyroidism and causing fetal anomalies. In addition, the association of MMI with aplasia cutis, a fetal scalp defect, and "MMI embryopathy", characterized by facial abnormalities and choanal atresia, growth restriction, developmental abnormalities and esophageal atresia/tracheo-esophageal fistula, has minimized its use in the US [29]. It has been suggested that PTU be used in the first trimester and MMI thereafter, with continuation of MMI therapy postpartum [30].

Despite the fact that it has been proven that PTU and MMI cross the placenta equally and have equal chance of inducing fetal and/or neonatal hypothyroidism and goiter and fetal anomalies, there is still a continued preference of PTU over MMI use in pregnancy [31–33]. In an analysis of 643 neonates from mothers with Graves' disease, Momotani et al. were unable to demonstrate any significant teratogenic effects in those infants whose mothers took MMI [24]. In fact, significant teratogenicity was only observed in the neonates of mothers with untreated, uncontrolled hyperthyroidism. Finally, Chen et al. did a matched case–control study of 2830 mothers with hyperthyroidism and 14,150 age-matched controls to compare the risk of adverse pregnancy outcomes among pregnant women with hyperthyroidism who were receiving PTU, MMI or no medical treatment [34]. They found that women taking PTU had an increased risk of having a low birth weight infant when compared to women not receiving treatment. In contrast, women taking MMI during pregnancy did not have an increased risk of any adverse fetal outcomes when compared to women not receiving treatment.

The goal of treatment is to keep the patient euthyroid with maternal FT4 within the high-normal range, or in the upper one-third of each trimester-specific reference interval, in order to avoid fetal hypothyroidism, goiter, and abnormal brain development

from transplacental passage of thionamides [8, 30]. As a result, the lowest possible dosage of PTU or MMI should be used while adequately controlling the signs and symptoms of hyperthyroidism. MMI can be given once daily because it has a longer duration of action than PTU. The oral dosing regimen of MMI is typically started at 10 to 15 mg a day and adjusted accordingly, with the maximum dose being 40 mg a day. As symptoms improve, a maintenance dose of 5–15 mg a day is usually sufficient. Because of its shorter half-life, less thyroidal tissue concentration, and decreased maximal concentration when compared to MMI, PTU requires twice daily to three times daily dosing in pregnancy. As a result, PTU is not ideal for the noncompliant patient, and appropriate dosing may be difficult to both determine and achieve. PTU is started at 100–150 mg every 8–12 hours up to a maximum dose of 600–800 mg a day [18, 35]. A maintenance dose of 50–150 mg a day is ideal. If a patient requires more than 300 mg a day, dosing every 4–6 hours is recommended [36]. Monitoring of thyroid function tests (TSH, FT4, FT3) every 4 weeks is recommended after initiation of therapy in the mildly symptomatic patient. This can be decreased to every 6 weeks once the patient is euthyroid. Although information on the effectiveness of PTU versus MMI in the treatment of hyperthyroidism in pregnancy is limited, studies thus far have shown that they are equally effective. In a retrospective cohort study by Wing et al. examining the maternal and fetal outcomes of 185 patients treated for hyperthyroidism with PTU or MMI, both drugs were found to be equally effective, with similar rates of normalization of thyroid hormone levels [37]. Finally, the pharmacokinetics of PTU and MMI do not appear to differ significantly in the pregnant and non-pregnant patient in the limited number of studies addressing this issue.

Therapy with PTU and MMI can be started at moderate doses in order to bring the disease under control more quickly, i.e. in cases with a large goiter or significant symptoms. MMI can be started at 20–30 mg a day in divided doses and PTU can be started at 100 mg three times daily for a period of 2–3 days, with tapering once symptoms are under control. Treatment with PTU and MMI may take 6–8 weeks to see a change both clinically and in laboratory assessments. After initiation of therapy with higher doses, thyroid function tests (TSH, FT4, FT3) should be evaluated in 2 weeks followed by levels every 4–6 weeks depending on response to therapy. When monitoring response to therapy, normalization of FT4 precedes that of FT3 making FT4 a better indicator for the adjustment of medication dosage [38]. However, maternal TSH may remain suppressed for weeks to months following normalization of FT4 [21]. Monitoring of maternal thyroid function

frequently during pregnancy is important in order to avoid overtreatment and the potential development of fetal hypothyroidism and goiter, especially when starting at a higher dose [21]. Approximately, 25% of cases of transient neonatal hypothyroidism can be attributed to treatment of maternal hyperthyroidism with thionamides, which can cause neuropsychological damage in severe cases when the fetus is overtreated [31].

Although maternal Graves' disease is associated with the passage of TRAb across the placenta to the fetus, whether or not to check antibody levels during pregnancy is debated. In those patients who enter pregnancy with a history of Graves' disease, but who have no active disease and do not need treatment, neonatal hyperthyroidism may still occur [16]. As a result, it is argued that TRAb should be monitored, and if the level is high, the fetus should be evaluated early in gestation and at 32–36 weeks. If there is a detectable level of TRAb at 32–36 weeks, evaluation of the neonate for hyperthyroidism is warranted [16]. If the patient enters pregnancy already on adequate treatment and is asymptomatic, there is usually no need to measure TRAb as clinical and laboratory maternal thyroid function gives a reliable estimate of fetal thyroid status and the risk of neonatal hyperthyroidism is very low in these cases [16]. In those patients where therapy can be stopped, discontinuation of PTU or MMI should occur no later than 36–37 weeks if maternal and fetal conditions are stable and allow for discontinuation of therapy [39]. Whether or not TRAb are followed, serial sonograms and fetal heart rate monitoring to assess the fetus for tachycardia, goiter, and growth are recommended during the course of the pregnancy [39]. (See Table 20.3.)

The occurrence of minor and major side effects with the use of thionamides does not appear to change in frequency in pregnancy. Minor side effects occur in approximately 5% of patients and include the development of a papular urticarial rash, pruritus, joint pain, headache, nausea, and hair loss [36, 40, 41]. These side effects can often be managed conservatively with antihistamines, by switching therapy, or stopping treatment [28]. However, if arthralgias develop this may indicate the development of severe transient migratory polyarthritis, or "antithyroid arthritis syndrome", and discontinuation of thionamide therapy is recommended [28]. The more major side effects include drug fever, bronchospasm, agranulocytosis, hepatotoxicity, and vasculitis, which includes a lupus-like syndrome [8, 42, 43]. Agranulocytosis, believed to be autoimmune mediated, occurs in approximately 0.35% of patients taking thionamides and 0.1% of patients taking PTU [8, 44]. It has been associated with higher doses of MMI, but is not related to any particular dosage of PTU. Agranulocytosis is

Table 20.4 Maternal side effects with thionamides

Minor (5% of patients)	Major
Papular urticarial rash	Arthralgias – severe transient migratory polyarthritis, or "antithyroid arthritis syndrome"
Pruritus	Drug fever
Joint pain	Bronchospasm
Headache	Agranulocytosis – 0.35% (more common with PTU)
Nausea	Hepatotoxicity – 0.1–0.2% (more common with PTU)
Hair loss	Vasculitis – "lupus-like" syndrome (more common with PTU)

a contraindication to further thionamide therapy [8]. A baseline white blood cell count should be obtained prior to starting therapy, and if fever and sore throat develop, agranulocytosis should be suspected and therapy immediately stopped. Hepatotoxicity, in the form of allergic hepatitis followed by hepatocellular injury, is reported to occur in 0.1–0.2% of patients and is more common with PTU [40]. Vasculitis, which is considered to be autoimmune mediated as in agranulocytosis, is also a major side effect and is more common with PTU than MMI. (See Table 20.4.)

20.4 Hypothyroidism in pregnancy

Hypothyroidism occurs in 2.5% of pregnant women with approximately 1–2% of patients entering prenatal care already on thyroid replacement therapy for hypothyroidism [45, 46]. Most patients diagnosed in pregnancy are asymptomatic but are found to have an elevated TSH on antenatal screening [16]. The percentage of pregnant women with abnormal TSH that have autoimmune thyroiditis (AITD) is 40–60% compared to a prevalence of 7–11% of antibody-positive non-pregnant women in the same age range [45]. In pregnant women TSH is the primary screening test for thyroid disease and should especially be obtained in high-risk women, those with other autoimmune diseases (i.e. diabetes), thyroid nodules, or goiter, exposure to radiation, or personal or strong family history of thyroid disease [1]. Of note, women can have a firm painless goiter and be euthyroid initially during pregnancy, but then become hypothyroid as the pregnancy progresses [8].

The most common cause of hypothyroidism in pregnancy is a primary thyroid abnormality known as Hashimoto's thyroiditis, or chronic autoimmune thyroiditis (AITD), which is caused by the presence of thyroid antibodies [15]. In this disorder, titers of antithyroglobulin antibodies (TgAb) are elevated in 50–70% of patients and almost all patients have antithyroid peroxidase antibodies (TPOAb) present [47]. TPOAb are also found in 10% of euthyroid women in early pregnancy and are associated with the subsequent development of hypothyroidism during pregnancy [48]. In addition, the presence TPOAb at 32 weeks of gestation is associated with a significant decrease in the IQ of children even if the mothers were euthyroid [49]. Although TgAb and TPOAb are known to cross the placenta during the last trimester, they do not negatively affect fetal thyroid function [15]. Conversely, TRAb and TBII also cross the placenta, and if the patient has a high titer of one or both of these antibodies, the fetus is at risk for hypothyroidism or transient neonatal hypothyroidism [50, 51]. TRAb are found in less than 1% of pregnancies and as previously discussed indicate the presence of Graves' disease [19]. (See Table 20.3.)

The signs and symptoms of hypothyroidism are similar in the non-pregnant and pregnant patient, and some symptoms are considered to be a normal response to the hypermetabolic state of pregnancy [45]. Symptoms include modest weight gain, lethargy, decrease in exercise capacity, intolerance to cold, constipation, hoarseness, hair loss, dry skin, goiter, or delayed relaxation of the deep tendon reflexes [8]. A combination of these symptoms may be seen with overt hypothyroidism or symptoms may be subtle and thus attributed to the normal physiologic changes of pregnancy. If hypothyroidism is suspected at any point during pregnancy, serum TSH and FT4 should be measured. If the TSH is above normal and/or the FT4 is below normal, hypothyroidism should be suspected. Measurement of thyroid antibodies, TgAb and TPOAb, can be obtained to aid in the diagnosis especially when TSH and FT4 levels are not fitting the typical pattern for hypothyroidism. If serum TSH is greater than 4 mU/L and/or FT4 is below normal, regardless of the presence of thyroid antibodies, the thyroid is likely underfunctioning and replacement is needed [45]. If the TSH is less than 2 mU/L, regardless of thyroid antibody status, treatment is not indicated, but monitoring of thyroid function tests throughout pregnancy is warranted. If the TSH is 2–4 mU/L and thyroid antibodies are positive, treatment is usually necessary. The decision to treat in this scenario can be based on FT4 levels. If FT4 is low to low-normal, treatment is beneficial [45]. Finally, as mentioned above, the presence of TPOAb and a normal to high-normal TSH level at the beginning of pregnancy

has been shown to correlate positively with the risk of developing hypothyroidism in pregnancy [21]. As a result, if the decision is made not to initiate treatment, monitoring with TSH and FT4 during pregnancy is recommended.

Subclinical hypothyroidism (elevated TSH and normal to low-normal FT4) occurs in up to 2.5% of pregnancies, with a majority of patients being asymptomatic [10]. The decision as to whether or not to treat these patients has been controversial [46]. However, recent evidence suggests that treatment with thyroid hormone replacement in this setting is not harmful and in fact is likely advantageous for the patient and fetus [52–55]. It is well established that normal maternal thyroid function is essential for normal fetal brain and neurologic development [39]. As a result, a diagnosis of subclinical hypothyroidism warrants thyroid replacement in order to keep maternal FT4 and FT3 levels in the normal to high-normal range and allow for normal fetal neurodevelopment [45, 55–60]. In addition, subclinical hypothyroidism has been associated with other adverse maternal–fetal outcomes. In a retrospective cohort study of nearly 26,000 pregnant women screened for TSH levels, those with subclinical hypothyroidism had three times the incidence of placental abruption and almost twice the incidence of preterm birth at less than 34 weeks [55, 61]. Finally, in the 62 pregnant women who had TSH levels at or above the 98% for pregnancy, IQ testing of their children at ages 7–9 showed that they performed slightly less well on all tests when compared to controls [55]. Although routine screening for subclinical hypothyroidism is not recommended by ACOG, other societies do recommend it [62]. The decision to screen at this time is based on provider preference.

Although the most common cause of hypothyroidism worldwide is iodine deficiency, it is typically not a cause in the US due to dietary iodine supplementation [8]. It is well established that the transplacental passage of maternal T4 is necessary for fetal brain development during the first trimester as the fetal thyroid has yet to develop and start producing its own thyroid hormones. As a result, lack of maternal iodine during the first trimester may lead to impaired fetal neurological development. Furthermore, if there is inadequate iodine substrate for the fetal thyroid gland to use once it has developed, the fetus is unable to synthesize its own thyroid hormones [8]. In fact during the second trimester, when there is development of the fetal brain, fetal thyroxine is derived almost exclusively from the mother [45, 63]. If a woman enters pregnancy with low iodine levels, the available iodine can decrease even further due to the increased renal clearance of iodine and the fetal–placental unit competing for available iodine [64, 65].

Severe iodine deficiency during the first trimester causes cretinism, with infants developing severe mental retardation, deafness, muteness, and pyramidal symptoms [8]. Other causes of maternal hypothyroidism include history of radioactive iodine treatment for Graves' disease or thyroidectomy, subacute viral thyroiditis, suppurative thyroiditis, and hypothyroidism secondary to pituitary disease [8, 66]. Some drugs, i.e. ferrous sulfacrate, sucralfate, carbamazepine, phenytoin, and rifampin, can also depress thyroid function causing symptomatic hypothyroidism.

There are significant consequences of unrecognized or undertreated hypothyroidism in pregnancy. In general, there is an association between hypothyroidism and decreased fertility which is primarily due to ovulatory disturbances attributed to modified levels of gonadotropin, estradiol, testosterone, and sex hormone-binding globulin (SHBG) [45, 67]. When a hypothyroid woman does become pregnant there is an increased rate of miscarriage, anemia, postpartum hemorrhage, preeclampsia, placental abruption, growth restriction, prematurity and stillbirth, neonatal respiratory distress and impaired neurologic development of the fetus [8, 68]. Furthermore, the presence of thyroid antibodies in the maternal circulation is associated with a two- to three-fold increased risk for preterm delivery and lower birth weight [69]. In addition, the presence of circulating thyroid antibodies in the maternal circulation is associated with an increased rate of early spontaneous abortions in both the overt hypothyroid patient and in the patient that is euthyroid [70, 71]. As a result, the presence of thyroid immunity represents an independent marker of an at-risk pregnancy [45]. Finally, because diabetes and thyroid disorders are both autoimmune conditions, monitoring the hypothyroid patient for the development of diabetes is important.

20.5 Pharmacotherapy with levothyroxine in pregnancy

Treatment with thyroid hormone replacement should be initiated once the diagnosis of hypothyroidism is made so that potential adverse obstetrical outcomes, especially abnormal fetal neurodevelopment, can be minimized. Levothyroxine (LT4) is the drug of choice for thyroid hormone replacement therapy in pregnancy. Synthetic LT4 is a levo-isomer of thyroxine with identical activity to the endogenous hormone [72]. It has a long half-life (6–7 days), thus allowing once daily dosing [73]. LT4 is converted to

T3 supplying active hormone in the maternal circulation, with T3 concentrations rising much later than T4 concentrations due to the time needed for conversion of T4 to T3 [72, 73]. The initial dose is typically between 100 and 150 mcg a day, with dosage adjustments every 4 weeks to keep the TSH at the lower end of normal and the FT4 and FT3 at the upper limit of normal [8]. The goal of therapy is to keep TSH between 0.5 and 2.5 mIU/L and FT4 in the upper normal range. Monitoring of thyroid function is accomplished through routine measurement of maternal serum TSH and FT4.

If the patient is newly diagnosed in pregnancy and she is symptomatic and with significantly abnormal thyroid function testing, treatment with LT4 may be initiated at a dose that is 2–3 times the estimated maintenance dose for a period of 2–3 days [45]. This approach should allow for rapid normalization of the T4 pool and circulating T4 levels, and euthyroidism can be achieved more quickly [45]. In this scenario, TSH and FT4 should be evaluated 2 weeks after initiation of therapy rather than 4 weeks. As the pregnancy progresses, it is not uncommon for T4 requirements to increase due to increased maternal demand and the decreased maternal intestinal absorption that is associated with prenatal iron replacement therapy [8]. As a result, patients should be instructed to take their iron and thyroxine at least 4 hours apart to minimize the effect of the decreased intestinal absorption. (See Table 20.2.)

Women who enter pregnancy on LT4 will often require an increase in dosage as early as the fifth week of gestation in order to stay euthyroid [21, 59, 60]. Ideally this should be accomplished before the onset of pregnancy, but the patient can immediately increase her pre-pregnancy maintenance dose once pregnancy is diagnosed. The dose of LT4 may need to be increased even further as the pregnancy progresses. This is a result of the estrogen-dependent increase in serum TBG concentration, increased placental production of Type II and III deiodinases that degrade T4 and increased tissue volume of distribution, which all contribute to the decrease in serum maternal T4 [5, 74, 75]. Typically a 40–50% increase in dosage (50–100 mcg a day) is necessary in 75–85% of patients, and this increase should occur in the first trimester in order to minimize the morbidities associated with undertreatment of maternal hypothyroidism [16, 21, 60, 76, 77]. Women with a history of radioiodine ablation for hyperthyroidism tend to need a more significant increase in LT4 dosage, whereas women with AITD typically need a smaller increase in dosage [45]. Women on a minimal dosage of LT4 for a diagnosis of subclinical hypothyroidism may not require any change in dosage with the onset of pregnancy [45].

20.6 Summary

To date, much is known about thyroid and maternal physiology and how they interplay during the course of the gestation; however, the physiologic changes of pregnancy can not only make the diagnosis of maternal thyroid disease difficult, but make appropriate pharmacotherapy more challenging as well. Adequate treatment of hyperthyroidism and hypothyroidism is necessary not only to treat the mother, but also to allow for normal fetal neurodevelopment. Despite a wealth of evidence that MMI is equally as safe in pregnancy as PTU, there still remains a divide on whether MMI can be used in the first trimester or throughout the gestation. A trial is desperately needed in order to quell these concerns. In addition, pharmacokinetic and pharmacodynamic studies on each of these drugs throughout the different gestations of pregnancy are largely lacking, and more information in these areas would likely put to rest any concerns that remain on whether MMI is safe to use, especially in the first trimester. When considering hypothyroidism, the data largely suggest that treatment of subclinical hypothyroidism is beneficial for the fetus. However, many pregnant women are still not treated when subclinical hypothyroidism is diagnosed. More research into the benefits of treatment is warranted in order to make treatment of subclinical hypothyroidism commonplace in obstetrics. Finally, as with the antithyroid drugs, pharmacokinetic and pharmacodynamic studies on thyroid replacement drugs are needed in order better to understand how pregnancy affects their pharmacotherapeutic profiles.

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Dermatological Medications and Local Therapeutics

21

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21.1 Introduction

With change as the only constant element during pregnancy or in the postpartum period the clinical practitioner may be confronted with a variety of clinical scenarios of different skin conditions. In this context, when facing pregnant or lactation patients (or patients considering pregnancy), physicians' portfolio of clinical options generally consists of:

1. the postponement of the treatment, especially for the common dermatoses which do not necessitate immediate therapy,

2. the preservation of the treatment, but under strict supervision (if the used medication is considered safe in pregnancy or unlikely to cause fetal malformations),
3. the revision of the treatment and the search for safe alternatives, or
4. the temporary interruption of breastfeeding (with the patient pumping breast milk) and the resuming of breastfeeding at the end of the treatment.

However, the ethically induced absence of controlled studies or clinical trials on medication safety during pregnancy and also the existence of multiple yet disunified Pregnancy Risk Assessment Systems (e.g. Australia, Switzerland, Denmark, or Sweden) are severely increasing the difficulty and the complexity of treatment.

This chapter provides a set of updated practical therapeutic options tailored to the particular clinical scenarios of frequent skin conditions like acne, psoriasis, and bacterial, viral, fungal, and parasitic skin infections, including the clinically recommended doses for all the drugs involved in the medication. The minimization of any possible fetal risk and of the increase of the maternal body weight during pregnancy act as critical therapeutic filters in all treatments. In addition, the chapter covers the use and administration of antipruritics, glucocorticosteroids, immunomodulators, analgesics, and antiseptics.

21.2 Acne

21.2.1 Systemic treatment for acne

Erythromycin (category B) is the antibiotic of choice when systemic therapy is needed for gestational acne [1], yet with some important safety-related specifications. More specifically the use of erythromycin esolate should be avoided in all stages of pregnancy since according to some studies [2] extended exposure to the drug (more than 3 weeks) might trigger maternal subclinical hepatotoxicity (cholestatic hepatitis) in up to 10–15% cases. Moreover, clinicians should refrain from using erythromycin in early pregnancy, due to possible risks of cardiovascular malformations after oral maternal ingestion of the substance [3–5].

The recommended oral dose is 400 mg every 8 hours (maximum 2 g/day), administered 1 hour before meals [6], the drug being compatible with lactation (although 50% of the medication passes into the breast milk) [2].

Of note, tetracycline (category D) – the first-line treatment in the case of non-pregnant patients – is considered extremely unsafe for pregnant/lactating patients. According to multiple studies, administration of tetracycline after the first trimester of pregnancy exhibits associations with decreased bony growth, deciduous dental staining in offspring, and fatty liver atrophy (a rare syndrome) in the mother [1, 3].

Other systemic drugs used in normal acne treatment, like isotretinoin or tazarotene, are contraindicated during pregnancy and lactation (they belong to category X). Isotretinoin manifests a teratogenic effect during gestation with the possible development of malformations such as central nervous system defects, craniofacial defects, cardiovascular defects, thymic defects etc. In particular, since only one dose of isotretinoin can cause embriopathia, patients with childbearing potential should be allowed to conceive only after a period of a minimum of 1 month after administration. On the other hand, despite clinical evidence presenting six cases of women having healthy babies after taking tazarotene, its administration has been proved to cause multiple retinoid-like malformations in animals studies [1, 2], thus maintaining the drug's classification as extremely risky and absolutely contraindicated during pregnancy/lactation.

21.2.2 Local treatment for acne

Whenever the pregnant/lactating mother opts not to postpone the acne treatment until the postpartum/post-lactation period, topical therapy represents the method of choice. In this context, the prescribed medication consists of erythromycin (category B) 1–3% in petroleum jelly once daily; clindamycin (category B) 1% once daily; or benzoyl peroxide (category C) 2.5% once daily, all with a clinical history which qualifies them as safe [2, 7]. Topical metronidazol (category B) 0.75% once daily is also considered to be a safe alternative in the treatment of acne, and also in the treatment of rosacea [1]. Azelaic acid (also in category B) represents another therapeutic option, with studies in animals revealing no mutagenic, teratogenic, or embryotoxic effects after its administration [8] and also a systemic absorption of less than 4% after one application [2]. Yet, as in the case of any substance with a short market history, it is recommended rather as a marginal option, at least for a while.

In addition, there is no scientific consensus regarding tretinoin (category C). Although generally classified as a safe alternative therapy during pregnancy [7], several published case reports link the intake of the medication during the first trimester of pregnancy

with subsequent fetal malformations, thus recommending its avoidance [9, 10]. A similar situation is recorded also in the case of another topical retinoid adapalene (category C), the use of which was causally linked with congenital ocular anomaly reports [11]. Tazarotene (category X) is absolutely contraindicated (see systemic treatment).

21.3 Psoriasis

21.3.1 Systemic treatment for psoriasis

Cyclosporine (category C) – an immunosuppressive agent which mostly inhibits the T helper lymphocytes – is considered an acceptable alternative in psoriatic patients during pregnancy (in doses of 3–5 mg/kg/day) [12, 13], as its administration revealed no teratogenic effects in pregnant patients who had had an organ transplant [14]. Its introduction, however, should seriously take into consideration the extent to which the potential benefits outweigh the potential risks. Of extreme importance is the fact that the drug is contraindicated during lactation due to its possible immunosuppressive dimension, to its unknown effects on fetal growth and carcinogenesis [15]. Other systemic therapies, based on acitretin (category X) or methotrexate (category X), first-line treatments in non-pregnant psoriatic patients, are absolutely contraindicated in pregnancy. Acitretin, a systemic retinoid, is known to have a strong teratogenic effect and a long persistence in the adipose tissue, thus recommending the avoidance of pregnancy for up to 3 years in the case of the patients treated with the substance. Methotrexate, an antagonist of folic acid, is also known to have a teratogenic effect and to cause fetal malformations like anencephalus, cleft palate, abnormal ears or skeletal abnormalities [1]. Due to these aspects, all patients with childbearing potential should be advised to conceive only after a period of a minimum 1 month after the last administration of the substance.

On the other hand, the limited published data on the safety of biologic agents restricts their status to that of a relatively marginal alternative for the treatment of psoriasis during pregnancy.

However, when biologics are chosen, the portfolio of therapeutic options consists of category B agents like alefacept, infliximab, adalimumab, and etanercept [1, 3]. In this context, clinical data from animal reproduction studies, and also evidence from

women unaware of their pregnancy to whom alefacept (category B) – a mouse analog of efalizumab (category C) – was administered in the incipient phase of gestation, reveal no proof of teratogenicity [16]. Similarly, etanercept (category B) is also considered safe in pregnancy, with no malformations reported in both animal studies and contextual human data from patients treated for rheumatoid arthritis [17]. Another clinical study on 65 pregnant patients treated with etanercept (B) or infliximab (B), revealed no evidence of teratogenicity for either substance [18]. Of interest is the study of Carter et al. [19], who reported adverse effects after anti-TNF therapy (etanercept or infliximab), consisting of 61 congenital abnormalities in 41 women. Fifty-nine percent of the newborns presented one or more congenital anomalies of what was defined as the VACTERL syndrome – anomalies of the vertebrae (V), anal atresia (A), cardiovascular defects (C), tracheal (T), esophageal (E), renal system (R), and limb (L) abnormalities.

21.3.2 Local treatment for psoriasis

The use of keratolytics (salicylates with concentrations of 2–10% in petroleum jelly) administered once daily is considered safe if performed only for short periods of time and only for small skin surfaces [20]. Likewise, the therapy based on mild to moderate topical corticosteroids (category C) and calcipotrione ointment (category C), considered the first-line and most efficacious topical therapy for patients with localized psoriasis, is also considered safe for use in pregnancy [21, 22]. Of note, according to pharmacokinetic notes 3% of the topical application of the corticosteroid is absorbed after 8 hours of contact with normal skin, and approximately 6% of calcipotrione ointment is absorbed systemically following contact with psoriatic plaques [1]. Special caution is, however, needed with the super-potent/potent topical corticosteroids, as their application on a big surface of the body is considered to have the same effects as systemic therapy with steroids [2]. Another safe option for the local treatment of psoriasis during pregnancy is tacrolimus (category C), a topical calcineurin inhibitor which has been reported to have no teratogenic or fetal loss effects, after being tested in animal reproduction studies [6, 22]. Other medications frequently administered in the case of non-pregnant psoriatic patients, like anthralin (category C) – an anthracenic compound – or coal tar products (category C) must be avoided, due to their relatively high mutagenic and carcinogenic potential [23, 24].

21.3.3 Phototherapy

Narrowband ultraviolet B therapy is frequently conceptualized as a second-line treatment for localized psoriasis [25]. In particular, whenever the therapy based on topical corticosteroids and calcipotrione ointment proves inefficient and the lesions are becoming extensive, ultraviolet B phototherapy (either narrowband or broadband) is the treatment of choice [22, 25]. However, in this case, caution must be taken in order to avoid any overheating during treatment.

On the other hand, pregnant patients should avoid – whenever possible – the psoralen plus ultraviolet A (PUVA) therapy, due to its possible mutagenic effects [26–28] in spite of studies reporting no adverse reactions in more than 30 pregnant women exposed to PUVA therapy [27, 29]. One interesting side note, especially regarding patients with localized palmo-plantar psoriasis, is the absence of a rise in blood levels of 8-methoxypsoralen after topical PUVA [28].

21.4 Bacterial infections

21.4.1 Systemic treatment of bacterial infections

The first-line treatment with antibiotics during pregnancy consists of erythromycin (category B) and penicillins (category B). Overall, erythromycin (with the exception of erythromycin esolate) is classified as safe in pregnancy and lactation, but its administration should be strictly avoided in the early pregnancy stages (for dosage and explanations, see Section 21.2.1) [4, 5]. The long clinical history of penicillins qualifies them also as a safe therapeutic alternative during pregnancy and lactation. Penicillin G is administered in doses varying between 1,200,000 and 6,000,000 UI/day IM (very painful) or IV every 4–6 hours for skin conditions like syphilis, ectimes, erysipelas, or impetigo. The excretion of the drug in breast milk reaches a concentration of 2–20% [3].

Safe alternatives in the systemic therapy of bacterial infections are cephalosporins (category B) and azythromicin (category B). The use of cephalosporins – cephalexin (category B) 500 mg every 6–12 hours, cefaclor (category B) 250–500 mg every 8 hours, cephradine (category B) 250–500 mg–1 g every 6–12 hours, ceftriaxone (category B) 1–2 g IV or IM – is generally considered to be non-teratogenic, with a myriad of studies reporting no adverse fetal effects after their administration, even when this occurred in the first trimester of pregnancy. Nevertheless, one specific study

[6] indicates the presence of congenital malformations associated with the use of the above- mentioned cephalosporins in the first trimester of pregnancy [6]. In conclusion, in order to avoid any risks which might outweigh the benefits, the safest therapeutic approach would be to administer cephalosporins only after the first trimester of pregnancy. Azithomycin (category B) therapy, consisting of daily doses of 250–500 mg, is also considered a safe substitute for the first-line treatment. Experimental studies on gestating animals exposed to high doses of the drug revealed no side effects [1].

As there are many safer alternatives, clarithromycin (category C) or dirithromycin (category C) should be avoided. Fluoroquinolones like ciprofloxacin, norfloxacin, levofloxacin or nalidixic acid (all category C) should also remain on the list of excluded drugs, as their use can damage growing cartilage [1, 30].

Likewise, tetracycline (category D) and also minocycline (category D) should be avoided for the whole period of pregnancy, and especially in the second and third trimester, as their administration could produce enamel hypoplasia – a dental staining and decreased bony growth to the offspring, and a fatty liver atrophy (a rare syndrome) for the mother [31].

Finally, the list of clinically invalidated drugs which should not be used in the systemic therapy of bacterial infections concludes with sulfonamides (category B normally, but involving category D near term). In this context, physicians should refrain from using sulfonamides, especially during the third trimester, near term, as their use has been associated with an increased risk of kernicterus and hyperbilirubinemia, and also hemolytic anemia for the newborns (especially if the glucose-6-phosphate dehydrogenase [G6PD] is deficient) [32].

21.4.2 Local treatment of bacterial infections

Overall, topical antibacterial treatment follows the basic tenets of systemic treatment and especially the axiomatic rule stating that whatever antibiotics are safe in the systemic therapy are equally safe for topical use. For example, erythromycin (category B) – the first-line treatment in systemic treatment – can be safely used in topical treatment, with the following dosage: 0.5–1–2 g in petroleum jelly (vaseline) 50–100 g once a day, but only for a short period of time. In addition, bacitracin (category C) or mupirocin (category C) could be considered as acceptable treatment options [2]. As a second axiomatic rule, the clinician has always to take into account the possible sensitization and bacterial resistance after topical use of antibiotics and thus stop the ongoing treatment [31].

21.5 Viral infections

21.5.1 Systemic treatment of viral infections

Acyclovir (category B) in doses of 1 g/day (200 mg every 4 hours) is the first-line treatment for herpes simplex virus infections which might occur during pregnancy and lactation. Its use – even from the first trimester of pregnancy – has not been reported to cause any adverse effects [15]. Due to their newer clinical history, antiviral agents such as famcyclovir (category B) or valacyclovir (category B) remain for the time being only secondary alternatives within the viral infections' therapeutic portfolio. Of note, vaccination of pregnant women for human papilloma virus is not recommended due to the limited clinical data available [20].

21.5.2 Local treatment of viral infections

Physical methods like cryotherapy, electrodesiccation, or CO_2 laser are considered to be the safest treatment for human papilloma virus infections during pregnancy. Whenever the clinical manifestation occurs in the form of small warts, trichloracetic or dichloracetic acid in concentrations up to 85% in alcohol are also safe therapeutic options [1].

The newer antiviral agent, imiquimode (category B) 5% cream – with a standard application of three times/week – can be considered as a secondary option, with the strong reservation that there are limited data on its safety when used in the treatment of viral infections during pregnancy. So far, several reports have indicated minimal systemic absorption after topical applications and the absence of any adverse fetal effects [34–36].

In addition, the list of absolutely contraindicated agents includes podophyllin/podophyllotoxin (category C), which has been associated with multiple fetal malformations – and even death – and also bleomycin (category D) [37–39].

21.6 Fungal infections

21.6.1 Systemic treatment for fungal infections

In use for a long time, amphotericin B (category B) – although an agent with high toxicity – has proven to be neither embryotoxic or teratogenic, thus gradually evolving into the agent of choice for extensive and severe fungal infections. The recommended dosage consists of 0.5–1.5 mg/day for 4–12 weeks [40]. There are no data

available in lactation. The closest challenger, and a safe alternative in pregnancy and lactation, would probably be terbinafine (category B) – administered in daily doses of 250 mg – which was reported as non-embryotoxic in animal reproduction studies, yet lacking any clinical evidence from pregnant or lactating human patients [6, 26, 40].

The list of substances whose administration is contra indicated or forbidden during pregnancy includes griseofulvine (category C) – which has been reported to cause adverse effects in animal studies – and other antifungal agents such as ketoconazole (category C), fluconazole (category C) or itraconazole (category C). Ketoconazole has been shown to be embryotoxic and teratogenic and to cause sexual ambiguity in male fetus by inhibiting androgen synthesis [2]. The clinical reports on the use of fluconazole and itraconzole reveal contrasting and sometimes ambiguous results. For instance, fluconazole, a new imidazole, has been tested on 226 women in the first trimester of pregnancy, who took it for vaginal candidosis in low doses (50–150 mg) with no result of congenital malformations or other adverse effects. Yet, when administered in high doses of 400 mg/day it has been proved to be teratogenic. Likewise, itraconazole was shown to have teratogenic effects after the administration of high doses in animal studies [5], while a prospective cohort study reported the use of itraconazole to be safe in pregnancy [41].

21.6.2 Local treatment for fungal infections

Low percutaneous absorption makes topical antifungal therapy as the treatment of choice for mycotic infections, whenever treatment is really needed. Nystatin (category B) administered once/twice daily, clotrimazole (category B) once/twice daily, and miconazole (category C) once/twice daily, represent the first-line treatment with no reported teratogenic or embryotoxic effects after their use in pregnant patients. Natamycin (category C), econazole (category C), and bifonazole (category C) are the second-line treatments for local antimycotic therapy [20].

21.7 Parasitic infections

21.7.1 Systemic and local treatment for parasitic infections

Permethrin (category B) 5% cream represents the first-line topical therapy for the treatment of scabies during pregnancy and

lactation. The actual treatment consists of the application of the cream from head to toe, leaving it for 12 hours before washing it off, then repeating the whole process after 1 week. Alternatively, permethrin 1% lotion is indicated for the treatment of pediculosis; the recommended treatment involves an evening application of the lotion on dry clean hair, lasting for about 12 hours (thus it is left on the hair during the night under a shower cap), followed by another identical session after 1 week. Other antiscabies agents – although safe in pregnancy but which are less effective – are benzyl benzoate (category N) 25% or malathion (category B) 0.5%. Crotamiton (category N) cream and lotion 10% are not yet considered a therapeutic option, due to the absence of controlled clinical trials. With proven teratogenic effects when administered in high doses in animal reproduction studies, ivermectin (category C) is to be avoided [1, 42]. Furthermore, mebendazole (category C), an antinematode agent (enterobius, ascaris, trichuris, hookworms, ankylostoma, whipworms, roundworms), reported as not manifesting major teratogenic risk in human studies in the treatment of *Enterobius vermicularis* infestation [43], can be used in pregnancy, except during the first trimester.

Albendazole (category C), an antiechinococcosis agent, is generally contraindicated in pregnancy, with clinical data from animal studies pointing out the existence of teratogenic effects [6], despite other studies revealing the absence of any fetal malformations after use of albendazole, and thus classifying it as tolerable in severe cases, during all trimesters of pregnancy [44, 45]. Finally, other antiparasitic medications like thiabendazole (category C) are not recommended in pregnancy, due to the absence of relevant clinical data which can establish its levels of safety in pregnant humans.

21.8 Antipruritics

21.8.1 Systemic antipruritics

With a clinical history going back decades, the first-generation H_1 antihistamines such as chlorpheniramine (category B), dexchlorpheniramine dimetindene (category B), mebhydrolin (category C), and clemastine (category C) are considered relatively safe in pregnancy. However, with no available data regarding their use during lactation, physicians should focus on other means of treatment in this period. Overall, these agents are considered the first-line therapy during early pregnancy for all

allergic skin conditions [2, 33]. It is important that, whenever administered, the medical practitioner takes into account the possible side effects on the central nervous system (e.g. sedative effect) as an important causal factor which may trigger changes in the quality of a patient's life [46]. In this context, the standard prescription involves the intake of the substance, once a day, before sleeping. When selecting a drug of choice from the therapeutic portfolio of the first-generation H_1 antihistamines, some authors propose (dex)chlorpheniramine (category B) [46], while others suggest diphenhydramine (category B) [47]; administration of the latter should be avoided in the last 2 weeks of pregnancy [6, 26] as it might trigger oxytocin-like effects with consecutive uterine contraction and fetal hypoxia if administered intravenously or in overdose [48]. In addition, a withdrawal syndrome has been reported after diphenhydramine administration [49]. On the other hand, other first-generation H_1 antihistamines, e.g. hydroxyzine (category C), associated with fetal malformations in 5.8% of cases if administered in the first trimester of pregnancy [6, 50, 51], should be avoided.

With the exception of loratadine (category B) and cetirizine (category B), there are limited clinical data regarding the administration of second and third generation H_1 antihistamines during pregnancy. Loratadine and cetirizine can be administered with no risks during late pregnancy and lactation for allergic skin conditions. In particular, neither animal reproduction studies [2], nor human clinical trials – e.g. Schaefer et al.'s study on 4000 pregnancies [20] – revealed any teratogenic effects associated with the use of loratadine. A contrasting possible association with hypospadias reported by a Swedish study [52] was later classified as a random unrelated occurrence [53].

The list of antipruritics to be (partially) excluded from any therapy for pregnant and lactating women includes H_2 inhibitors such as cimetidine (category C) whose administration in high doses has proven to have antiandrogenic effects, with the possible result of feminization of a male fetus, and doxepin (category C), a tricyclic antidepressant, whose use in the last part of pregnancy is associated with multiple side effects such as cardiac dysrhythmias, respiratory distress, paralytic ileus, or irritability for the fetus/newborn [26].

21.8.2 Local antipruritics

Topical antipruritic medication like menthol (category N), polidocanol (category C), camphor (category N) or emollients with

urea (3–10%) are complementary therapies for the cessation of pruritus, and are safe for use in pregnancy [33].

21.9 Glucocorticosteroids

21.9.1 Systemic glucocorticosteroids

Despite the fact that during pregnancy the pharmacokinetics of the systemic corticosteroids are changing, clinical experience indicates the absence of any fetal malformations following the administration of regular doses of prednisone (category C), prednisolone (category C), or methylprednisolone (category C) during the first trimester of pregnancy [6]. Nevertheless, clinical trials in animal reproduction studies indicate that high doses of systemic corticosteroids may cause cleft palate. Furthermore, according to a series of clinical reports, both betamethasone (category C) and dexamethasone (category C) are known to cause intrauterine growth retardation or, rarely, lip/palate cleft if exposed in the first trimester of pregnancy [54–56], mainly due to the fact that both drugs are crossing the placenta in higher amounts than, for instance, prednisone, prednisolone, and methylprednisolone. Due to this specific clinical behavior, betamethasone and dexamethasone can be used to induce fetal lung maturation.

In conclusion, the first-line treatment for cases of severe inflammatory skin diseases during pregnancy or lactation consists of prednisone, prednisolone, or methylprednisolone. A start-up prescription can be based on prednisolone – a metabolite of prednisone – at an initial dose of 0.5–1 mg/kg/day. In severe cases, in which these doses prove unsatisfactory for achieving the planned clinical objectives, physicians can opt for an increase in the dose to up to 2 mg/kg/day, yet only for a short period (weeks). The golden rules of prednisolone administration involve avoiding a long exposure to high dosage (2 mg/kg/day) and monitoring the neonatal adrenal function and also fetal growth [33].

21.9.2 Local glucocorticosteroids

First-line topical treatment involves the daily/half-daily application of mild to moderate potent corticosteroids like hydrocortisone acetate 1% (category C) or betamethasone valerate 0.1% (category C) for no more than several weeks [57]. On the other hand, there is no academic consensus regarding the

overall safety of what is proposed to be the second-line topical treatment for maternal inflammatory skin diseases, namely the therapy focused on potent/more potent corticosteroids like clobetasol propionate (category C), especially due to reports which associate it with infant lip/palate cleft after being used during the first trimester of pregnancy [58], and also with possible low birth weight.

21.10 Immunomodulators/immunosuppressive therapy

Topical calcineurin inhibitors like tacrolimus (category C) or pimecrolimus (category C) can be used in pregnancy, once daily, for the treatment of atopic dermatitis, if no alternatives are available and if the potential maternal benefits outweigh the potential fetal risks. According to the existing clinical data tacrolimus is not associated with human teratogenicity [6] while pimecrolimus shares a similar classification, yet only in animal reproduction studies [59]. No data are, however, available regarding the safety of the products in lactation.

On the other hand, the safest procedure to be performed on pregnant patients is immunopheresis – a new variant of plasmapheresis consisting of the removal of the circulating immunoglobulins from the serum; this is especially helpful in severe autoimmune skin conditions [33].

21.11 Analgesics

21.11.1 Systemic analgesics

Acetaminophen (paracetamol) is a category B analgesic and antipyretic agent whose administration is generally considered to be safe during all trimesters of pregnancy and lactation. The standard therapeutic plan consists of doses of 500 mg ingested by the mother every 6–8 hours, but only for a short period of time. The peak plasmatic concentration occurs after 30–60 minutes and the diffusion is in all body tissues. Acetylsalicylic acid (aspirin), belonging to category C, represents the second-choice analgesic and antipyretic agent. The prescribed medication involves the ingestion of 500 mg of substance every 6 hours, with the pill crunched in the mouth after meals. The main negative effect of

aspirin therapy is its association – when used in the first trimester of pregnancy – with an increased risk of gastroschisis [60].

Another possible therapeutic alternative, codeine (category C), commonly used for its analgesic or antitussive effects, is only partially safe when chosen for the treatment of pregnant patients. In particular, clinical reports associate it with respiratory malformations in human fetuses – mainly occurring when the mother was exposed to the substance in the first trimester of pregnancy [1], with withdrawal symptoms after stopping the drug intake – especially during late pregnancy if ingested in high doses. However, when needed low doses of codeine (7.5–15 mg) can be occasionally administered to pregnant patients [26].

The nonsteroidal anti-inflammatory agents NSAIDs (ketoprofen, ibuprofen, diclofenac, naproxen, indomethacin) are classified as belonging to category B during the first two trimesters of pregnancy, but evolve to category D in the last trimester of gestation as – due to the inhibition of prostaglandin synthesis – side effects like oligohydramnios, prolonged labor or premature closure/constriction of the ductus arteriosus might appear [2]. If anti-inflammatory therapy is needed the standard prescription consists of ibuprofen in doses of 200–400 mg, 3 times a day, after meals, or diclofenac 50 mg 2–3 times daily, after meals, but exclusively if the patient is in the first and second trimester of pregnancy or in the lactation period. Starting with the 28th week of pregnancy, as they become category D agents, their use is contraindicated [1].

Furthermore, the use of opioid narcotics during pregnancy has not been associated with teratogenicity, if administered in small occasional doses [26]. Nevertheless, morphine (category C) is contraindicated as it can cause infant withdrawal syndrome, if the mother becomes addicted [26, 61], neonatal respiratory depression [26], or inguinal hernias during childhood [62].

21.11.2 Local analgesics (Anesthesia)

Local anesthesia for excisions or skin biopsies during pregnancy or lactation should raise no concerns, as lidocaine (category B) – used with or without adrenaline (epinephrine) (category B) – is classified as safe during pregnancy. Another local analgesic which can be considered is EMLA (lidocaine 2.5% and prilocaine 2.5%), also a category B agent. Mepivacaine or bupivacaine, classified within category C, are outclassed by the already mentioned safer alternatives [1].

21.12 Antiseptics (disinfectants)

The first-line therapeutic portfolio of disinfectants consists of alcohols such as ethanol (category C) or isopropanol (category N), topically applied to the skin, mucosa or wounds. Chlorhexidine (category B) is also considered equally safe, especially when used on intact skin or mucosa. Iodine-containing agents (category C), which can theoretically trigger functional disturbances of the fetal thyroid gland (transient hypothyroidism), should be avoided if the area on which the substance is to be applied involves body cavities [20].

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Vitamins, Minerals, Trace Elements, and Dietary Supplements

22

Jean-Jacques Dugoua

22.1 Introduction

During pregnancy, a woman is in a unique physiological state in comparison to a non-pregnant woman. Drug exposure over the course of a pregnancy is a concern to women due to the potential risk of fetal malformations. A study on the pharmaceutical drug use of 295 pregnant women found that 37% of them reported non-compliance with their existing drug regimen due to hesitations on drug use during pregnancy [1]. In a similar study where women taking antidepressants during pregnancy were compared to controls, 15% of antidepressant users chose to discontinue their medication despite receiving evidence-based reassuring information of relative safety [2]. Another study found that a significant number of pregnant women had misperceptions and distorted information regarding the potential teratogenic risk of drugs and chemicals [3].

In cases where women hesitate with their existing drug regimen or choose to discontinue their drug use during pregnancy, they may seek natural health products (NHPs) as alternatives to pharmaceutical drugs. “NHP” is an “umbrella” term for supplements,

dietary supplements, natural medicines or other such commonly used designations and includes: vitamins, minerals, herbal medicines, fatty acids, amino acids, probiotics, and nutraceuticals. The term NHP will be used throughout this chapter to refer to this group of compounds.

For many women, NHPs may seem a reasonable alternative to pharmaceutical drugs as they may equate the term "natural" with apparent safety. In many parts of the world, women still use herbal medicines for fertility and childbirth even when attended by Western medicine [4, 5]. In traditional Chinese medicine, there are approximately 20 herbal medicines used in pregnancy [6]. Research into native North Americans' medicinal plants has found over 100 plants used as abortifacients and approximately 350 plants used as female gynecological aids [7]. The use of NHPs by pregnant women is somewhere between 7 and 55% [8]. A survey in the United States (US) of 734 pregnant women found that 7.1% of women used herbal medicines during their pregnancy; most commonly Echinacea, St. John's wort, and ephedra [9]. A US survey of 242 pregnant women found that 9.1% of women used herbal supplements during their pregnancy and 7.5% of women used these at least weekly; most commonly garlic, aloe, chamomile, peppermint, ginger, Echinacea, pumpkin seeds, and ginseng [10]. Another US survey of 150 pregnant women found that 13% of women used dietary supplements during their pregnancy; most commonly Echinacea, pregnancy tea, and ginger [11]. A survey in South Africa of 229 pregnant women found that 55% of women reported ingesting herbal medicines during pregnancy [12].

Although hesitant, some health care providers may recommend herbs during pregnancy. A survey of 242 medical and naturopathic doctors and students reported that only one physician actually recommended a herbal product to a pregnant patient whereas 49% of the naturopathic doctors felt comfortable doing so [13]. According to a survey of midwives in the US, between 45 and 93% of midwives will prescribe some form of NHP to women during their pregnancy [14]. Of the midwives who used herbal preparations, 64% used blue cohosh, 45% used black cohosh, 63% used red raspberry, 93% used castor oil, and 60% used evening primrose oil [14].

Despite the prevalent use of NHPs by pregnant women, there is a large knowledge gap on NHP safety and efficacy during pregnancy. Many modern and classic texts warn against the use of herbal medicines during pregnancy for up to one-third of the products listed in their monographs [15–18]. However, most resources provide little information on the data used to evaluate reproductive toxicity apart from reports of historical use of herbs

as abortifacients or uterine stimulants or animal data of genotoxicity or teratogenicity [15–18]. In some cases, pregnant women who inclined toward NHP treatments during their pregnancy and lactation will seek the advice of clinicians. In other cases, women may seek information on the internet. With knowledge that the evidence of NHP safety in pregnancy and lactation is perceived to be poor, clinical pharmacologists are faced with a dilemma on how to counsel these women.

With this in mind, the purpose of this chapter is to review the existing clinical and pharmacologic data on commonly administered NHPs during pregnancy. This chapter will present clinical studies of NHPs given throughout pregnancy according to trimester.

22.2 First trimester

The first trimester of pregnancy is arguably the riskiest time in a women's gestation. Organogenesis for the majority of the body systems occurs in this period, with some continuing onto the second trimester. Women are vulnerable to teratogens, potentially leading to birth defects in their offspring. Women are also at risk of miscarriages during this period. The NHPs discussed in this section are the most commonly administered for their preventive or therapeutic benefit, or most commonly reported as potential teratogens.

22.2.1 Vitamin B_6 (pyridoxine)

Vitamin B_6, also known as pyridoxine, is a water-soluble vitamin that is part of the B vitamin group. In the body, vitamin B_6 is required for amino acid, carbohydrate, and lipid metabolism, for neurotransmitter synthesis (serotonin and norepinephrine), and for myelin formation. Through a number of metabolic reactions, pyridoxine is converted to coenzymes pyridoxal phosphate and pyridoxamine phosphate.

Clinically, pyridoxine is best known in pregnancy as a treatment for pregnancy-induced nausea and vomiting. A randomized controlled trial (RCT) was conducted on 59 pregnant women where 31 women received 25 mg of pyridoxine hydrochloride tablets orally every 8 hours for 72 hours while 28 women received a placebo following the same regimen [19]. At study end, there was a significant difference in mean nausea scores favoring the pyridoxine group versus placebo ($p<0.01$) [19]. Only 8 of the 31

women experienced vomiting in the pyridoxine group compared to 15 of the 28 women in the placebo group ($p<0.05$) [19]. In another RCT, 342 women were randomized to receive either oral pyridoxine hydrochloride 10 mg every 8 hours or placebo [20]. Post-therapy, there was a significant decrease in the mean of nausea scores in the pyridoxine versus the placebo group ($p<0.01$) [20]. Although non-significant, there was a greater reduction in the mean number of vomiting episodes in the pyridoxine group versus the placebo group ($p=0.0552$) [20].

Pyridoxine has also been studied comparatively with ginger, another commonly used pregnancy antiemetic, for their efficacy in the treatment of pregnancy-induced nausea and vomiting. One study showed no difference in efficacy between the two while the other study favored ginger. An RCT was conducted on 138 pregnant women (GA ≤ 16 weeks) where they received either 500 mg of ginger orally or 10 mg of pyridoxine three times daily for 3 days [21]. At study end, both ginger and pyridoxine significantly reduced nausea scores ($p<0.001$) and the number of vomiting episodes ($p<0.01$) [21]. When comparing the efficacy, there was no significant difference between ginger and vitamin B_6 for the treatment of nausea and vomiting during pregnancy [21]. An RCT was conducted on 126 pregnant women where they randomly received either 650 mg of ginger or 25 mg of pyridoxine three times daily for 4 days [22]. Both ginger and pyridoxine significantly reduced nausea and vomiting scores ($p<0.05$) where the mean score change after treatment with ginger was significantly greater than with pyridoxine ($p<0.05$) [22].

Vitamin B_6 may also have preventive benefits to the newborn and mother. A case–control study showed that treatment with pyridoxine during pregnancy does not indicate a teratogenic risk to the fetus, but may provide some protective effect for cardiovascular malformations [23]. Pyridoxine taken orally as capsules or lozenges was shown to decrease the risk of dental decay in pregnant women (capsules: relative risk (RR) 0.84 [0.71 to 0.98]; lozenges: RR 0.68 [0.56 to 0.83]) [24].

Vitamin B_6 status appears to be important in pregnancy as a deficiency may increase the risk of certain conditions and symptoms. A study found an association between oral lesions and vitamin B_6 deficiency during pregnancy [25]. Another study observed lower Apgar scores in infants whose mothers were vitamin B_6 deficient compared to those with adequate vitamin B_6 status [26].

Pyridoxine appears to be generally well tolerated in pregnancy. Minor side effects, such as sedation, heartburn and arrhythmia, have been reported [22]. A small clinical trial reported a decrease

in mean birth weight with pyridoxine supplementation during pregnancy [27]. Although there is conflicting evidence and disagreement in the scientific literature, there may be a risk that high dose maternal pyridoxine intake may cause neonatal seizures [28–31].

22.2.2 Vitamin B_9 (folic acid)

Vitamin B_9, most commonly referred to as folic acid or folate (general term for folic acid), is a water-soluble vitamin that is part of the B vitamin group. Folic acid plays a key role in intracellular metabolism where it plays a role in DNA synthesis. In pregnancy, folic acid is best known for preventing neural tube defects. In 2007, new recommendations were published for dosing folic acid for pre-conception, pregnancy, and lactation [24]. These recommendations are summarized in Figures 22.1 and 22.2.

In addition to preventing malformations, folic acid may play a role in the development of Down syndrome. A case–control study was conducted on 31 women who had pregnancies affected by Down syndrome where blood samples were collected from these women and compared to 60 age-matched controls from mothers who had not experienced miscarriages or abnormal pregnancies [32]. Plasma levels of homocysteine were significantly increased in Down syndrome mothers ($p=0.004$) and serum levels of folic acid were significantly decreased in Down syndrome mothers ($p=0.0001$). No significant differences in vitamin B_{12} and B_6 levels were observed between groups [32]. Based on these results, low levels of serum folic acid and elevated levels of plasma homocysteine may contribute to the occurrence of Down syndrome [32].

There is some conflicting evidence that folic acid supplementation during pregnancy may increase *or* decrease the risk of atopy and asthma in children. A prospective birth cohort study ($n=557$) found that folic acid supplementation in late pregnancy was associated with an increased risk of childhood asthma at 3.5 years (relative risk (RR) =1.26 [1.08–1.43]) and with persistent asthma (RR=1.32 [1.03–1.69]) [33]. At 5.5 years of age, childhood asthma levels did not reach statistical significance (RR=1.17 [0.96–1.42]) [33]. The KOALA Birth Cohort Study ($n=2834$) found opposite results [34]. In this study, maternal folic acid supplementation during pregnancy was not associated with an increased risk of wheeze, lung function, asthma or related atopic outcomes in the offspring [34]. Higher maternal intracellular folic acid in pregnancy tended toward a small

1. Women of reproductive age should be advised about the benefits of folic acid in addition to a multivitamin supplement during wellness visits (birth control renewal, Pap testing, yearly examination) especially if pregnancy is contemplated.
2. Women should be advised to maintain a healthy diet, as recommended in Eating Well With Canada's Food Guide (Health Canada). Foods containing excellent to good sources of folic acid are fortified grains, spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn, and oranges. However, it is unlikely that diet alone can provide levels similar to folate-multivitamin supplementation.
3. Women taking a multivitamin containing folic acid should be advised not to take more than one daily dose of vitamin supplement, as indicated on the product label.
4. Folic acid and multivitamin supplements should be widely available without financial or other barriers for women planning pregnancy to ensure the extra level of supplementation.
5. Folic acid 5 mg supplementation will not mask vitamin B12 deficiency (pernicious anemia), and investigations (examination or laboratory) are not required prior to initiating supplementation.
6. The recommended strategy to prevent recurrence of a congenital anomaly (anencephaly, myelomeningocele, meningocele, oral facial cleft, structural heart disease, limb defect, urinary tract anomaly, hydrocephalus) that has been reported to have a decreased incidence following preconception/first trimester folic acid ± multivitamin oral supplementation is planned pregnancy ± supplementation compliance. A folate-supplemented diet with additional daily supplementation of multivitamins with 5 mg folic acid should begin at least three months before conception and continue until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4-6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4-1.0 mg).

   From Wilson et al. (2007). Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can Dec 29(12): 1003-26.

Figure 22.1 Folic acid recommendations for pre-conception, pregnancy, and lactation [24].

- OPTION A: Patients with no personal health risks, planned pregnancy, and good compliance require a good diet of folate-rich foods and daily supplementation with a multivitamin with folic acid (0.4-1.0 mg) for at least two to three months before conception and throughout pregnancy and the postpartum period (4-6 weeks and as long as breastfeeding continues).
- OPTION B: Patients with health risks, including epilepsy, insulin dependent diabetes, obesity with BMI >35 kg/m^2, family history of neural tube defect, belonging to a high-risk ethnic group (e.g., Sikh) require increased dietary intake of folate-rich foods and daily supplementation, with multivitamins with 5 mg folic acid, beginning at least three months before conception and continuing until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4-6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4-1.0 mg).
- OPTION C: Patients who have a history of poor compliance with medications and additional lifestyle issues of variable diet, no consistent birth control, and possible teratogenic substance use (alcohol, tobacco, recreational non-prescription drugs) require counselling about the prevention of birth defects and health problems with folic acid and multivitamin supplementation. The higher dose folic acid strategy (5 mg) with multivitamin should be used, as it may obtain a more adequate serum red blood cell folate level with irregular vitamin/folic acid intake but with a minimal additional health risk.

From Wilson et al. (2007). Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can Dec 29(12): 1003-26.

Figure 22.2 Recommended strategies (Options A, B or C) for folic acid supplementation during pre-conception, pregnancy, and lactation.

decreased risk for developing asthma, i.e. inverse association with asthma risk at age 6 to 7 years in a dose-dependent manner (P for trend=0.05) [34]. In the Avon Longitudinal Study of Parents and Children (ALSPAC), they found no association between the common polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene associated with allergic sensitization and dietary folic acid intake [35].

22.2.3 Vitamin A

Vitamin A is a fat-soluble vitamin involved in vision, gene transcription, skin health, and immune function. In pregnancy, vitamin A may be teratogenic in a dose-dependent manner. A clinical trial showed that daily intake of 6000 IU of vitamin A during pregnancy did not increase the incidence of fetal malformations [36]. In doses above 10,000 IU daily, vitamin A intake may be teratogenic. A prospective cohort study of 22,748 pregnant women found a higher prevalence of cranial neural crest defects in women consuming >15,000 IU and >10,000 IU of vitamin A daily than in women consuming only 5000 IU daily; approximately one infant in 57 had a malformation attributable to vitamin A supplementation [37]. The most marked frequency of malformations was observed in newborns born to women who had consumed high levels of vitamin A before the seventh week of gestation [37]. A case–control study of 1000 livebirths reported that a teratogenic effect might exist for exposures to high doses of vitamin A (>40,000 IU daily), particularly during the first 3 months of pregnancy [38]. On the other hand, another case–control study on 955 newborns found no association between vitamin A exposure at doses >8000 IU or >10,000 IU daily and malformations in general, cranial neural crest defects, or neural tube defects [39]. Based on the current research, women should not exceed 6000 IU of vitamin A daily during their pregnancy. It should be noted that most prenatal multi-vitamin/mineral products are set at 6000 IU or lower as a daily dose; in some cases, the vitamin A component is removed entirely to be replaced by beta-carotene, a vitamin A precursor. Clinicians should be careful to ensure that women planning a pregnancy are taking a prenatal multi-vitamin/mineral and not a "general" multi-vitamin/mineral, which typically contains higher doses of vitamin A.

Despite its teratogenic risk, vitamin A has many benefits in pregnancy. A systematic review of five trials involving 23,426 women found that weekly vitamin A supplementation resulted in a reduction in maternal mortality up to 12 weeks postpartum and a reduction in night blindness [40]. A study of women with habitual miscarriages showed that vitamin A levels were significantly lower in these women versus controls [41].

Special attention should be placed on pregnant women with an HIV infection or acquired immune deficiency syndrome (AIDS) and vitamin A supplementation. There is conflicting evidence that vitamin A may either increase vertical transmission of HIV to the fetus or have no effect on vertical transmission [42–46]. A systematic review and meta-analysis published in the Cochrane Database of Systematic Reviews concluded that based on the current

best evidence, antenatal or postpartum vitamin A supplementation probably has little or no effect on mother-to-child transmission of HIV [47].

22.2.4 Vitamin E

Vitamin E is a fat-soluble vitamin that does not appear to have a specific metabolic role. The major function of vitamin E is as a chain-breaking antioxidant that prevents the formation of free radicals; thereby, most of its action is due to its antioxidant properties. In pregnancy, vitamin E may be of potential concern when taken in the first trimester. A case–control study compared 276 mothers of children with congenital heart defects (CHD) to 324 control mothers with healthy children [48]. Vitamin E intake above 14.9 mg/day in the first 8 weeks of pregnancy was associated with a 1.7- to 9-fold increased CHD risk [48].

A study of 50 spontaneously aborting women compared to pregnant women whose pregnancies terminated uneventfully found a significantly higher percentage of aborting women had individual values of serum alpha-tocopherol above the 0.50 mg/100 mL normal limit [49]. However, a study of 40 women with habitual abortion (HA) compared with controls showed that vitamin E levels were significantly lower in women with HA [41]. Based on the current published scientific literature, it is unclear what the safe dose of vitamin E is in the first trimester, excluding its use in a prenatal multi-vitamin/mineral.

22.2.5 Calcium

Calcium is a mineral found in the human body, particularly bones, teeth, blood, extracellular fluid, muscle, and other tissues. Calcium is essential for nerve transmission, muscle contraction, vascular contraction, vasodilation, glandular secretion, cell membrane and capillary permeability, enzyme reactions, respiration, renal function, and blood coagulation [50]. In pregnancy, calcium has been studied for its effect of improving bone mineralization.

A systematic review and meta-analysis were conducted on the effects of calcium supplementation during pregnancy focusing on hypertensive disorders of pregnancy and related maternal and child outcomes [51]. The meta-analysis included 13 RCTs, involving 15,730 pregnant women, comparing at least 1 g daily of calcium during pregnancy versus placebo [51]. In comparison to the placebo group, calcium supplementation led to a reduction in the following average risks for pregnant women: high blood pressure (RR = 0.65 [−0.53–0.81]), preeclampsia (RR = 0.45 [0.31–0.65]), preterm birth (RR = 0.76 [0.60–0.97]), preterm birth

among women at high risk of developing preeclampsia (RR=0.45 [0.24–0.83]), and composite outcome maternal death or serious morbidity (RR=0.80 [0.65–0.97]) [51]. The protective effect of calcium was greatest in women with high-risk hypertensive disorders (RR=0.22 [0.12–0.42]) and women with low baseline calcium intake (RR=0.36 [0.20–0.65]) [51]. One death occurred in the calcium group and six in the placebo group, a difference which was not statistically significant (RR=0.17 [0.02–1.39]) [51]. In the offspring, calcium supplementation reduced systolic blood pressure where childhood systolic blood pressure greater than the 95th percentile was reduced (RR=0.59 [0.39–0.91]) [51]. In these RCTs, most of the women were of low hypertensive disorder risk and consumed a low calcium diet at baseline [51].

22.3 Second trimester

After the challenges of morning sickness, miscarriage, and birth defect prevention, the second trimester is usually a time of respite for the pregnant mother. Nonetheless, neonatal bone mineralization is an important concern as is the treatment of pregnant-associated disease, such as gestational diabetes. NHPs related to these topics will be discussed in this section.

22.3.1 Calcium

An RCT was conducted on 256 pregnant women who received 2000 mg daily of elemental calcium or placebo from 22 weeks' gestation till delivery [52]. Post-therapy, there were no significant differences between treatment groups in gestational age, birth weight, or length of the infants, or in the total body or lumbar spine bone mineral content [52]. Total body bone mineral content, however, was significantly greater in infants born to calcium-supplemented mothers in the lowest quintile of dietary calcium intake (less than 600 mg/day) versus controls [52]. Thus, maternal calcium supplementation of 2000 mg daily during the second and third trimesters can increase fetal bone mineralization in women with low dietary calcium intake [52]. In a prospective cohort study of 87 pregnant women belonging to poor socioeconomic groups, daily calcium supplementation of 300 and 600 mg of elemental calcium from the 20th week of gestation onward until term brought a significant increase in the bone density of the offspring born to these mothers versus offspring from unsupplemented mothers [53].

22.3.2 Vitamins C, E, and zinc

A meta-analysis was conducted on seven studies involving the administration of vitamins C and E to 5969 pregnant women at risk of preeclampsia [54]. The meta-analysis found that combined vitamin C and E supplementation had no potential benefit in improvement of maternal and neonatal outcome but increased the risk of gestational hypertension in women at risk of preeclampsia (RR=1.3 [1.08–1.57]) and the risk of low birth weight in newborns (RR=1.13 [1.004–1.270]) [54].

Maternal intake of foods containing vitamin E and zinc during pregnancy was associated with a reduction in the risks of developing childhood wheeze and asthma [55]. A longitudinal cohort study was conducted on 1861 children born to women recruited during pregnancy and followed up at 5 years [55]. Maternal nutrient status was assessed via food frequency questionnaire and plasma levels [55]. Maternal vitamin E intake during pregnancy was negatively associated with wheeze in the previous year (OR=0.82 [0.71–0.95]), asthma ever (OR=0.84 [0.72–0.98]), asthma and wheeze in the previous year (RR=0.79 [0.65–0.95]), and persistent wheezing (OR=0.77 [0.63–0.93]) [55]. Maternal zinc intake during pregnancy was negatively associated with asthma ever (OR=0.83 [0.71–0.78]) and active asthma (OR=0.72 [0.59–0.89]) [55].

22.3.3 Chromium

Chromium is an essential trace element most commonly used in the management of type 2 diabetes. In pregnancy, a small study was conducted on eight women with gestational diabetes where they received 8 mcg/kg of body weight daily of chromium picolinate and reported improved blood glucose control [56].

22.3.4 Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a vitamin-like fat-soluble substance found in the mitochondria of human cells. CoQ10 is involved in the electron transport chain and generation of adenosine triphosphate (ATP). A study demonstrated that CoQ10 supplementation during pregnancy may prevent preeclampsia in at-risk women [57]. An RCT was conducted on 235 women at risk of preeclampsia where they received 200 mg of CoQ10 or placebo daily from 20 weeks of pregnancy until delivery [57]. There was a significant reduction ($p=0.035$) (RR=0.56 [0.33–0.96]) in preeclampsia where 30 women (25.6%) in the placebo group developed preeclampsia compared with 17 women (14.4%) in the CoQ10 group [57].

22.4 Third trimester

The third trimester is another risky period for a pregnant woman as she may be at risk of preterm delivery and many complications with delivery. The NHPs discussed in this section are mostly herbal medicines or fatty acids that are typically administered for labor induction.

22.4.1 Castor oil (*Ricinus communis*)

Castor oil is produced by cold pressing ripe seeds from the castor plant. Unlike the seeds, castor oil does not contain the deadly poison ricin [58]. Castor oil is mostly known for its strong laxative effect. In pregnancy, it is used to induce labor where 93% of US midwives reported using castor oil for labor induction [14].

A prospective cohort study was conducted on 103 pregnant women with intact membranes at 40 to 42 weeks' gestational age [59]. Women were assigned to receive a single oral dose of castor oil (60 mL) or no treatment [59]. Groups were compared for onset of labor in 24 hours, method of delivery, presence of meconium-stained amniotic fluid, Apgar score, and birth weight. Following administration of castor oil, 30 of 52 women (57.7%) began active labor compared to 2 of 48 (4.2%) receiving no treatment [59]. When castor oil was successful at initiating delivery, 83.3% (25/30) of the women delivered vaginally [59]. Castor oil appears to work on the uterus by producing hyperemia in the intestinal tract, which causes reflex stimulation of the uterus [60]. Castor oil may also increase prostaglandin production, which stimulates uterine activity [59].

There have been some case reports of adverse effects associated with castor oil intake at delivery. One case reported precipitous and tumultuous labor, meconium-stained fluid, and an amniotic fluid embolism causing cardiorespiratory arrest [61]. A survey of midwives in Texas, US, reported that castor oil was more likely to cause adverse effects, including reports of an emergency c-section as a result of abruption, severe gastric cramping and diarrhea, and dehydration [62].

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Herbs and Alternative Remedies

23

Henry M. Hess

Pregnancy can be an ideal time to use herbal and alternative remedies. Herbs are often mild preparations of natural compounds that can be just perfect for some of the discomforts and illnesses during pregnancy. Several studies have shown that as many as 50% of women will choose herbs and alternative remedies as therapies during pregnancy [8, 13–15, 18].

Although herbal therapies have been used for centuries, herbs are complex mixtures of many compounds, and some have potentially significant negative effects for both the pregnant woman and the fetus. In the companion book *Drugs during Pregnancy and Lactation*, 2nd edition, edited by Schaefer, Peters, and Miller [13] we focused on the safety of herbs during pregnancy and counseled health care providers that the use of some herbs during pregnancy can have significant risks depending on the herb, the purity of the preparation, and the timing of use during pregnancy. In this

chapter, we have focused on the herbs and alternative remedies that are safe and efficacious for many conditions during pregnancy. Using the best available up-to-date scientific evidence, evidence based and traditional, we have listed and categorized herbs, supplements, and other alternative remedies that are safe and efficacious for many of the common medical conditions and discomforts that occur during pregnancy.

For herbs and supplements, we have listed forms and dosage. It is important to recognize that herbs are extracts of plants or plant roots, and they therefore contain numerous compounds. This is very different to a pharmaceutical preparation, which is usually a single active ingredient. Different forms of herbal preparations will have different compounds and concentrations depending on how the plant or plant root is extracted. Herbal preparations are usually available in the following forms: teas or infusions (hot water extracts of dried herbs), capsules, dried extracts, and tinctures (alcohol extracts of dried herbs). The most common forms of herbs used in pregnancy are teas or infusions. These usually have the lowest concentration, contain the least amount of compounds, and therefore are the safest. Capsules and dried extracts are the next most commonly used. Tinctures should be avoided during pregnancy because of their higher concentrations as well as the use of alcohol as a carrier.

A very important difference between the use of herbs or supplements and a pharmaceutical preparation is the integrity and purity of the specific herb or supplement preparation [13]. There is no Food and Drug Administration (FDA) oversight of these products so patients as well as providers need to find guidance on product selection from sources such as ConsumerLab.com [3]. We strongly recommend frequent evaluation of the integrity of the individual preparation.

We also have discussed the use of hypnosis and meditation as alternative remedies for many of the common discomforts and illnesses in pregnancy and delivery, where otherwise medications might be needed.

23.1 Herbal teas frequently used during pregnancy

The herbs most frequently used during pregnancy are teas or infusions. Some herbal teas have specific indications; others are used by patients as general health tonics. Although there are minimal clinical trials available, and minimal evidence-based proof of safety and efficacy in terms of Western medical standards, herbal

teas have been used for centuries and are regarded as safe and efficacious during pregnancy. It is the general recommendation [13] that consumption of herbal teas be limited to two cups per day during pregnancy. This is similar to the safety data regarding coffee. The safety is unknown when used at higher levels. The following herbal teas are frequently and safely used during pregnancy [1, 5, 13, 15]:

- **Red raspberry leaf** – Relief of nausea, increase in milk production, increase in uterine tone, and ease of labor pains. **There is some controversy over the use of red raspberry leaf in the first trimester**, primarily because of concern of stimulating the uterine tone and potentially causing miscarriage. Use in the second and third trimester is generally considered safe.
- **Peppermint** – Nausea, flatulence. Tea is the most common; enteric-coated tablets (187 mg three times a day maximum) are also used. Peppermint may cause gastroesophageal reflux.
- **Chamomile (German)** – Gastrointestinal irritation, insomnia, and joint irritation.
- **Dandelion** – A mild diuretic, and to nourish the liver; known for high amounts of vitamins A and C, and the elements of iron, calcium, and potassium, as well as trace elements.
- **Alfalfa** – General pregnancy tonic; a source of high levels of vitamins A, D, B, and K, minerals and digestive enzymes; thought to reduce the risk of postpartum hemorrhage in late pregnancy.
- **Oat and oat straw** – Sources of calcium and magnesium; helps to relieve anxiety, restlessness, insomnia, and irritable skin.
- **Nettle leaf** – Traditional pregnancy tonic; source of high amounts of vitamins A, C, K, calcium, potassium, iron. NB: nettle root is different from nettle leaf; it is used for inducing abortions and is not safe in pregnancy.
- **Slippery elm bark** – Nausea, heartburn, and vaginal irritations.

23.2 Essential oils used as aromatherapy during pregnancy

Some essential oils are frequently used as aromatherapy during pregnancy, and the ones described below are considered to be safe and efficacious during pregnancy based on traditional and historic use. They should always be used carefully, in

well-diluted form, and in an aromatherapy diffuser. They should not be ingested. Such essential oils and their uses are listed [1, 13, 15]:

- **Chamomile** – Respiratory tract disorders.
- **Tangerine** – Antispasmodic, decongestant, general relaxant.
- **Grapefruit** – Stimulant, antidepressant.
- **Geranium** – Dermatitis, hormone imbalances, mood dysfunction, viral infections.
- **Rose** – Astringent, used for mild inflammation of the oral and pharyngeal mucosa.
- **Jazmine** – Stimulant, antidepressant, anxiety.
- **Ylang-ylang** – Antispasmodic, cardiac arrhythmias, anxiety, antidepressant, hair loss, intestinal problems.
- **Lavender** – Loss of appetite, nervousness and insomnia.

23.3 Herbs used as capsules or dried extracts

23.3.1 Ginger

- Nausea and vomiting of pregnancy. Dose: 250 mg 3 to 4 times per day.
- Ginger is the herb with the most evidence-based data showing efficacy and safety in pregnancy. When used at 250 mg 3 to 4 times a day, it is considered safe and effective for nausea and vomiting of pregnancy, as well as hyperemesis gravidarum [1, 6, 8, 13–15, 18]. Most of the antiemetic activity is believed to be due to the constituent 6-gingerol which acts directly in the gastrointestinal tract. The constituent galanolactone also acts on 5-HT3 receptors in the ileum, which are the same receptors affected by some prescription antiemetics. Ginger's antiemetic activity may also involve the central nervous system, where the constituents 6-shogaol and galanolactone act on serotonin receptors [18].

23.3.2 Cranberry

- Prevention and treatment of urinary tract infection. Dose: 300 to 400 mg 3 times a day. Can cause gastrointestinal upset.
- Cranberry is one of the most commonly used herbs during pregnancy, primarily for the prevention and treatment of urinary tract infections. Although there is a long history of the

safe and efficacious use of cranberry during pregnancy, there are very little evidence-based data [1, 8, 13–15, 18, 24]. The literature does suggest that cranberry capsules may be more efficacious than cranberry juice. Studies on the pharmacology of cranberry show that the proanthocyanidins in cranberry interfere with bacterial adherence to the urinary tract epithelial cells [18].

23.3.3 Echinacea

- Prevention and treatment of upper respiratory tract infections, vaginitis, herpes simplex virus. Dose: 900 mg of dried root or equivalent 3 times a day.
- There is a long history of safe and efficacious use of Echinacea in pregnancy [1, 7, 8, 13–15, 17, 18]. Two scientific studies are frequently cited as evidence-based studies showing its safety in pregnancy [9, 18]. The efficacy is based on tradition, not evidence based. Echinacea is known to inhibit the influenza virus and the herpes simplex I and II viruses. It has been shown to increase the proliferation of phagocytes in the spleen and bone marrow, stimulate monocytes, increase the number of polymorphonuclear leukocytes and promote their adherence to the endothelial cells, and activate macrophages [18].

23.3.4 St. John's wort

- Treatment of mild to moderate depression, anxiety, and seasonal affective disorder. Dose: 300 mg 3 times daily, of a standardized extract.
- Although there is minimal evidence-based medicine of its safety or efficacy in pregnancy, St. John's wort is considered safe in pregnancy by the German Commission E, the American Herbal Products Association, and much traditional literature [1, 7, 8, 13–15, 17, 18]. It is very commonly used in pregnancy for mild to moderate depression. Studies have shown that St. John's wort acts as an SSRI (selective serotonin reuptake inhibitor), and inhibits the reuptake of serotonin, norepinephrine, and dopamine. Also of significance is that the hypericin in St. John's wort induces some of the cytochrome P450 enzymes and may interfere with the metabolism of other drugs similarly metabolized [1, 18]. St. John's wort can cause photo-sensitization, so caution must be exercised, and patients advised [1].

23.3.5 Valerian

- Treatment of anxiety and insomnia. Dose: 2 to 3 g of crude herb as a capsule or tea at bedtime.
- Valerian root is also very commonly used in pregnancy, but there is lack of any evidence-based medicine showing either its efficacy or safety. Some scientific publications as well as the World Health Organization [1] suggest caution in the use of valerian during pregnancy because its safety has not been clinically established. However, the German Commission E [1, 7, 13] and the *Botanical Safety Handbook* [17], as well as several articles and books, support the use of valerian during pregnancy and generally conclude that occasional use is safe and efficacious when used in the dose described above. Valerian has sedative, anxiolytic, antidepressant, anticonvulsant, hypotensive, and antispasmodic effects. The major constituents, valerenic acid and kessyl glycol, are known to cause sedation in animals. Valerenic acid may inhibit the enzyme system responsible for the catabolism of gamma-aminobutyric acid (GABA), thereby increasing GABA concentrations and decreasing central nervous activity [18].

23.3.6 Milk thistle/silymarin

- Treatment for intrahepatic cholestasis of pregnancy, alcoholic and non-alcoholic liver cirrhosis, chronic and acute viral hepatitis, drug-induced liver toxicity, fatty degeneration of the liver. Dose: 400 mg of standard silymarin extract in 2 to 3 divided doses per day. Recommended to be used in the second and third trimester of pregnancy only [11, 18, 20, 21].
- There are many references in the natural and herbal literature to the use of milk thistle in pregnancy for liver dysfunctions and for enhancement of milk production [18]. There are also concerns and warnings about possible significant side effects and insufficient evidence-based studies to recommend milk thistle in pregnancy. However, the few evidence-based studies do support the safety and efficacy for use of this herb for specific situations described above. In four studies, no evidence of adverse effects was reported in the mothers and offspring [18, 20, 21]. There are no reports of estrogenic effects on the fetus, a potential concern because the constituents of milk thistle are flavonolignans [18]. There have been many suggestions as to the mechanism of action, but silybin has been shown to stimulate RNA polymerase A and DNA synthesis, increasing the regenerative capacity of the liver. Silymarin, the active constituent, is thought to competitively bind some toxins and act

as a free radical scavenger [18]. Clinically, regular consumption of milk thistle has been shown to reduce elevated liver enzymes [18].

23.3.7 Senna

- Treatment of constipation. Dose: 10 to 60 mg at bedtime for a maximum of 10 days, in the second and third trimester [10, 13, 14, 18].
- The use of senna in pregnancy is very controversial because senna is a member of the anthraquinone laxatives group, thought to be contraindicated in pregnancy because overstimulation of the bowel or bladder has the potential to irritate/stimulate the uterus, potentially causing premature labor, or even miscarriage in the first trimester [13]. The *Compendium on Herbal Safety* offered the opinion that senna should be avoided during pregnancy [13, 18]. However, there are no reports in the literature showing senna to be contraindicated during pregnancy. A review article has reported that senna would appear to be the stimulant laxative of choice during pregnancy, probably because of the poor intestinal absorption of senna compared to the other anthraquinone laxatives [10, 18]. Traditional use has shown that with careful use, senna may be used in the second and third trimester with minimal risk. There are no studies showing a risk in the first trimester either, but avoidance of use in the first trimester is recommended based on the potential for senna to be an abortifacient [12]. The literature reports that sennosides irritate the lining of the large intestine, causing its contraction and evacuation. Sennosides A and B also induce fluid secretion from the colon, softening the stool, and may also induce prostaglandins for more effective contractions of the colon. The laxative effect occurs 8 to 12 hours after administration, although sometimes up to 24 hours can be required. It is important not to overuse senna in pregnancy. Diarrhea, fluid loss, electrolyte imbalance, as well as habituation, have been reported [18].

23.3.8 Horse chestnut

- Chronic venous insufficiency – 300 mg twice daily of Venostasin (reg)retard (240 to 290 mg of horse chestnut seed extract, standardized to 50 mg escin). NB: Do not use unprocessed raw horse chestnut preparations. These can be very toxic and lethal when ingested in adults [18, 22].
- Oral horse chestnut has been shown in the literature to significantly reduce leg edema and varicose veins and chronic venous

insufficiency when taken orally [1, 18, 22]. While oral horse chestnut has been found very useful, caution is advised when recommending this herb to a pregnant woman, as there is minimal evidence-based study of efficacy or safety in pregnancy. However, there is a randomized placebo-controlled trial of 52 women with symptomatic leg edema attributed to pregnancy-induced venous insufficiency where improvements were found with horse chestnut, and the authors did not observe any serious adverse effects after 2 weeks [18, 22].

23.4 Herbal topical preparations used in pregnancy

23.4.1 Aloe vera gel

- Treatment of skin burns. Topical use only [1, 7, 13, 15, 18].
- There is a long history of safe and efficacious topical use of aloe vera gel during pregnancy, but no evidence-based studies.

23.4.2 Horse chestnut

- Treatment of severe hemorrhoids in pregnancy. Topical 2% gel (Escin) 2–4 times a day [4, 18].
- The few studies done have shown safe and efficacious use, particularly with severe hemorrhoids in pregnancy.

23.5 Non-herbal supplements used in pregnancy

23.5.1 Fish oils

- Support for the development of a healthy mother and baby – including prevention of colds in infants of treated mothers, support for the heart, immune system, inflammatory response, the development and maintenance of the brain, eyes, and central nervous system. Dose: 300–400 mg DHA (docosahexaenoic acid) and 100–220 mg of EPA (eicosapentaenoic acid) daily. The freshness of the oil is important because rancid fish oils have an extremely unpleasant odor and also may not be as effective [3, 18].
- Omega 3s have been found to be essential for both neurological and early visual development of the baby. Research has confirmed that adding omega 3s to the diet of pregnant women has a positive effect on visual and cognitive development of

the child. Studies also have shown that higher consumption may reduce the risk of allergies in the fetus, may help to prevent preterm labor and delivery, lower the risk of preeclampsia, may increase birth weight, and may decrease the incidence of maternal and postpartum depression [3, 18]. Omega 3s are a family of long-chain polyunsaturated fatty acids that are essential nutrients for health and development. They are not synthesized by the human body, and must be obtained through diet or supplementation. The typical American diet is greatly lacking in omega 3s. The two most beneficial omega 3s are EPA and DHA, and they work together in the body [3].

- Because of the potential for contamination of fish oils by mercury and other potential contaminants, the use of purified fish oils is essential [3]. Flaxseed is not a substitute for fish oils in pregnancy, as flaxseed constituents have potential estrogenic properties [13, 18].

23.5.2 Probiotics

- Prevention and treatment of vaginal infections (yeast vaginitis and bacterial vaginosis). Dose: At least 4 billion organisms daily, with at least 1 billion each of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* [3, 5, 18].
- May prevent preterm labor in the third trimester when caused by these infections. Maintains digestive systems in the face of pregnancy-related problems, eases diarrhea, constipation, hemorrhoids, as well as boosting the immune system. Studies have also shown that babies and toddlers up to 2 years old were 40% less likely to suffer eczema/atopic dermatitis when mothers took probiotics. Limited studies have also shown that probiotics help limit excessive weight gain in pregnancy.

23.6 Herbs used to induce labor

In the traditional literature [16, 23], there are herbs and herbal mixtures reportedly used to induce labor. According to the recent literature [16, 18], many midwives in the US and elsewhere in the world use herbal mixtures to induce labor. There is no evidence-based literature establishing the safety or efficacy of the herbs used, but there exists some literature expressing concern regarding significant risks and bad outcomes. Currently, there simply is not enough evidence of safety to recommend these treatments for this indication.

23.7 Acupuncture and acupressure therapy in pregnancy

There is a significant amount of evidence-based medicine in the literature regarding the use, efficacy, and safety of acupuncture and acupressure therapy in pregnancy [2, 8].

The practice of acupuncture and acupressure dates back 5000 years. Acupuncture is based on a belief that a vital energy called "qi" (chee) flows through the body along pathways called meridians. Along these meridians there are some 2000 acupuncture points where the thin needles (or pressure) are inserted to relieve symptoms, cure the disease, and restore balance.

In pregnancy, both the mother and infant benefit. Acupuncture has been used successfully in pregnancy for maintenance of health, treatment for preexisting medical issues, and treatment of pregnancy related issues (including psychological issues, physical problems, fatigue, morning sickness, heartburn, constipation, hemorrhoids, back pain and sciatica, edema, carpal tunnel syndrome, and rhinitis of pregnancy). Acupressure is popular for relief of nausea and vomiting in pregnancy. It has also been successfully used to assist with versions in breech presentations, and for pain analgesia in labor. Acupuncture has also been found efficacious for many postpartum disorders such as fatigue, postpartum vaginal discharge, postpartum depression, mastitis, insufficient or excessive lactation, and postoperative healing. A trained and experienced acupuncturist understands and knows the target points for the needle insertions during pregnancy, and for specifically related pregnancy problems. Efficacy rates are significant, and there are no known risks. Acupuncture (and acupressure) may be very useful for pregnancy-related situations where otherwise a medication may be necessary.

23.8 Meditation and hypnosis in pregnancy

Meditation [19] and hypnotherapy [12] are excellent natural therapies for managing health during pregnancy, including the discomforts of pregnancy and labor and delivery as well as prevention of illnesses, and management of illnesses. Used for centuries, there are recent and long-term evidence-based studies showing their efficacy and safety. These modalities, like other natural therapies, are becoming very popular with pregnant and postpartum women. The internet has several sites as well as CD products making it easier for patients to learn about and practice mindfulness meditation and self-hypnosis.

Mindful meditation and hypnosis have many similarities. Hypnosis is a slightly deeper process where it is easier for suggestions to be incorporated by the subconscious. Hypnosis has been used for pregnancy-related symptoms including labor and delivery and has become particularly popular since the 1930s. Evidence-based data show that hypnosis in particular helps with an easier and less painful labor. For mindful meditation during pregnancy, studies have shown that it decreases stress, and produces endorphins which reduce physical pain. It has also been shown to increase the production of dehydroepiandrosterone (DHEA), which stimulates the production of T and B lymphocytes, supporting the immune system. DHEA has also been linked to decreasing sadness and depression, both before and after birth. Studies have also shown that the meditation increases the level of melatonin, supporting the immune system and increasing the quality of sleep and improved mood. Endorphins are similarly increased, which have a strong pain relieving effect in preparation for childbirth. Studies also show that mindfulness meditation can be very effective in lowering blood pressure and heart rate, potentially lowering the risk of preeclampsia.

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Envenomations and Antivenoms During Pregnancy 24

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24.1 General principles about envenomation

Envenomation is the exposure to a poison or toxin resulting from a bite or sting from an animal such as a snake, scorpion, spider, or insect, or from marine life. Information about a bite or sting is often obtained secondhand from patients or primary caregivers, and additional exposures may go unreported.

US poison centers assist in the assessment and management of envenomations and the national database is a source of demographic and clinical data regarding such cases, although the database is subject to a number of limitations. The database does not include all envenomations, as there is no mandatory reporting requirement, and the source of information on clinical effects and treatments is secondhand and often incomplete and

Table 24.1 Cases of envenomation in pregnancy, 2000–2011. American Association of Poison Control Centers Database

Envenomation	Common name	Cases
Scorpion		2136
Spider		217
	Black widow	214
	Brown recluse	1
Snake		161
	Unidentified	57
	Copperhead	51
	Rattlesnake	39
	Constrictor	10
TOTAL		2514

variably documented [1]. Shown in Table 24.1 are the most common envenomations during pregnancy reported to poison control centers.

Symptoms from an envenomation often produce a characteristic reaction, depending on the venomous animal involved, which may be the same as in the non-pregnant patient, or may be more pronounced during pregnancy due to physiologic circulatory changes. For example, black widow envenomation may produce hypertension, tachycardia, sweating, and other signs of adrenergic excess in both the pregnant and non-pregnant patient. The effect of stimulating muscle contraction, however, may result in uterine contractions, with other consequences in pregnancy [17].

Pharmacologic therapy of envenomations is directed at symptomatic and supportive care, as well as specific therapy, if available and appropriately indicated. In general, symptomatic and supportive drugs are used sparingly and at the lowest effective doses in order to avoid confounding clinical assessment [3]. The need for tetanus toxoid should be assessed and administered to people at risk of tetanus regardless of pregnancy status. Human studies have not suggested an increase in adverse outcome after maternal inoculation [3]. Routine use of antibiotics (e.g. dicloxacillin, cefazolin, metronidazole) after envenomation is questionable unless signs suggestive of infection are present [4], which is unlikely to be seen prior to 24–48 hours after an envenomation. There is no evidence in support of prophylactic antibiotics, even in snake envenomation, with its extensive tissue injury effects,

unless tissue necrosis occurs. Any short-term course of standard antibiotics is presumed to be safe during pregnancy.

Any decision to use a specific antidotal therapy – antivenom – must take into account the potential for allergic reactions, either Type 1 (anaphylaxis or anaphylactoid) or Type 3 (serum sickness) and the risk–benefit assessment in pregnancy includes the potential for adverse effects on the fetus. Antivenoms are generally indicated when there is: [1] evidence of systemic envenomation (e.g. neurotoxicity, coagulopathy, rhabdomyolysis, persistent hypotension, or renal failure) or [2] severe local envenomation effects, for example extensive local tissue injury in snakebite [5, 6]. Although no antivenoms have been specifically evaluated in pregnant patients, long experience has not demonstrated any particular risks, and, in general, the management which is most beneficial to the mother will provide the best outcome for the pregnancy. Consultation with a poison center and its medical toxicologist or other clinician with expertise in managing envenomations is recommended when treating an envenomated pregnant patient. The poison center can also be helpful in locating and obtaining antivenom for unusual or nonnative (exotic) envenomations, which may not be stocked at the hospital pharmacy.

Pregnancy tests are recommended for any woman of reproductive age who is envenomated. Other laboratory studies are guided by the usual assessment of any particular envenomation. Additional serum testing (electrolytes, coagulation tests, liver enzymes, etc.) may be needed depending upon the scenario and clinical course. As an example, it is standard to obtain a complete blood count, platelets, and coagulation studies with certain *Crotalinae* (rattlesnake, copperhead, cottonmouth) snakebites.

Concerns about pregnancy, or obvious pregnancy-related risks or effects, may prompt providers to observe envenomated patients longer in an emergency department, or to admit them to the hospital for monitoring or additional treatment. There are few data on pregnancy outcomes in most envenomations. Some studies and reports of high rates of fetal loss in other parts of the world may be secondary to venomous animals with higher degrees of maternal or fetal toxicity or may be secondary to a lack of appropriate medical care in their native environments. In the US there are few reports of significant, adverse pregnancy outcomes with envenomations, other than when there is significant maternal toxicity. Regardless, before discharge from a health facility, patients should be coherent, tolerate oral intake, have no progression of symptoms, and any pain should be adequately controlled with oral analgesics. Pregnant patients should have no pregnancy-related

risks and appropriate discharge instructions and follow-up care should be given. More long-term evaluations of individual cases are encouraged to better characterize the long-term results of specific envenomations in pregnancy and to determine any additional strategies other than standard therapies.

24.2 Snake bites

Snake bites account for approximately 125,000 annual deaths worldwide [7]. There are five families of snakes: Atractaspididae, Colubridae, Elapidae, Hydrophiidae, and Viperidae. In the United States, viperids are represented by three genera and over 30 species of the subfamily Crotalinae (rattlesnakes, copperheads, and cottonmouths) and two genera and three species of one Elapid, the coral snake. Crotalinae generally produce a syndrome characterized by local tissue injury, which may include necrosis, and hematologic toxicity, including thrombocytopenia, hypofibrinogenemia, and other coagulation abnormalities. There may be systemic effects, such as nausea and diaphoresis or hypotension and, rarely, neurotoxicity such as muscle fasciculations or weakness, that usually do not result in respiratory compromise. The coral snake, typical of elapids, generally does not produce significant local tissue effects and primarily produces neurotoxicity, which can include respiratory arrest. In other parts of the world, elapids may produce significant local tissue injury, rhabdomyolysis, renal injury or other effects [8]. Knowledge about the toxicity profiles of local snake species is vital, and expert advice should be sought when managing a snake envenomation in a pregnant patient, when the envenomation is unfamiliar to the clinician or severe or unusual effects occur.

Snakes vary widely in appearance, and identification is rarely possible by the clinician. A digital photo taken at a safe distance may be useful. Venom detection kits can be useful in determining the appropriate monovalent antivenom [9]. If there is doubt about the snake's identity, treatment should be administered for an unidentified snake bite.

24.2.1 Management during pregnancy

Initial first aid is directed at reducing spread of the venom and expediting transfer to an appropriate medical center [10, 11]. The patient should be removed from the snake's territory, kept warm and at rest, and be reassured. The injured part of the body

should be immobilized in a functional position below the level of the heart. As with non-pregnant adults, ongoing management is largely supportive but may be accompanied with significant allergic phenomena. Investigations into venom suctioning or removal devices do not show additional benefit and are therefore not recommended [11].

Use of antivenom for systemic or severe local envenomation warrants consideration of corticosteroids, epinephrine, or antihistamines beforehand. Corticosteroids are often used with early and late allergic reactions. Prolonged corticosteroids are associated with fetal growth impairment in humans [12]. These medications increase oral clefting in experimental animals yet are less likely to do so in humans [13, 14]. Premedication, especially with epinephrine, is appropriate in settings in which either antivenom is associated with high rates of allergic reactions, or the management of acute allergic reactions is problematic due to limited staffing or facilities [9]. Injection of epinephrine in experimental animals interferes with embryo development, possibly through hemodynamic effects and decreased uterine perfusion [15]. Human studies on inhaled beta-sympathomimetics during pregnancy have not suggested an increased risk of birth defects [16].

Snake envenomations during pregnancy may be accompanied by blood coagulation abnormalities, so prolonged monitoring in the hospital is understandable [16–19]. We recommend a minimum of 8 hours of fetal heart rate (FHR) monitoring if the pregnancy is at a viable stage (usually beginning at 24 weeks) [18]. Reports of decreased fetal movements and fetal death a few days after clinically significant envenomations suggest ongoing outpatient surveillance with daily FHR monitoring for up to 1 week may be helpful in identifying pregnancies at risk for adverse outcome [20, 21].

24.2.2 Reports during pregnancy

Several reports about snake bites during pregnancy have revealed normal outcomes, even when antivenom was necessary [16, 22, 23]. Adverse pregnancy affects may be due largely to maternal illness. For example, there are case reports of placental abruptions associated with a maternal hypercoagulable state following snake bite [24, 25]. In another report, death of a gravid woman after a snake bite was believed to be associated with supine hypotension from aortocaval compression rather than entirely from the venom itself [9]. A third case involved a woman bitten by a pit viper at 10 weeks' gestation [19]. Although the woman recovered from systemic symptoms, a fetal demise was confirmed 1 week later on ultrasound examination.

In a letter to the editor from Sri Lanka in 1985, indirect evidence of placental transfer was described with adverse fetal effects in the absence of maternal symptoms [26]. Four cases of maternal snake bites were reported in which fetal movements were perceived as being less or became absent before or in the absence of maternal illness. In three of those cases, where bites occurred at 32 to 36 weeks' gestation, the fetuses survived and were delivered alive at term. In the fourth case, of unspecified gestational age, fatal maternal illness developed, although not until after fetal movement had slowed. The fetus was stillborn the day before the mother's death, after the onset of maternal signs and symptoms of illness.

A 2010 report from Nepal described a 33 week pregnant woman who was bitten by a green tree viper [24]. She developed vaginal bleeding, anemia, and severe abnormalities in her coagulation profile. Her fetus was dead when she presented for care. After correction of the coagulation profile, labor was induced and she subsequently recovered.

A 1992 review of 50 cases of non-rattlesnake viper snake bites during pregnancy in the United States reported a 10% maternal mortality rate and a 43% fetal demise rate [17]. A 2002 series of 39 snake-envenomated pregnant women had a fetal loss rate of 30% [20]. Our report in 2010 with rattlesnake bites specifically, using the American Association of Poison Control Centers (AAPCC) database, suggested a lower short-term risk in pregnancy than prior reports [18]. Sixty-one poison control centers reported a total of 8413 rattlesnake bites, with 767 (9.1%) involving reproductive-age women. Of these, 11 (1.4%) were pregnant. There were no significant differences between pregnant and nonpregnant victims with regard to rates of hospital admission, antivenom administration, or overall outcome codes. There were no adverse reactions to antivenom in pregnant women and no maternal deaths or fetal losses while in the hospital or during the period of poison control center follow-up.

24.3 Spider bites

Spider bites are rare medical events, since only a handful of species cause difficulties in humans [2]. Very few species have muscles powerful enough to penetrate human skin, and most of those spiders bite humans only in rare circumstances. Furthermore, the venom of most spiders has little or no effect [59]. The most likely to inflict significant bites in humans are widow and false black widow spiders and recluse spiders.

A spider bite usually presents acutely as a localized solitary papule, pustule, or wheal. Systemic symptoms can accompany some envenomations [2]. Allergic reactions typically result from contact with spiders. Widow bites cause unremarkable local lesions but are sometimes accompanied by prominent, proximally-spreading pain and localized diaphoresis. Bites from recluse spiders are notorious for becoming necrotic.

Most patients' reports of spider bites are unreliable. The diagnosis of a spider bite is thus highly suspect, unless the patient actually observes a spider inflicting the bite and can retrieve it for identification. Those who did not clearly witness the bite should be presumed to have some other disorder, and the finding of multiple skin lesions essentially excludes the diagnosis of spider bite. Papules and pustules should be carefully unroofed and cultured to identify infectious causes. Common infections that could be mistaken for spider bites include staphylococcal and streptococcal infections, a skin lesion of early Lyme disease, and atypical presentations of herpes zoster or herpes simplex.

24.3.1 Management during pregnancy

Most patients who sustain a spider bite require only topical therapy (clean with mild soap and water; apply cold, not frozen, packs; elevate affected body part). Patients with moderate to severe envenomations, such as those from widow spiders as characterized by severe local symptoms or the presence of regional or systemic symptoms, require supportive care and monitoring for complications. Oral analgesia, parenteral benzodiazepines, and tetanus toxoid may be used safely during pregnancy in the short term [2].

Early surgical excision or debridement is not recommended for patients with recluse spider bites that have a dusky center or other signs of developing necrosis. There are reports of approximately 1000 pregnant women who have been treated with dapsone without adverse effect [60–63]. Those reviews and case reports were not specifically designed to study possible reproductive effects of dapsone, however, and dosage and timing of dapsone use were not always clear. Some cases of hemolytic anemia have occurred in mothers and their offspring after exposure to dapsone, both during gestation and while breastfeeding [61, 64].

Mortality from widow bites is low, although envenomation can cause significant pain and require hospitalization [59]. Antivenom reduces the pain and the need for hospitalization, especially when other therapies are unsuccessful [65]. Several widow spider antivenoms are commercially available, although there is sufficient

chemical similarity among widow venoms that all widow antivenoms provide some degree of relief. Representative symptoms in which antivenom therapy may be valuable include the following: severe and persistent local pain or muscle cramping, significant pain or diaphoresis extending beyond the immediate site of the bite, alterations in vital signs, difficulty breathing, and nausea and vomiting.

24.3.2 Reports during pregnancy

Black widow spider envenomation is a rare occurrence in pregnant women, and short-term outcomes appear to be favorable [66]. There are four published case reports of widow spider bites in pregnant women, whose gestational ages ranged from 16 weeks to 38 weeks [67]. In addition, we reported a large observational study based on a review of the AAPCC database from 2003 to 2007 [68]. Of the 12,640 human black widow spider envenomations, 3194 (25.3%) involved women of reproductive age and 97 were pregnant. Comparing pregnant with non-pregnant women, there were no significant differences in recommended or administered treatments. A significantly higher percentage of pregnant than non-pregnant patients were treated at a health care facility where they were either released (36.1% vs. 19.9%, $p<0.001$) or admitted (13.4% vs. 4.0%, $p<0.001$). There were no documented immediate pregnancy losses in that series.

There have been six reported cases of *Loxosceles* (recluse spider) bites in pregnant women. Although the victims were apparently in considerable discomfort, pregnancy outcomes were favorable in all instances [69, 70]. We have been unable to locate any reference about the use of *Loxosceles* antivenom during pregnancy.

24.4 Scorpion stings

Although scorpion envenomation is not usually a significant problem, stings from *Centruroides exilicauda* (*sculpturatus*) can lead to major neurologic toxicity. *C. exilicauda* is found primarily in northern Mexico and the southwestern United States (e.g. Arizona, New Mexico, western Texas, southeastern California, and near Lake Mead, Nevada). The tubercle at the base of the stinger of its lobster-like body is helpful in differentiating this highly neurotoxic scorpion from other species [27, 28].

Envenomations involve injection of a scorpion toxin protein which acts as a neurotoxin [29]. In neuronal membranes,

these toxins cause incomplete inactivation of sodium channels which lead to membrane hyperexcitability, and consequent repetitive uncontrolled firing of axons [30]. Enhanced release of neurotransmitters at synapses and the neuromuscular junction leads to excessive neuromuscular activity and autonomic dysfunction [31].

After *C. exilicauda* envenomation, symptoms typically begin immediately, progress to maximum severity within 5 hours, and improve within 9 to 30 hours without antivenom therapy [32]. Local pain and paresthesias occur at the sting site. The puncture wound is usually too small to be observed initially, and local inflammation does not occur customarily. Symptoms often radiate proximally up the affected extremity but may present in remote sites as generalized paresthesias. Rarely, envenomations produce cranial nerve or somatic skeletal neuromuscular dysfunction.

24.4.1 Management during pregnancy

Most scorpion stings result in mild envenomations [32]. Management would be the same during pregnancy by cleansing of the sting site, using oral medications (e.g. ibuprofen 10 mg/kg; maximum single dose 800 mg), and administering tetanus prophylaxis. An increased risk of miscarriage was reported with use of ibuprofen or naproxen particularly near the time of conception, but a reanalysis of the data weakened the association [33]. Some, though not all, epidemiology studies have suggested that use of nonsteroidal anti-inflammatory drugs, including ibuprofen, during pregnancy may increase the risk of cardiac defects and gastroschisis. Use during late pregnancy should be avoided due to concerns about premature ductal closure [33, 34].

Pregnant patients should be observed for about 4 hours to ensure that there is no further progression. Those with rare but significant systemic symptoms, including restlessness, muscular fasciculation, hypersalivation, or cranial nerve palsies require immediate supportive interventions [35]. Airway management, including frequent suctioning of oral secretions or endotracheal intubation may be indicated in patients with pulmonary edema accompanied by hypoxemia or significant difficulties maintaining airway patency. Maintaining adequate maternal oxygenation is of upmost importance to the fetus. Close monitoring for and treatment of myocardial ischemia is also warranted in patients with severe symptoms. Short-term treatments during pregnancy may include intravenous fentanyl (1 mcg/kg) for pain, and intravenous benzodiazepines (lorazepam or continuous midazolam infusion) may be given for sedation and to treat muscle spasticity.

Use of antivenom in the United States has been controversial because of the low risk of mortality (even with severe envenomations given proper supportive care), lack of availability of an FDA-approved antivenom, and an approximately 3% risk of anaphylaxis from administration of the antivenom (no longer available) [35]. Antivenom (Nasacort®, US; Alacrity®, Mexico) is widely available in Mexico and approved for use in the United States [36]. No immediate hypersensitivity reactions, serum sickness, or deaths have been reported in studies of adults and children from Mexico receiving the antivenom [32].

24.4.2 Reports during pregnancy

Evidence regarding the natural history and treatment of scorpion envenomations in pregnancy is derived from animal data. Investigations in gravid rodents have revealed mixed results. Turkish investigators reported that pregnant rats treated with venom from the scorpion *Androctonus amoreuxi* had an elevated incidence of fetal resorption, ossification defects, and reduced weight [27]. Use of radiolabeled venom indicated only a small fraction (0.08–0.331/0) was detected in fetuses or placenta [27]. A single subcutaneous injection in pregnant rats with venom from the scorpion *Tityus serrulatus* at 0.3 or 1 mcg/kg on gestation day 5 or 10 did not produce adverse effects on the offspring [37]. Pregnant rats exposed to *Tityus bahiensis* venom at doses not toxic to the dame bore offspring with alterations in the time to achieve developmental milestones [38].

The 5-hydroxytryptamine in some scorpion venoms may act as a uterine stimulant and induce abortion [39–41]. There are also anecdotal reports about pregnant women treated with antivenom without adverse fetal effects [42]. We have been unable to locate any additional references on possible adverse reproductive or lactation effects from these agents.

24.5 Hymenoptera

Hymenoptera of clinical relevance include winged insects such as bees, wasps, hornets, and yellowjackets, as well as wingless insects such as imported fire ants. Stings related to these hymenoptera involve the injection of venom, which is almost always acutely painful and noticed by the patient. Although most stings require only symptomatic relief for acute pain, anaphylactic hypersensitivity occurs in 0.3–3% of patients with a venom allergy [43].

24.5.1 Winged hymenoptera

Exposure to the venom of winged hymenoptera is common. Depending on the climate, 56.6–94.5% of the general adult population remember receiving a hymenoptera sting at least once from the Apidae family (honey bees and bumblebees) or the Vespidae family (yellowjackets and wasps) [44]. The venom of winged hymenoptera consists of 95% aqueous proteins, which are the substrate in human hypersensitivity reactions [45]. In the setting of hymenoptera venom allergy (HVA), the stings of the Apidae and the Vespidae families can result in life-threatening anaphylaxis, and the most severe reactions can be refractory to single or multiple doses of epinephrine [46, 47]. Hymenoptera venom allergy is an IgE-mediated disease. Its clinical manifestations result from the degranulation of mast cells or basophils, triggered by the binding of allergens to specific IgE on the surface of these cells.

In the HVA setting, sequelae of stings range from large local reactions at the sting site to life-threatening anaphylaxis [48]. Initial management of the winged hymenoptera sting should include removal of foreign bodies such as the detached aculeus or "stinger", and application of cold compresses. Uncomplicated local reactions should resolve within hours. Large local reactions may be treated with oral prednisone and antihistamines [49]. Rarely, the stings of the winged hymenoptera can result in life-threatening anaphylaxis, and the most severe reactions can be refractory to single or multiple doses of epinephrine [46, 47].

24.5.2 Imported fire ants

Imported fire ants are aggressive venomous insects found in the southern half of the United States from Florida to California [50]. These ants have been known to attack in large numbers when a nest is disturbed and when food availability is scarce. Strong mandibles and an aculeus on the mandible allow the ant to powerfully inject venom, rotate, and inject several more times [51]. The stings of imported fire ants create an immediate burning sensation appropriate for their name. Their venom consists primarily of alkaloid compounds with hemolytic and cytotoxic properties. The small amount of aqueous proteins is responsible for systemic reactions and anaphylaxis, while the alkaloid component is likely only relevant to humans in cases of mass attacks with numerous stings [52].

Initial management of this sting includes measures similar to treatment of winged hymenoptera stings. Often a sterile pustule, which is pathognomonic for an imported fire ant sting, develops along with an intense pruritis. Topical steroids and antihistamines

are appropriate, and the pustule should be left intact to prevent infection.

24.5.3 Management during pregnancy

In the pregnant patient, as in the general population, the primary concern after hymenoptera venom exposure is identification and treatment of life-threatening anaphylaxis. In this setting, optimization of maternal cardiopulmonary status is of primary concern. Standard treatment for signs of anaphylaxis (widespread hives, wheezing, airway compromise, or altered mental status) should be administered, including early administration of intramuscular epinephrine in the anterolateral aspect of the thigh. We recommend trendelenberg/left lateral recumbent positioning, which may be especially important as poor cardiac return has been suggested as the final step in anaphylactic deaths [53]. An anaphylactic death during pregnancy has been attributed *primarily* to uterine compression of venous return [53].

Immunotherapy for venom allergy for prevention of future reactions in previously stung patients with large local or systemic reactions has been available for over 30 years and is highly effective [54]. Initiation of venom immunotherapy in pregnancy is generally avoided by allergists due to a lack of safety data, though limited reports of use in pregnancy do not suggest an increased risk of adverse outcomes. As such, pregnant women may be allowed to continue venom immunotherapy if initiated prior to pregnancy [55]. Care should be taken to monitor for signs of preterm labor in this group, because uterine contractions have been reported during or after venom immunotherapy in several case reports [44]. Victims of hymenoptera envenomation who develop systemic reactions or severe local reactions should be referred upon discharge to an immunologist for evaluation and possible treatment with immunotherapy [56].

24.5.4 Reports during pregnancy

Few case reports of hymenoptera envenomation are in the obstetric literature, and predictably focus on clinically significant events such as anaphylaxis. It is unknown if pregnancy makes systemic reactions to hymenoptera venom more or less likely. Unfavorable outcomes are most likely to be reported, and fetal effects of envenomations are speculative.

A case report from Croatia described a multigravida who presented at 27 weeks' gestation with anaphylaxis after a wasp sting. The authors note that delivery occurred at 35 weeks despite tocolysis and a cerclage and attribute the delivery to a

"postanaphylactic reaction". The child developed normally after the delivery [57].

Another adverse outcome was reported in association with anaphylaxis after a bee sting. A 31-year-old was stung at 30 weeks' gestation and developed severe anaphylaxis. Subsequently, the fetus was noted to have an increased biparietal diameter and decreased movement. Spontaneous preterm labor occurred at 35 weeks, and the infant was noted to be cyanotic and hypotonic. The infant died at 64 days, and autopsy demonstrated cystic cavitation of the white matter consistent with hypoxic injury. Infantile encephalomalacia was attributed to maternal anaphylaxis after bee envenomation [58].

A case from the United Arab Emirates linked placental abruption and intrauterine death with an ant sting. A 21-year-old woman at 40 weeks' gestation presented with dyspnea and swelling after a Samsun ant sting. She was treated for anaphylaxis, then developed vaginal bleeding 16 hours later. On ultrasound, a placental separation and fetal demise were diagnosed. A retroplacental clot was confirmed at delivery [59].

24.6 Jellyfish

Jellyfish are responsible for more exposures as well as more severe sequelae than any other source of marine envenomation. Jellyfish stings are common in both warm and cold coastal waters of the United States and Australia [83]. The Florida coast alone reports between 60,000 and 200,000 envenomations each year [71]. Although there are over 100 species of jellyfish known to cause human envenomations, the most clinically relevant species include *Chironex fleckeri*, *Carukia barnesi*, and the Portuguese man-of-war [72].

The mechanism of injury in jellyfish stings starts with skin-to-tentacle contact, which allows transfer of multiple venomous capsules called nematocysts. The nematocysts discharge rapidly on contact, allowing intradermal injection of proteinaceous toxins [73]. The subsequent local and potentially systemic reactions range from minor nuisance to myocardial injury or Irukandji syndrome, a life-threatening cascade of multisystem organ failure due to systemic hypersensitivity [74].

If a jellyfish sting is suspected or confirmed, symptom relief and observation is usually the only necessary treatment. Tentacles and nematocysts should be removed with a plastic object such as a credit card and washed with seawater. Vigorous rubbing

and immersion in cold freshwater should be avoided due to the potential to trigger nematocyst discharge [75]. Immersion in water heated to 110 to 113 degrees Fahrenheit and treatment of affected areas with acetic acid (household vinegar) have both been shown to be beneficial [76].

Severe jellyfish stings with systemic effects require immediate medical care and possibly antivenom administration [77]. In Australia, major box jellyfish (*Chironex fleckeri*) stings have caused more than 70 known deaths. Large tentacle exposure can produce cardiotoxic, neurotoxic, dermonecrotic, and hemolytic effects [78]. *Carukia barnesi*, found in Australia, Hawaii, and Florida, can cause a hypersensitivity reaction marked by myocardial injury and pulmonary edema known as Irukandji syndrome [72]. Sheep serum antivenom and magnesium sulfate may play a role for patients with cardiogenic shock, pulmonary edema, or deteriorating critical condition [79].

A delayed hypersensitivity reaction can occur 7–14 days after jellyfish envenomation. Symptoms can include papules, urticaria, and an erythematous welt in the shape of the jellyfish tentacles [78]. Antihistamines and topical corticosteroids are recommended. Resolution is expected within 10 days, although some reactions can be refractory.

24.6.1 Management during pregnancy

We recommend steps to limit jellyfish exposure during pregnancy. Protective clothing and commercially available Safe Sea lotion have been shown to reduce sting frequency [80, 82]. Pregnant women with a small-area sting and mild, strictly local symptoms do not require medical attention other than tentacle removal, seawater and vinegar application, and topical management of any symptoms.

Any sign of systemic reaction should be taken seriously and would include inpatient evaluation or prolonged observation. If cardiopulmonary compromise is present or suspected, supportive intervention should be initiated as with a non-pregnant patient. Sheep serum antivenom may be considered in severe cases with life-threatening processes such as airway compromise or cardiovascular collapse if maternal benefit would be expected [79]. Magnesium sulfate adjuvant therapy is considered to be safe in pregnancy and is commonly used for other obstetric conditions.

24.6.2 Reports during pregnancy

Only one case report of serious jellyfish envenomation was found in the obstetric literature. This case involved a 20-year-old woman at 34 weeks' gestation in Australia [16]. She was stung by the

box jellyfish *Chironex fleckeri*, began screaming in pain, and then experienced pallor and altered mental status. A park official reported that she developed apnea and cyanosis. He doused the tentacles and stings with methylated spirits and began cardiopulmonary resuscitation (CPR) with expired air. A nurse was summoned, who also happened to be pregnant at 37 weeks. She also observed cyanosis and performed CPR, which led to spontaneous ventilation. In doing so, the gravid nurse suffered stings from adherent tentacles. The original victim was transported by ambulance to a hospital and antivenom was administered within 30 minutes of the envenomation. She recovered and was discharged from hospital after 4 days. Both pregnant women subsequently delivered healthy term infants [81].

The above case is too limited to draw conclusions. There were, however, no documented adverse fetal outcomes associated with the two known jellyfish stings during pregnancy. Furthermore, the single case report of severe jellyfish sting in pregnancy demonstrated the worthwhile use of antivenom.

24.7 Antivenom use during pregnancy

A systematic review of antivenom use during pregnancy was published in 2003 [52]. Most reports are anecdotal. The most reported experience has been with snake bites, and observations from limited case reports are reassuring. Reproduction studies regarding the crotalid antivenom have not been reported in animals. Black widow spider antivenom was not associated with apparent adverse effects beyond those inherent to the antidote [53]. While there are limited long-term evaluations of children whose mothers were administered black widow spider antivenom, it appears to be a reasonable therapy if indicated after clinical evaluation.

Current evidence indicates that antivenom is effective and may significantly reduce the duration of suffering and hospitalization. Antivenoms are administered for the following moderate to severe symptoms that are unresponsive to other therapies: severe and persistent local pain or muscle cramping, significant pain or diaphoresis extending beyond the immediate site of the bite, alterations in vital signs, difficulty breathing, and nausea and vomiting. Consultation with a medical toxicologist or other physician with experience in managing various envenomations is recommended before any antivenom administration. Several antivenoms may be commercially available, and toxicologists can be helpful in ordering the antivenom which may not be at the hospital pharmacy.

Frequencies of allergic reactions and delayed serum sickness-like reactions from antivenom are presumed to be similar regardless of pregnancy. Allergic reactions should be managed by immediately stopping intravenous infusion of the antivenom (if applicable) and treating symptoms appropriately. Before administrating any antivenom, medications and equipment for the treatment of anaphylaxis should be immediately available, including intravenous fluids, epinephrine, and intubation equipment. Delayed serum sickness-like reactions are unlikely. However, any patient receiving antivenom should be informed about possible symptoms suggestive of serum sickness (rashes, pruritas, arthralgia, fever) and advised to seek medical care if such symptoms develop.

Thimerosal (merthiolate; thiomersal) is an anti-infective and preservative that has been used as an additive in many biologics, vaccines, and antivenom [61]. There are insufficient data to make a causal connection between thimerosal and any increased risk for birth defects in exposed offspring. Epidemiologic studies have not demonstrated a causal relationship between thimerosal and autism or autism spectrum disorders. The manufacturer cautions that the thimerosal (0.11 mg of mercury per vial) may be associated with mercury-related toxicities, including neurologic and renal toxicities in the fetus and very young children [61]. The amount of mercury in a typical dose would not otherwise be likely to produce fetal harm.

Conclusions

Envenomations from snake or spider bites or from scorpion, hymenoptera, or jellyfish stings likely occur with similar frequencies among reproductive-aged women regardless of pregnancy. Although adults appear to be envenomated more often, children are more likely to develop severe illness. Futhermore, any adverse outcomes may not result directly from the venom in the fetal circulation but indirectly from maternal illness or from placental compromise. For these reasons, more prolonged or more frequent monitoring of both the patient and her fetus is justified. The same fundamental principles of conservative and drug therapy apply when someone is pregnant. Very limited experience with antivenom therapy suggests that it is well tolerated during pregnancy with standard precautions. Prospective evaluations of individual cases that require prolonged monitoring or hospitalization, especially with antivenom administration, would permit a clearer understanding of long-term pregnancy outcomes.

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Gastrointestinal Disorders

Noel Lee, Veronika Gagovic and Sumona Saha

25

25.1 Gastroesophageal reflux disease

Heartburn is estimated to affect 30 to 50% of pregnant women. In some populations, the incidence may be as high as 80% [1]. Risk factors for heartburn in pregnancy include increasing gestational age, parity, and a history of heartburn [2]. Although the terms "heartburn" and "gastroesophageal reflux disease" (GERD) are often used interchangeably, the two are distinct entities.

Heartburn is a symptom, whereas GERD is a disorder associated with symptoms, the most common being heartburn and potential complications [3].

The pathophysiology of GERD is believed to be multi-factorial. Decreased resting lower esophageal sphincter (LES) pressure due to the effects of estrogen and progesterone are thought to be important contributors to gestational GERD along with decreased sensitivity of the LES to physiologic stimuli [4]. Other proposed factors include decreased esophageal peristalsis, esophageal dysmotility and delayed gastric emptying due to hormonal and mechanical changes [5].

While most pregnant women with heartburn experience this for the first time in pregnancy some may suffer from GERD [6]. Most patients have a benign disease course, with only a few experiencing GERD-related complications such as gastrointestinal bleeding or stricture formation. In general, symptoms begin at the end of the first trimester, worsen through the remainder of pregnancy, and then resolve promptly after delivery.

25.1.1 Treatment

25.1.1.1 Therapeutic lifestyle modifications

Treatment of GERD in pregnancy should follow a "step-up" approach. Treatment should begin with therapeutic lifestyle modifications including strict abstinence from tobacco and alcohol and avoiding late-night meals, recumbency after eating, and trigger foods (e.g. spicy or sour foods, carbonated beverages, coffee, and chocolate). Eating several small meals throughout the day and elevating the head of the bed by 6 inches may provide additional benefit [7]. In addition, medications known to provoke GERD such as anticholinergics, sedatives, theophylline, prostaglandins, and calcium channel blockers should be discontinued, when possible. It is estimated that 25% of patients with uncomplicated GERD resolve their symptoms by making these modifications [8].

25.1.2 Antacids

For patients who fail to respond to conservative measures antacids and alginic acid constitute first-line pharmacologic therapy. Aluminum, magnesium, and calcium-based antacids have no Food and Drug Administration (FDA) classification and are generally considered safe in pregnancy. Calcium-based antacids have the added benefit of increasing calcium intake which has been associated with the prevention of preeclampsia [9].

Patients taking antacids, however, should be aware of the possibility of aluminum-containing antacids causing constipation,

and magnesium-containing antacids causing diarrhea [10]. Magnesium-containing antacids should be avoided later in pregnancy, due to their ability to arrest labor and precipitate seizures. Also patients on iron should be advised not to take iron and antacids together in order to maximize iron absorption by an acidic gastric pH. Sodium bicarbonate should not be taken due to the risk of metabolic alkalosis and fluid overload in the mother and fetus [11].

Alginic acid is considered effective and fast acting in most pregnant patients. Although it has not been studied extensively it should be safe because it is not absorbed systemically. An open-label trial reported "very good" or "good" symptom relief in the majority of women taking alginic acid within 10 minutes [12].

25.1.3 Sucralfate

Sucralfate (FDA category B) is an aluminum salt of a sulfated disaccharide. As it is poorly absorbed from the GI tract, it acts mainly as a local mucosal protectant. Sucralfate has been shown in a randomized controlled trial in pregnancy to provide greater relief from heartburn and regurgitation than lifestyle and dietary modifications alone [13].

25.1.4 Promotility agents

Metoclopramide (FDA category B) is a prokinetic, dopamine agonist which may be useful in the treatment of GERD by increasing LES pressure, improving esophageal acid clearance, and promoting gastric emptying. Use of metoclopramide is often limited by its poor tolerability and the risk for extra-pyramidal side effects. It has been associated in rare cases with tardive dyskinesia, causing the FDA to issue a black-box warning concerning the use of this drug in 2009. The risk of the development of this complication increases with high dose or long-term use of the drug and continues even after the drug has been discontinued.

25.1.5 H_2-Receptor antagonists

The H_2-receptor antagonists (H_2-RAs) form the next tier of therapy. The four H_2-RAs (ranitidine, cimetidine, famotidine, and nizatidine; FDA category B) are considered safe in pregnancy. A recent meta-analysis by Gill et al. with data from 2398 H_2-RA-exposed pregnancies and 119,892 unexposed controls found no increased risk of fetal malformations with the use of H_2-RAs in pregnancy [14]. No increased risks for spontaneous abortions, preterm delivery, and small for gestational age were found either.

Despite the longstanding availability of H_2-RAs, only ranitidine, studied at a dose of 150 mg twice daily, has been shown in a randomized, double-blind trial to be efficacious in pregnancy, making it the preferred H_2-RA for gestational GERD [15]. Cimetidine is likely equally effective; however, due to the anti-androgenic effects seen in animals and non-pregnant humans, some authors advise against its use in pregnancy [16,17]. Although it appears to be safe, famotidine carries fewer safety data in pregnancy and is considered a second-line H_2-RA in pregnancy. Nizatidine recently changed FDA pregnancy classification from C to B. Although it is approved for use in pregnancy, as studies in some animal models have reported abortions, fewer live fetuses, and low fetal weights with high dose exposure [18], it is a less preferred option among the H_2-RAs [6].

25.1.6 Proton pump inhibitors

Proton pump inhibitors (PPIs) are typically reserved for patients with severe symptoms refractory to lifestyle modification and the older generation medications. Four of the five PPIs (lansoprazole, rabeprazole, pantoprazole, and esomeprazole) are FDA category B. Omeprazole, however, is FDA category C rating due to fetal toxicity in animal studies.

Despite their favorable pregnancy classification, concern over the long-term safety of PPIs has limited their use. However, there is now a large amount of data supporting their safety in pregnancy. A 2009 meta-analysis by Gill et al. which included 1530 PPI-exposed and 133,410 non-exposed controls found no increased risk for major malformations, spontaneous abortions or preterm delivery with first-trimester use of PPIs [19].

A Danish cohort study examining 840,968 live births, of which 5082 were exposed to a PPI between 4 weeks before conception and the end of the first trimester, did find a minor difference in abnormalities in the newborns of exposed (3.2%) and non-exposed (2.6%) women (adjusted prevalence odds ratio, 1.23; 95% CI, 1.05 to 1.44) [20]. The risk of birth defects, however, was not significantly increased in secondary analyses of exposure to individual PPIs during the first trimester.

Thus, based on the available data, PPI use in pregnancy does appear to be safe. First trimester exposure, however, should be avoided when possible due to the possible increased risk for fetal malformations. While most patients can be effectively treated with once-a-day dosing some may need to be dosed twice daily.

The various medical therapies for GERD are summarized in Table 25.1.

Table 25.1 Medications for gastroesophageal reflux disease

Drug		FDA pregnancy category	Recommendations in pregnancy	Recommendations in lactation
Antacids	Calcium-based	NA	Safe	Compatible
	Magnesium-based		Avoid in late pregnancy as may arrest labor and precipitate seizures; can cause diarrhea	
	Aluminum-based		Can cause constipation and possibly fetal neurotoxicity	
	Alginic acid		Safe	
	Sodium bicarbonate		Contraindicated due to risk for maternal fluid overload and metabolic alkalosis	
Sucralfate		B	Safe	Compatible
Metoclopramide		B	Avoid long-term, high dose use due to risk for tardive dyskinesia	Limited human data: potential toxicity
H_2-receptor antagonists	Ranitidine	B	Preferred H_2-RA in pregnancy	All safe except nizatidne
	Cimetidine		May have anti-androgenic properties	
	Famotidine		Probably safe	
	Nizatidine		Probably safe but less preferred H_2-RA	
Proton pump inhibitors	Omeprazole	All B except omeprazole (C)	Reserve for refractory patients; avoid first trimester use	Not recommended
	Lansoprazole			
	Pantoprazole			
	Rabeprazole			
	Esomeprazole			

NA – Not applicable.

25.2 Peptic ulcer disease

Older studies suggest the incidence of peptic ulcer disease (PUD) is decreased in pregnancy [21]. The reported incidence rate of 0.005% is likely an underestimate, however, due to the under-reporting of symptoms by patients and the reluctance to perform diagnostic tests by physicians. Risk factors for PUD in pregnancy include smoking, non-steroidal anti-inflammatory drug use, alcoholism, genetic predisposition, gastritis, *Helicobacter pylori* infection, and advanced maternal age [21].

25.2.1 Treatment

H_2-RAs constitute first-line therapy for PUD. In patients who remain symptomatic PPIs should be used. These drug classes are covered in detail in the section on gastroesophageal reflux disease. Patients found to have *H. pylori* infection during their work-up should generally be treated for this after pregnancy and lactation have been completed.

The most common treatment regimen is triple therapy with a 10-day course of twice-daily PPI, amoxicillin, and clarithromycin. For patients who are penicillin allergic or have resistant infection, quadruple therapy with twice daily PPI, metronidazole, bismuth, and tetracycline is used. In the rare case when treatment is warranted during pregnancy, tetracycline and bismuth should not be used. Bismuth is discussed below while the antibiotics used to treat *H. pylori* are discussed in the section on "Gastrointestinal infections" and summarized in Table 25.3.

25.2.1.1 Bismuth subsalicylate

Bismuth subsalicylate (FDA category C) is hydrolyzed in the gastrointestinal tract into organic bismuth salts which are poorly absorbed and salicylates which are readily absorbed. Although bismuth has not been reported to cause fetal abnormalities in humans, chronic administration of bismuth tartrate in animal studies has been associated with poor outcomes [22]. Furthermore, chronic ingestion of salicylates during pregnancy may lead to fetal malformations, premature closure of the ductus arteriosus *in utero*, and intrauterine growth retardation [23]. Thus, bismuth subsalicylate should not be used in pregnancy or lactation.

25.2.1.2 Pancreatitis

Acute pancreatitis occurs with the same frequency in the pregnant as in the non-pregnant population. In pregnancy, it is most commonly caused by gallstones [24]. It generally resolves with

supportive care. For patients requiring analgesia, meperidine (FDA category B) and fentanyl (FDA category C) are preferred. Occasionally, patients require treatment with antimicrobials for selective decontamination of the gut. This is usually reserved for patients with necrotizing disease. Use of the fluoroquinolones (FDA category C), amphotericin (FDA category B), and/or imipenem (FDA category C) should be considered in this setting. These antibiotics are discussed in the section on "Gastrointestinal infections" and summarized in Table 25.3.

Chronic pancreatitis is often the result of alcohol abuse. Patients should be monitored for malabsorption. Pancreatic enzymes (FDA category C) supplement endogenous enzyme production. They are likely safe in pregnancy; however, due to limited safety data they should be avoided if non-essential.

25.2.1.3 Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habits [25]. Patients typically report abdominal pain, bloating, constipation, or diarrhea. Despite the prevalence of IBS among women [26], large studies of pregnant women with IBS have not been conducted, thus the natural history and the need for medications in pregnancy are not known [27]. Below is a discussion of the most common symptoms of IBS including recommendations for treatment in pregnancy.

25.3 Constipation

Constipation is one of the most frequently diagnosed gastrointestinal disorders in pregnancy [28]. It is estimated to affect up to 40% of pregnant women [29]. Low frequency of stools (<3 per week), hard stools, and/or difficulties on evacuation of feces have been suggested to be good clinical criteria for constipation in pregnancy [30].

The pathophysiology of constipation in pregnancy is multifactorial. Decreased colonic motility, poor oral intake of food and fluid due to nausea and vomiting, psychological stress, iron supplementation, and mechanical pressure on the rectosigmoid colon by the gravid uterus may all contribute to its development [31].

25.3.1 Treatment

25.3.1.1 Conservative treatment

The initial management of constipation in pregnancy includes patient education and reassurance about normal bowel function

in pregnancy. In addition, patients should increase their physical activity, gain better control of pelvic floor musculature using Kegel exercises, and schedule defecation after meals to take advantage of the gastrocolic reflex. Patients should also avoid constipating foods such as those containing iron and calcium and increase their fluid and fiber intake [32].

25.3.1.2 Stool-bulking agents

Stool-bulking agents such as methylcellulose, psyllium, and unprocessed bran are the preferred first-line therapy in pregnancy as they are not systemically absorbed and thus considered safe for the developing fetus and the neonate during lactation. Stool-bulking agents soften stool and increase stool volume by drawing water into the gastrointestinal tract. A recent Cochrane review found clear evidence of the effectiveness of fiber supplements on the frequency of defecation (OR 0.18, 95% CI 0.05–0.67) and softening of stools [33].

25.3.1.3 Hyperosmotic agents

Hyperosmotic agents increase osmolar tension, thereby causing an increase in water secretion into the gut lumen. These include saline osmotics (magnesium and sodium salts), saccharated osmotics (lactulose, sorbitol) and polyethylene glycol (PEG). Saline osmotic laxatives such as magnesium citrate (FDA category B), magnesium hydroxide (no FDA category), and sodium phosphate (FDA category C) work rapidly, but only provide short-term, intermittent relief and are not advisable for daily use [34]. In addition, magnesium citrate and magnesium hydroxide can cause sodium retention in the mother and thus they are contraindicated in patients with renal and cardiac disease. Their general side-effect profile includes GI upset, hypotension, and hypermagnesemia [35].

Lactulose (FDA category B) and sorbitol (FDA category C) have not been associated with fetal malformations in animal models; however, human studies are lacking. Both agents can be given either orally or rectally in similar doses. Side effects of these agents include abdominal pain, flatulence, and electrolyte imbalances [35].

Polyethylene glycol (PEG) (FDA category C) is the preferred treatment of the American Gastroenterological Association for chronic constipation in pregnancy [36]. It is generally very well tolerated.

25.3.1.4 Stimulant laxatives

Stimulant laxatives directly stimulate colonic smooth muscle and/or interfere with water and sodium reabsorption. Derivatives

of diphenylmethane phenolphthalein (bisacodyl), the anthraquinones (sennosides, aloe, dantron, cascara), and castor oil are drugs in this category. Stimulant laxatives have been found to be more effective than stool-bulking agents for constipation in pregnancy (OR 0.30, 95% CI 0.14–0.61) in randomized trials; however, they also carry more side effects [33]. In a study of 236 newborns exposed to phenolphthalein during the first trimester, no increased risk for congenital defects was found [37].

Bisacodyl (FDA category C) is available in oral and suppository form. Bisacodyl should not be taken within an hour of consuming calcium-containing compounds as it can cause early medication release and gastric irritation. The most common side effects are electrolyte and fluid imbalance, abdominal pain, nausea, and vomiting.

Senna (FDA category C) was not found to be associated with a higher risk for congenital abnormalities or adverse birth outcomes [38]. It is considered acceptable for short-term use [34]. Adverse effects include abdominal cramps, diarrhea, nausea, and vomiting. Dantron is a sennoside which has been associated with congenital malformations [39,40]. It should not be used in pregnancy.

Castor oil (FDA category X) works quickly; however, it is contraindicated in pregnancy as it may induce uterine contractions [11].

25.3.1.5 Emollient laxatives

Docusate sodium (FDA category C) is widely used to treat constipation in pregnancy; however, studies on efficacy in pregnancy are lacking. It is a non-ionic surfactant that allows for the penetration of intestinal fluids into the fecal mass, thereby creating softer stools.

Mineral oil (FDA category X) use is associated with decreased maternal absorption of fat soluble vitamins including vitamin K and increased risk for neonatal hypoprothrombinemia and hemorrhage [41]. It is contraindicated in pregnancy.

25.3.1.6 Others

Tegaserod (FDA category B) is a serotonin 5-HT_4 receptor agonist initially approved for the treatment of constipation-predominant IBS in women. It was temporarily unavailable due to post-marketing reports of an increased risk of cardiovascular events in tegaserod users. It can now be obtained through a treatment investigational new drug protocol from the FDA. Experience with tegaserod is limited in pregnant and nursing women; thus, routine use is not recommended in these populations [27].

Lubiprostone (FDA category C) is a chloride channel activator which increases intestinal fluid secretion. As there are no data currently on its safety in pregnant women, it is not recommended for use in pregnancy.

25.4 Diarrhea

The prevalence of diarrhea in pregnancy has not been firmly established. One study found that 34% of pregnant women reported more frequent bowel movements [42]. Prostaglandins, via their ability to stimulate smooth muscle, increase GI tract motility, and increases in intestinal secretion of water and electrolytes have been implicated in the pathophysiology of diarrhea in pregnancy. As in the treatment of constipation, treatment of diarrhea in pregnancy should begin with dietary modification. Reduction of fats and dairy products may be particularly helpful. Therapeutic options for patients with persistent diarrhea are discussed below.

25.4.1 Treatment

Loperamide (FDA category B) is the preferred anti-diarrheal treatment during pregnancy. Loperamide is a peripherally acting opiate-receptor agonist which increases intestinal water and electrolyte absorption, decreases intestinal transit, and strengthens anal sphincter tone [43]. Loperamide was not found to increase the rate of congenital defects in women with first trimester use; however, it was associated with lower birth weights in 20% of exposed infants [44]. Diphenoxylate with atropine (FDA category C) has been found to have teratogenic effects in animals and humans and therefore is not recommended in pregnancy [45].

Cholestyramine (FDA category C) is a bile-acid sequestrant that can be used to treat diarrhea. As cholestyramine interferes with the absorption of fat-soluble vitamins it may lead to maternal coagulopathy.

Due to the addition of bismuth subsalicylate (FDA category C) to Kaopectate in 2003, Kaopectate should be avoided in pregnancy. Bismuth subsalicylate is discussed further in the section on "Peptic ulcer disease".

Alosetron (FDA category B) is a 5-HT_3 receptor antagonist approved for the treatment of diarrhea-predominant IBS. Use of alosetron is restricted due to concerns over ischemic colitis [46]. Use in pregnancy should be avoided.

25.5 Abdominal pain

25.5.1.1 Tricyclic antidepressants

Amitriptyline (FDA category C), desipramine (FDA category C), nortriptyline (FDA category D), and imipramine (FDA category

D) are tricyclic antidepressants (TCAs) which in low doses are helpful for the treatment of IBS. Although withdrawal symptoms have been reported in neonates exposed to TCAs *in utero*, a joint study of several European teratology information services on the effect of antidepressants during pregnancy found them to be safe [47,48]. Nevertheless, currently these drugs are only recommended for use in pregnancy in women with severe gastrointestinal symptoms of IBS [49].

25.5.1.2 Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs) (generally FDA category C) are also frequently used in the treatment of IBS and have been deemed safe in pregnancy [50]. Use of paroxetine (FDA category D) should be avoided, however, due to the potential risk of fetal heart defects, newborn persistent pulmonary hypertension, and other negative effects [51]. As with TCAs, use of SSRIs for the treatment of IBS in pregnancy should be limited to those women with severe symptoms.

25.5.1.3 Antispasmodics

Anti-spasmodics are used to treat abdominal pain in IBS. Dicyclomine (FDA category B) has been associated with congenital malformations when used in combination with the antihistamine doxylamine; however, findings of teratogenicity have not been consistent [52]. Hyoscyamine (FDA category C) has not been well studied in pregnancy. Routine use in pregnancy is not recommended.

The medications used to treat IBS are summarized in Table 25.2.

25.6 Gastrointestinal infections

Acute diarrhea is usually the result of viral or bacterial infections that are self-limited, and thus do not require specific treatment. Other gastrointestinal infections that may occur during pregnancy are cholecystitis, cholangitis, and appendicitis. The most commonly used antibiotics for the treatment of gastrointestinal infections are discussed below.

25.6.1.1 Amoxicillin

Amoxicillin (FDA category B) is used in the treatment of *H. pylori*. It is considered safe in pregnancy. Using a prescription database, a population-based study of amoxicillin exposure in pregnancy and pregnancy outcomes did not find any increased risk of fetal malformation or other adverse event [53].

Table 25.2 Medications used to treat irritable bowel syndrome

Drug		FDA pregnancy category	Recommendations in pregnancy	Recommendations in lactation
Stool-bulking agents	Methylcellulose	NA	Increase dose gradually to avoid bloating; take with fluid	Safe
	Psyllium			
	Unprocessed bran			
Hyperosmotic agents	Magnesium citrate	C	Safe but not advisable for daily use; contraindicated in patients with renal and cardiac disease as can cause maternal sodium retention	Compatible
	Magnesium hydroxide	NA	Safe but not advisable for daily use; contraindicated in patients with renal and cardiac disease	
	Sodium phosphate	C	Safe but not advisable for daily use	Safety unknown
	Polyethylene glycol	C	Preferred laxative in pregnancy	Low risk
	Sorbitol	C	Probably safe	
	Lactulose	B	Probably safe	
Stimulant Laxatives	Bisacodyl	C	Should not be taken within 1 hour of calcium-containing compounds as can cause early medication release and gastric irritation	May cause colic in breastfed infants
	Senna	C	Acceptable for short-term use	May cause diarrhea in breastfed infants
	Dantron		Contraindicated due to increased risk for malformations	
	Castor oil	X	Contraindicated as may induce uterine contractions	Possibly unsafe
Emollient laxatives	Docusate	C	Limited efficacy data in pregnancy	Compatible
	Mineral oil	X	Contraindicated due to decreased maternal absorption of fat-soluble vitamins and risk for neonatal hypoprothrombinemia and hemorrhage	Possibly unsafe

Tegaserod			B	Not recommended due to limited safety data	Safety unknown
Lubiprostone			C	Not recommended due to absence of safety data	
Loperamide			B	Preferred anti-diarrheal in pregnancy	Limited human data; probably compatible
Diphenoxylate/atropine			C	Not recommended due to possible teratogenicity	Limited human data; potential toxicity
Cholestyramine			C	Interferes with the absorption of fat-soluble vitamins and may lead to maternal coagulopathy	Compatible
Kaopectate			C	Not safe due to bismuth component	No human data; probably compatible
Alosetron			B	Not recommended due to limited safety data	
Tricyclic antidepressants	Amitryptyline		C	Limit use to patients with severe symptoms	Limited human data; potential toxicity
	Nortryptyline		D		
	Desipramine		C		
	Imipramine		D		
Selective serotonin reuptake inhibitors			Generally category C; paroxetine (D)	Generally safe; avoid use of paroxetine; limit use to patients with severe symptoms	Limited human data; potential toxicity
Anti-spasmodics	Dicyclomine		B	Not recommended due to limited safety data	Limited human data; potential toxicity
	Hyoscyamine		C		No human data; probably compatible

NA – Not applicable.

25 Gastrointestinal Disorders

25.6.1.2 Clarithromycin

Clarithromycin (FDA category C) has been associated with an increased rate of cardiovascular anomalies, cleft palate, and embryonic loss in animal reproductive studies. In a prospective study of clarithromycin in pregnancy, no significant differences were found between exposed and unexposed groups in the rates of major and minor malformations; however, spontaneous abortion rates in the exposed group were significantly higher [54]. Based on these data, some experts recommend delaying use until after the first trimester or until pregnancy had been completed [55].

25.6.1.3 Tetracycline

Tetracycline (FDA category D) when given in the second trimester has been associated with staining of newborn teeth [56]. It has also been associated with maternal fatty liver and jaundice [57]. Thus, use of tetracycline is not recommended in pregnancy or during lactation.

25.6.1.4 Metronidazole

Metronidazole (FDA category B) is first-line treatment for *Clostridium difficile*, amebiasis, giardiasis. Multiple studies have suggested that metronidazole use in pregnancy is safe [58–60].

25.6.1.5 Fluoroquinolones

Fluoroquinolone antibiotics (ciprofloxacin, levofloxacin, norfloxacin, all FDA category C) bind to fetal cartilage and may cause arthropathies in children. First trimester exposure in 200 women, however, was not found to increase the risk for major malformations when compared to matched controls; however, the rate of therapeutic abortion was higher in the fluoroquinolone group [61]. Long-term use of the fluoroquinolones is not advised in pregnancy.

25.6.1.6 Rifaximin

Rifaximin (FDA category C) is a newer non-absorbable antibiotic that is FDA approved for treatment of traveler's diarrhea and hepatic encephalopathy. It is also used in the treatment of some forms of irritable bowel syndrome. There have been reports of teratogenic effects in rifaximin-treated animal models; however, human data are lacking.

25.6.1.7 Amphotericin and imipenem

Amphotericin is not associated with an increased risk for congenital malformations and is the preferred antifungal during

pregnancy. There is limited safety data for imipenem in pregnancy. Because of changes in the pharmacokinetics of imipenem during pregnancy caution should be applied to dosing.

25.6.1.8 Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP/SMX, FDA category C) should be avoided in pregnancy because of the anti-folate properties of trimethoprim and the potential for sulfamethoxazole to cause kernicterus. Cardiovascular defects, in particular, have been reported with TMP/SMX use in pregnancy [62, 63].

25.6.1.9 Vancomycin

Vancomycin (FDA category C) is used in the treatment of refractory *C. difficile* colitis. When given orally systemic absorption is low. It is considered low risk in pregnancy.

25.7 Inflammatory bowel disease

The inflammatory bowel diseases (IBD) are chronic, idiopathic, inflammatory conditions of the gastrointestinal tract. The term IBD refers to two main entities: Crohn's disease and ulcerative colitis (UC). Since women with IBD are often diagnosed during the reproductive years, medication safety during pregnancy and lactation are important concerns.

Physicians counseling women about IBD-medication safety in pregnancy must first understand that pregnant women with Crohn's disease and UC have higher rates of such complications of pregnancy such as preterm birth, miscarriage, small for gestational age, and cesarean section [64,65]. Stopping medications before or during pregnancy significantly increases the risk for flare within 1 year. Thus, in general, women should be advised to continue their medications during pregnancy.

25.7.1 Treatment

25.7.1.1 Aminosalicylates

Most aminosalicylates (sulfasalazine, most forms of mesalamine, balsalazide) are FDA category B except olsalazine which is category C. They are considered low risk in pregnancy. A population-based study did not find a significant increase in the prevalence of congenital abnormalities in infants exposed to sulfasalazine *in utero* [66]. However, as sulfasalazine inhibits folate metabolism, it should be given with 2 mg daily of supplemental folate. Unlike with other sulfonamides, bilirubin displacement,

and therefore kernicterus, does not occur in sulfasalazine-exposed infants.

Prospective studies have found mesalamine to be safe in pregnancy [67]. Side effects of mesalamine include GI intolerance, headache, rash, and rarely pancreatitis and interstitial nephritis.

25.7.1.2 Antibiotics

Prolonged antibiotics for the primary treatment of IBD are generally avoided during pregnancy. Patients with abdominal abscesses, phlegmons impending perforation, fulminant colitis, or pouchitis may, however, require them. The antibiotics used most commonly in IBD are ciprofloxacin (FDA category C), metronidazole (FDA category B), and rifaximin (FDA category C). They are covered in the section on "Gastrointestinal infections" and summarized in Table 25.3.

Table 25.3 Medications used to treat gastrointestinal infections

Drug	FDA pregnancy category	Recommendations in pregnancy	Recommendations in lactation
Amoxicillin	B	Safe	Compatible
Clarithromycin	C	Avoid first trimester and/or delay use until after delivery as may increase risk for fetal loss	No human data; probably compatible
Tetracycline	D	Not recommended due to staining of newborn teeth and risk for maternal fatty liver and jaundice	Compatible
Metronidazole	B	Safe	Safe
Fluoroquinolones	C	Avoid long-term use as bind to fetal cartilage and may cause arthropathy in children	Limited human data; probably compatible
Amphotericin	C	Preferred anti-fungal in pregnancy	
Imipenem	C	Dose adjust in pregnancy	
Rifaximin	C	Probably safe as non-absorbed	No human data; probably compatible
Trimethoprim-sulfamethoxazole	C	Not safe due to anti-folate properties, risk for kernicterus	Compatible
Vancomycin	C	Probably safe when given orally due to low systemic absorption	Limited human data; probably compatible

25.7.1.3 Corticosteroids

Corticosteroids (FDA category C) have been used extensively for the treatment of various inflammatory conditions in pregnancy. Although there have been reports of an increased risk of oral clefts, especially with first trimester exposure [68], other studies suggest minimal teratogenicity [69]. Side effects and complications specific to pregnancy include maternal hyperglycemia, macrosomia, and fetal adrenal suppression [70]. Overall, the use of corticosteroids poses a small risk to the developing infant and is considered safe in pregnancy and lactation. Patients should be tapered to the lowest effective dose.

A small retrospective review of patients with IBD on the corticosteroid budesonide (FDA category C) during pregnancy did not demonstrate an increased risk for congenital malformations or other adverse outcome [71]. It is probably safe in pregnancy.

25.7.1.4 Thiopurines

The thiopurines (FDA category D), azathioprine and 6-mercaptopurine (6-MP) are used as maintenance therapy in patients with moderate IBD. Although animal studies have demonstrated teratogenicity, studies on their use in pregnancy in the transplant setting have not confirmed an increased risk of fetal malformations [72]. In addition, a study of pregnant women with IBD on thiopurines did not find any increase in preterm delivery, spontaneous abortion, congenital abnormalities or childhood cancer [73]. Human fetuses are likely protected from the potential harmful effects of the thiopurines during organogenesis as they lack the enzyme inosinate pyrophosphorylase which is required to convert the thiopurines to their active metabolites. Thus, most experts agree that the benefits of continuing these drugs in pregnancy outweigh their potential risks [34]. Side effects of the thiopurines include pancreatitis, bone marrow suppression, and pancreatitis.

25.7.1.5 Methotrexate and thalidomide

Methotrexate and thalidomide are used for moderate or refractory IBD. Both are known teratogens and therefore FDA category X [74]. Furthermore, methotrexate is an abortifacient. These drugs should be used with extreme caution in young patients and discontinued for at least 3 to 6 months before conception.

25.7.1.6 Anti-tumor necrosis factor alpha agents

Three anti-tumor necrosis factor alpha (anti-TNFα) agents are FDA approved for the treatment of IBD: infliximab (FDA category

B), adalimumab (FDA category B), and certolizumab pegol (FDA category B). These drugs neutralize membrane-bound and soluble TNFα, thereby decreasing inflammation. Infliximab and adalimumab have not been found to be teratogenic or associated with miscarriage [75,76] and are considered low risk in pregnancy and lactation. Long-term safety data are, however, lacking and it is recommended that exposed infants be monitored closely for unusual infections [77].

As infliximab and adalimumab are actively transported across the placenta in the latter half of pregnancy, dose adjustments should be considered to minimize fetal exposure. Experts recommend giving the last dose of infliximab at 32 weeks' gestation and the last dose of adalimumab at 34 to 36 weeks [77]. Dose adjustments are not felt to be necessary at this time for certolizumab as placental transfer is minimal.

25.7.1.7 Natalizumab

Natalizumab (FDA category B) is a monoclonal antibody of the IgG_4 class directed against alpha integrins that is approved for the treatment of refractory Crohn's disease. There are limited data regarding its use in pregnancy and at this time there are no firm recommendations about its use in this setting.

The medications used to treat IBD are summarized in Table 25.4.

▶ Liver diseases in pregnancy

25.8 Hepatitis B

An estimated 24,000 women with chronic hepatitis B virus (HBV) infection give birth in the United States per year [78]. Women are often first identified as being HBV positive during routine prenatal screening which in the United States is universal. The effect of chronic HBV on pregnancy is not well known; however, studies from Israel and Hong Kong have reported HBV as a risk factor for poor pregnancy outcome [79, 80].

Women newly diagnosed with chronic HBV during pregnancy should undergo staging of their disease in order to determine the need for therapy. Given the invasiveness of liver biopsy, the need for medical therapy in pregnancy is usually based on clinical information (e.g. disease duration), blood tests (liver function tests, prothrombin time, platelet count), hepatitis B antigen status, and non-invasive imaging (e.g. right upper quadrant ultrasound) [81]. If the liver disease is mild, treatment can be postponed until after delivery. For patients with advanced disease or for those with an

Table 25.4 Medications used to treat inflammatory bowel disease

	Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for lactation
	Mesalamine	Generally category B	Low risk	Limited human data; potential diarrhea in breastfed infants
	Sulfasalazine	B	Interferes with folate metabolism; give with 2 mg of folate	Limited human data; potential diarrhea in breastfed infants
	Corticosteroids	C	Possible increased risk of oral clefts with first trimester use; risk for fetal adrenal insufficiency, macrosomia, premature rupture of membranes	Compatible
	Azathioprine/ 6-mercaptopurine	D	Probably safe for continued use in pregnancy; avoid starting *de novo* in pregnancy	Not recommended
Immunomodulators	Methotrexate	X	Contraindicated due to teratogenicity; stop 6 months prior to conception	Contraindicated
Immunomodulators	Thalidomide	X	Contraindicated due to teratogenicity	Contraindicated
Anti-TNF agents	Infliximab Adalimumab Certolizumab pegol	B	Low risk; dose adjust infliximab and adalimumab in third trimester	Compatible
	Natalizumab	C	No human data	Not recommended

acute exacerbation in pregnancy or evidence of liver failure, treatment should be initiated. In addition, experts recommend measuring HBV DNA viral load at the end of the second trimester and considering initiation of therapy in the third trimester if the viral load is high or if there is a previous history of perinatal transmission [82].

Women on HBV therapy who become pregnant should continue treatment if there is significant liver disease, as withdrawing medication can prompt a flare which can be detrimental to both mother and fetus [83].

25.8.1 Treatment

25.8.1.1 Antiretrovirals

The FDA-approved antiretrovirals for the treatment of HBV are: lamivudine (FDA category C), adefovir (FDA category C), entecavir (FDA category C), telbivudine (FDA category B), emtricitabine, and tenofovir (FDA category B). Most of the safety data on HBV medications during pregnancy is derived from the Antiretroviral Pregnancy Registry (APR). Data from this registry have not detected an increased risk for congenital malformations with maternal antiviral use [84]. Of note, most of the included women were treated with lamivudine or tenofovir, thus extensive data on safety with the other antiretrovirals are lacking. Choice of antiretroviral should be based not only on safety profile, but also on efficacy, tendency to create resistance, and proposed length of treatment [82].

Lamivudine was the first oral drug approved for treatment of HBV. In a recent meta-analysis and systematic review Shi et al. reported that women with high viral loads who were treated with lamivudine late in pregnancy had lower rates of perinatal HBV transmission [85]. Tenofovir and entecavir, however, are now favored as first-line therapy as they are less likely to lead to resistant viral strains. Greater safety data exist for tenofovir than entecavir in pregnancy. Telbivudine may also be a good option for treatment. A study by Han et al. found marked reduction and normalization of ALT levels before delivery and no cases of perinatal transmission in 135 HBV-infected women with high viral load who received telbivudine from 20 to 32 weeks of gestation compared to 94 controls. In addition, no increased rate of congenital abnormalities or other adverse effects were found in the treated group [86].

Similar rates of HBV infection have been found in breastfed and formula-fed babies; thus at this time, breastfeeding is not contraindicated for HBV-infected mothers [87]. However, if the mother is on antiviral therapy, breastfeeding is not recommended [81].

25.8.1.2 Interferon-α

Use of interferon-α (FDA category C) is contraindicated during pregnancy. Although it has not been found to be harmful to the developing fetus, limited data are available.

25.9 Hepatitis C

The prevalence of hepatitis C virus (HCV) infection in pregnant women in Europe and North America is estimated to be between

0.2 and 4.3% [88]. Vertical transmission is the major cause of HCV infection among infants and children [89]. Several factors such as maternal HCV RNA levels, HIV co-infection, HCV genotype, prolonged membrane rupture, and intrapartum maternal blood exposure may influence the risk of transmission.

25.9.1 Treatment

Currently, the treatment for hepatitis C is a combination of interferon and ribavirin. Both of these medications are not recommended for use in pregnancy. Interferon is discussed in the section on "Hepatitis B". Ribavirin (FDA category X) is a known teratogen. Multiple teratogenic effects have been seen in several animal species exposed to ribavirin.

25.10 Wilson's disease

Wilson's disease is an autosomal recessive disorder caused by the accumulation of copper, primarily in the liver and brain, which can lead to cirrhosis. Successful conception and pregnancies have been reported in patients with Wilson's disease on or off treatment; however, fertility is commonly reduced and miscarriage rates may be higher [89].

25.10.1 Treatment

It is currently recommended that women with Wilson's disease on stable treatment continue with their medication with pregnancy as stopping therapy has led to significant disease reactivation [90].

25.10.1.1 Penicillamine

Penicillamine (FDA category D) is a copper chelator which in non-pregnant patients is first-line therapy for the treatment of Wilson's disease. Cutis laxa syndrome, micrognathia, low-set ears, and congenital goitrous hypothyroidism have been reported in infants with *in utero* exposure to penicillamine [91, 92]. Patients in these studies were generally treated with higher doses than are used for maintenance therapy in Wilson's disease. Furthermore, other studies have reported good pregnancy outcomes [93].

As penicillamine also chelates iron and zinc, patients should not take supplements of either at the same time as the drug. They should, however, be given supplemental pyridoxine (vitamin B_6) as penicillamine inactivates pyridoxine.

25.10.1.2 Trientine

Trientene (FDA category C) is also a chelating agent. Animal studies suggest it is teratogenic. Nevertheless, given the limited options in the treatment of Wilson's disease, the benefit of trientene is believed to outweigh the risk [34]. As with penicillamine, simultaneous use of iron and zinc supplements while taking trientene should be avoided.

25.10.1.3 Zinc

Zinc blocks intestinal cell absorption of copper and is associated with producing more steady serum copper levels than the chelating agents. It has not been found to be teratogenic in animal studies and is considered safe in pregnancy. The most notable side effect of zinc therapy in pregnancy is occasional gastric discomfort in the mother.

25.11 Autoimmune hepatitis

Autoimmune hepatitis is an idiopathic disorder that occurs more commonly in women than men. Flares during pregnancy are relatively common; thus it is advisable for women to continue with immunosuppression during pregnancy. Furthermore, as postpartum flares are very common, immunosuppression should be continued and perhaps escalated after delivery [94].

The most commonly used agents for the treatment of autoimmune hepatitis are azathioprine (FDA category D) and corticosteroids (FDA category C). Both of these agents are discussed in the section on "Inflammatory bowel disease".

25.12 Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disorder. Although it is typically a benign cholestatic disorder in the mother, it is associated with several fetal complications including meconium staining, preterm delivery, intrapartum fetal distress, and even intrauterine fetal demise [95]. Thus aggressive treatment to lower bile acids is warranted. In women with severe symptoms or in cases of significant fetal distress, early delivery may be needed.

25.12.1.1 Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) (FDA category B) modifies the bile acid pool and displaces toxic bile acids from haptocyte cell

membranes. A recent randomized trial found UDCA to be superior to cholesytramine for the treatment of pruritus in women with ICP. In addition, timing of delivery was closer to term in the UDCA-treated group and 5 minute Apgar scores were higher [96].

25.12.1.2 Cholestyramine

Treatment with cholestyramine (FDA category C) does improve pruritus in ICP, but does not improve fetal prognosis. Cholestyramine is discussed further in the section on "Irritable bowel syndrome".

25.12.1.3 Antihistamines

Antihistamines such as hydroxyzine (FDA category C) may be used to relieve itching; however, they may aggravate respiratory difficulties in premature infants [97].

25.12.1.4 Other agents

Dexamethasone (FDA category C) also has been used and normalizes serum concentration of bile acids in ICP. No adverse effects have been seen in long-term follow-up evaluations in children exposed to dexamethasone *in utero* [98].

Rifampicin (FDA category C) and phenobarbital (FDA category D) have been used after first-line agents have failed to relieve pruritus. Rifampicin eliminates bile acids through conjugation. In animal models it has been found to be teratogenic when administered at high doses. Studies in humans have not found it to be teratogenic; however, it has been associated with hemorrhagic disease of the newborn [99]. Phenobarbital works similarly to rifampicin. Third trimester exposure did not find it to be associated with fetal complications in two observational studies [98].

25.13 Primary biliary cirrhosis and primary sclerosing cholangitis

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic cholestatic disorders that destroy the bile ducts. There are limited data on either disease in pregnancy. Although definite treatment guidelines for PBC and PSC in pregnancy have not been developed, UDCA (FDA category B) is recommended [97]. UDCA is discussed in the section on "Intrahepatic cholestasis of pregnancy".

The drugs used to treat the liver diseases discussed above are summarized in Table 25.5.

Table 25.5 Medications used to treat liver disease

Drug		FDA category	Recommendations for pregnancy	Recommendations for breast feeding
Antiretrovirals	Adefovir	C	Limited human data; probably safe	Not recommended
	Entecavir	C	Limited human data; probably safe	Not recommended
	Tenofovir	B	Probably safe	Not recommended
	Telbivudine	B	Limited human data	Not recommended
	Lamivudine	C	Probably safe	Not recommended
Interferon α		C	Not recommended	Not recommended
Ribavirin		X	Contraindicated due to fetal neurotoxicity	Not recommended
Penicillamine		D	May cause fetal toxicity at high doses; avoid concomitant administration with iron or zinc; give supplemental pyridoxine	Probably compatible
Trientene		C	Possible fetal toxicity; avoid concomitant administration with iron or zinc	Probably compatible
Ursodiol		B	Low risk	Probably compatible

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