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REVIEW ARTICLE

CME

Pharmacokinetics and Pharmacodynamics of Drugs Commonly Used in Pregnancy and Parturition

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The majority of pregnant women will be treated with a medication other than a vitamin supplement during their pregnancy. Almost half of these medications will be category C or D according to the former US Food and Drug Administration classification system, indicating a lack of human studies with animal studies suggesting adverse fetal effects (category C) or evidence of risk in humans (category D). Changes in maternal physiology alter drug bioavailability, distribution, clearance, and thus the drug half-life in often unpredictable ways. For many drugs, good pharmacokinetic and pharmacodynamic data in pregnancy and parturition are lacking. For other drugs, recent studies demonstrate major pharmacokinetic or pharmacodynamic changes that require dose adjustment in pregnancy, but current dosing guidelines do not reflect these data. In this review, we address the principles that underlie changes in pharmacology and physiology in pregnancy and provide information on drugs that anesthesiologists commonly encounter in treating pregnant patients. (Anesth Analg 2016;122:786–804)

Pregnant women frequently require pharmacologic treatment for conditions both related and unrelated to their pregnancies. There are few studies of pharmacokinetics in women during pregnancy and lactation and even fewer linking pharmacokinetics to pharmacodynamic changes in pregnancy. One important reason is economic; sponsors consider economic return when planning clinical trials. The limited duration of pregnancy limits the potential economic return for pregnancy-specific dosing guidelines. Furthermore, a sponsor will necessarily consider the possibility that any adverse outcome for the newborn child will be blamed on the study drug, regardless of whether such an association is causative. With modest economic incentive and the risk of huge liability for any adverse outcome, it is not surprising that the pharmaceutical industry infrequently performs pharmacokinetic and pharmacodynamic studies in pregnant women and parturients.

Lacking pharmacokinetic and pharmacodynamic studies in parturients or pregnant women, clinicians may administer drugs based on the studies in healthy nonpregnant women. Here, the economics are better for the sponsor, because women account for half of the potential users of most drugs. Historically, even women who were not pregnant were excluded from research, partly because of concern by sponsors that any adverse outcome in a subsequent pregnancy might be blamed on the study drug.[1] In the past, virtually all clinical drug studies specifically excluded pregnant women and women of childbearing potential. In 2003, the National Institute of Child Health and Human Development formed the Obstetric Pharmacology Research Units Network. The network served as a proof-of-concept demonstration that clinical investigations could be performed in pregnant women.[2] Current regulations require pharmacokinetic and pharmacodynamic studies in women including women of childbearing potential. Thus, new drugs coming into the market will have dosing guidelines for women as part of the package insert.

In one retrospective study of 8 health maintenance organizations, 64% of pregnant women received at least 1 prescription medication during pregnancy, with an average of 2 prescriptions other than vitamin supplements or mineral nutrients per patient overall in the United States.[3] In Europe, there is wide variability in prescription practices during pregnancy (Fig. 1).[4] The studies did not include medications used during delivery. Despite the frequency of these prescriptions, few medications have been studied in the setting of pregnancy. Most drugs administered to pregnant patients are used off-label.[5] Currently, almost half of all pregnant patients receive drugs in former Food and Drug Administration (FDA) categories C and D, indicating complete lack of data or evidence for harm.[3]

The US FDA put the Pregnancy and Lactation Labeling Rule into effect on June 30, 2015, replacing previous labeling that designated drugs as category A to D and X for use in pregnancy. These categories have been eliminated because most drugs were category C, indicating a lack of data in humans. The designation of category C as opposed to B was highly idiosyncratic for historical reasons. Because this is a recent change, the categories are maintained in the tables for reference. Category A indicated that adequate and well-controlled studies had failed to demonstrate risk to the fetus in the first trimester. Category B indicated that human studies were not available but animal studies had failed to demonstrate a risk to the fetus. Category C indicated that animal studies had shown adverse effects to the

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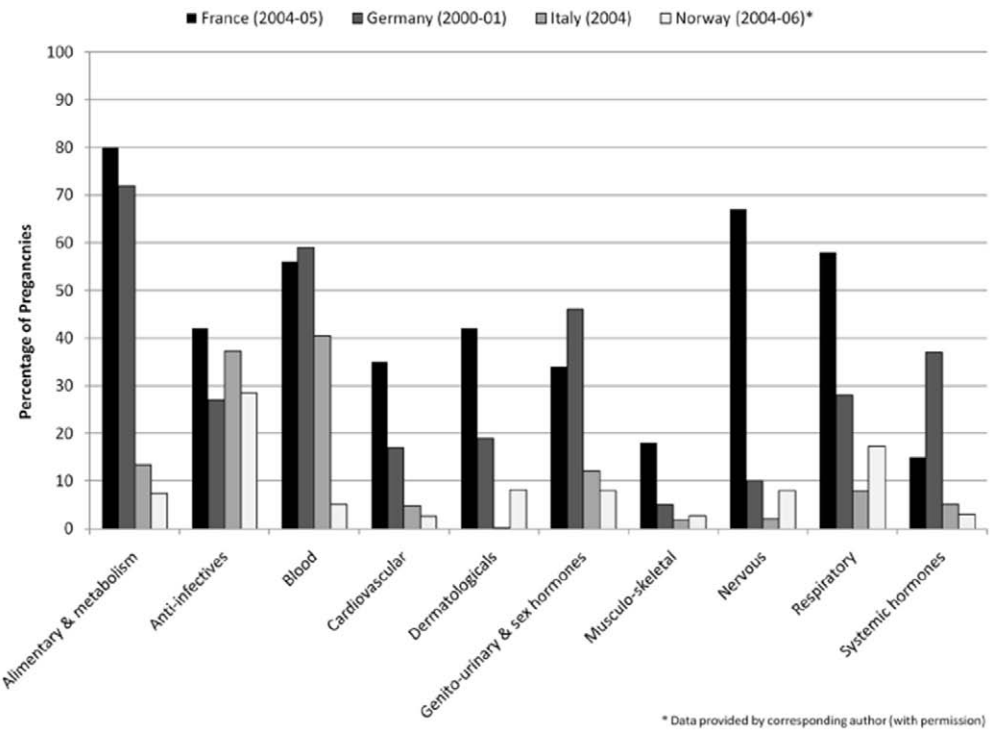

Figure 1. Percentage of pregnancies in which a prescription drug was used by drug class. Data do not include prescriptions for vitamin and mineral supplements. Reprinted with permission from Daw et al.[4]

fetus and there are no adequate human studies. Category D indicated that there was evidence of human risk based on the data from investigational or postmarketing experience in humans, but potential benefits might outweigh the risk. Category X indicated that human or animals studies had shown that fetal abnormalities and the risks of use in pregnancy clearly outweigh the benefits. Under the new labeling rule, a pregnancy exposure registry has been created, and updating is required as more data become available.

Pregnancy induces well-known physiologic changes that may alter drug pharmacokinetics. In addition, hormonal perturbations and placental physiology may affect drug pharmacodynamics. Currently, there are inadequate data for physicians and patients to make informed decisions as to the proper selection and appropriate dosing of many drugs used during pregnancy and lactation.[5] Many package inserts state that the indicated population excludes pregnant, peripartum, or lactating women because of the absence of data. One option would be to avoid these older drugs out of concern for potential maternal or fetal harm. However, they are often preferred given their longer history of use and track record of safety. Unfortunately, the recommended doses and dosing intervals for these drugs may be inaccurate because they are based on the pharmacokinetics usually determined in healthy male volunteers. The data referenced in the following sections represent information garnered mostly from small academic research studies because formal drug development programs that include pregnant women are not required by the FDA or other international governing bodies.

This review outlines known alterations in drug pharmacokinetics and pharmacodynamics that occur during pregnancy, as well as the impact of acute changes in physiology at the time of childbirth. We will highlight known differences induced by pregnancy for drugs commonly administered to pregnant women and parturients. We will specifically note several instances where current clinical guidelines do not reflect the recent findings from pharmacokinetic and pharmacodynamic studies conducted in pregnancy. Finally, we will point out areas where pharmacokinetic and pharmacodynamic studies in pregnant women are most urgently needed.

PHARMACOKINETIC CHANGES IN PREGNANCY

Pregnancy results in extensive anatomical and physiologic changes. Physiologic changes affecting the cardiovascular, respiratory, renal, gastrointestinal, and hematologic systems can significantly alter the pharmacokinetic and/or pharmacodynamic profile of drugs used in pregnancy. Specifically, physiologic changes during pregnancy can alter the bioavailability, distribution, and clearance of many drugs.

BIOAVAILABILITY

Multiple gastrointestinal changes in pregnancy may affect the bioavailability of oral medications. Gastric emptying is not changed during pregnancy before the onset of labor, and, thus, absorption time should not be changed after oral administration.[6,7] During labor, decreased gastric emptying caused by pain, anxiety, or the administration of opioids (including neuraxial opioids) may delay intestinal absorption of drugs.

The changes in liver enzyme activity can alter both activation of prodrugs (and therefore the time course of drug onset), as well as absorption, metabolism, and offset of drugs. For example, codeine is a prodrug. It is converted to morphine by CYP2D6 in the liver. In addition to significant

polymorphisms and multiple gene copies that result in variable CYP2D6 activity, the activity of CYP2D6 is induced in pregnancy. Ultrarapid metabolizers of codeine produce particularly high plasma morphine peaks in pregnancy.[8] In this setting, women would be expected to have rapid pain relief from codeine but may also have increased opioid toxicity. This is a particular problem during breastfeeding, because morphine is passed to the infant through breast milk. Because of these sources of variability, codeine is a poor choice of opioid for breastfeeding women.

In contrast, if a drug is subjected to significant first-pass metabolism, then an up-regulation in enzymatic activity will reduce bioavailability. For example, induction of CYP2D6 in pregnancy increases the rate of metoprolol metabolism, causing 12% to 55% reduction in peak plasma levels compared with the peak in nonpregnant women (Table 1).[9–13]

DISTRIBUTION

Pregnancy obviously increases the size of women. Larger people need larger doses of drugs, because they have larger volumes of distribution and greater clearance. It follows that, as a general rule, pregnant women will need a larger dose of drug than the nonpregnant woman, simply because the pregnant woman is larger.

Maternal intravascular fluid volume begins to increase in the first trimester of pregnancy as a result of increased production of renin–angiotensin–aldosterone, which promotes sodium absorption and water retention. With increasing plasma volume, there is an associated reduction in maternal plasma protein concentration. By term gestation, the plasma volume has increased approximately 50%. Increased plasma volume increases the volume of distribution for water-soluble drugs, and, therefore, pregnancy may be associated with lower peak and steady-state drug concentrations if the dosing is unchanged.[31]

Albumin concentration decreases during the second trimester and declines further throughout pregnancy. Plasma protein levels and therefore drug-binding ability is 70% to 80% of normal prepregnancy values at the time of delivery.[32] This is particularly relevant for drugs that are water soluble and highly protein bound. Reduction in plasma protein increases the free fraction of highly protein-bound drugs such as midazolam, digoxin, phenytoin, and valproic acid.

CLEARANCE

Drug metabolism and excretion rely on the liver and kidney blood flow and function. The enhanced cardiac output beginning in the first trimester increases renal blood flow in healthy pregnancy. Renal blood flow and the glomerular filtration rate are increased 50% by the second trimester and remain increased until 3 months postpartum. Alteration in renal function can significantly increase the clearance of renally excreted drugs such as heparin (Table 2). Because of more rapid clearance, guidelines for dosing based on the data in nonpregnant adults may result in tissue concentrations that are too low in pregnant women.

Although the proportion of cardiac output flowing to the liver does not change during pregnancy, markers of liver function including aspartate aminotransferase, alanine aminotransferase, and bilirubin increase to the upper limits of

Table 1. Antihypertensive Drugs

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
Atenolol	No change in dose required	0.94	1.6–6.8	D	Increased oral absorption compensates for increased renal clearance Unchanged $t_{1/2}$ 100% renally cleared	14–17
Clonidine	Increased dose/shorter dosing interval may be needed	1.0	1.5	C	Renal clearance increased 2× $t_{1/2}$ significantly decreased	14, 18, 19
Diltiazem	Unknown	Unknown	1	C	Unknown	20, 21
Furosemide	No change in dose required	~1	Excreted in breast milk	C	Clearance unchanged in third trimester	22, 23
Hydralazine	Unknown	0.72	Small amount of active compound in breast milk	C	Unknown	14, 24
Labetalol	Increased dose or more frequent dosing	0.4–0.8	0.8–2.6	C	Oral labetalol, clearance increased with advancing pregnancy (1.4× at 12 wk, 1.6× at term) Due to increased activity of hepatic blood flow and induction of UGT1A1	14, 25
Methyldopa	Unknown	1.2	0.19–0.34	B	Unknown	14, 26
Metoprolol	Increased dose or more frequent dosing	1	3	C	Oral clearance 4×greater in third trimester Peak serum concentrations 12%–55% Mechanism increased hepatic blood flow and CYP2D6 induction More effective at lower plasma concentrations in pregnancy	11, 13, 14
Nifedipine	Increased dose/shorter dosing interval	Unknown	<0.05	C	Oral clearance 4× higher $t_{1/2}$ decreased by 50% Mechanism increased hepatic blood flow and CYP3A4 induction	27–29
Sotalol	Unknown	1.1	>1	B	Unknown	14, 18, 30

FDA = Food and Drug Administration; F/M = fetal/maternal ratio; PK/PD = pharmacokinetic/pharmacodynamic.

Table 2. Anticoagulants and Antiplatelet Drugs

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
Acetylsalicylic acid	Unknown, possibly increased dose requirement based on PK	1 for salicylic acid, lower for acetylsalicylic acid due to placental esterases	Peak levels 9–12 h after dose	N	Slower uptake, lower peak plasma concentration after single dose	33–35
Argatroban	Unknown	Unknown, low molecular weight, moderate protein binding Likely crosses placenta	Unknown, low molecular weight, moderate protein binding Likely crosses into breast milk	B	Unknown	36
Clopidogrel	Unknown	Unknown likely crosses placenta, low molecular weight	Unknown likely crosses into breast milk, low molecular weight	B	Unknown	37
Dabigatran	Unknown	0.33	Unknown	C	Unknown	36, 38
Enoxaparin	Must titrate to Xa levels given wide swings in pharmacokinetics through pregnancy. Once daily dosing is likely insufficient given higher clearance	Does not readily cross placenta due to large molecular weight	Very little excreted into breast milk due to high molecular weight. Milk/plasma ratio of <0.025–0.224. Also not absorbed orally.		Increased clearance, larger volume of distribution with major increase in last 2 mo of pregnancy Progressive reduction in anti-Xa activity during pregnancy	39, 40
Fondaparinux	Unknown	0.1 large molecular weight	Unknown	B	Potentially unchanged, case report data	41
Heparin	Higher doses and/or more frequent intervals aPTT is not valid in pregnancy, measure Xa levels	Does not cross placenta due to large molecular weight	Not excreted into breast milk due to high molecular weight	C	Peak plasma concentration 50% that of nonpregnant controls Reduced efficacy in pregnancy ACCP recommends 10,000 U every 12h or monitoring anti-Xa levels	42–44
Rivaroxaban	Unknown	Unknown	Manufacturer reports rivaroxaban is excreted in breast milk	C	Unknown	36
Warfarin	Highly variable	0.15—not metabolized readily by fetal liver leading to higher INR in fetus	Not excreted into breast milk	X (D if mechanical heart valve)	PK unknown, postpartum patients require more drug than nonpregnant women to achieve therapeutic anticoagulation	44–46

ACCP = American College of Chest Physicians; aPTT = activated partial thromboplastin time; FDA = Food and Drug Administration; F/M = fetal/maternal ratio; INR = international normalized ratio; PK/PD = pharmacokinetic/pharmacodynamic.

normal. Some metabolic liver enzymes are induced in pregnancy such as CYP2D6 in the example of codeine mentioned earlier (Table 3). CYP3A4, CYP2B6, CYP2C9, and uridine 5′-diphosphate glucuronosyltransferase are also induced in pregnancy. Other metabolic enzymes are unchanged in pregnancy. A few metabolic enzymes have reduced activity, such as CYP1A2, which is the primary enzyme for caffeine metabolism. As a result of the reduction of CYP1A2 activity, caffeine plasma concentration is doubled during the third trimester compared with the concentrations after a typical dose (e.g., a cup of coffee) in nonpregnant women.[47]

HALF-LIFE

Half-life is a function of the ratio of volume to clearance. The interaction of volume and clearance can be envisioned as a tank full of drug (volume) and a pump that removes the drug from the tank (clearance). Increasing the size of the tank while maintaining the same pump removing drug results in increasing the time needed for the pump to drain the tank. Using a bigger pump with the same tank drains it faster. Similarly, if volume increases more than clearance, then half-life increases. If clearance increases more than volume, then half-life decreases.

Because both volume and clearance increase during pregnancy, changes in half-life are not predictable. Half-life may increase, decrease, or stay the same. Each drug must be studied individually to determine whether the half-life changes in pregnancy. The volume of distribution primarily determines the concentration from the first dose of a drug (e.g., propofol for induction of anesthesia). The clearance of drug primarily determines the concentration with steady-state dosing (e.g., metoprolol for hypertension in the last

trimester). The half-life determines the dosing interval at steady state, how often the drug must be given to maintain adequate drug levels. In the absence of specific guidance based on the pharmacokinetic studies in pregnancy, the safest assumption is that the half-life is unchanged in pregnancy, and, therefore, drugs should be dosed with the same frequency in pregnant and nonpregnant women. However, we will provide examples of pharmacokinetic studies in pregnant women that suggest important changes in dosing interval.

PLACENTA DRUG TRANSFER AND FETAL METABOLISM

Pregnancy is unique in that it is associated with the formation and the subsequent sloughing of a metabolically active organ. The placenta is a semipermeable barrier to drug passage much like the blood–brain barrier. For drugs that can pass through the placenta, or are metabolized by the placenta, uptake, distribution, and metabolism by the placenta and fetus will contribute to the changes in drug pharmacokinetics associated with pregnancy.

Passive placental transfer is determined by lipid solubility, charge, molecular weight, and concentration difference across membranes. Some drugs are actively restricted, whereas others are readily taken up by the placenta and fetus. As a general rule, drugs that cross the blood–brain barrier will cross the placenta. Changes in the acid–base status of the mother or fetus can alter placental drug transfer. An example is the relatively acidotic fetus that can trap high concentrations of weak bases such as lidocaine administered to the mother, potentially causing fetal toxicity.

The placenta is also capable of drug metabolism. Although less metabolically active than the liver, the placenta expresses both phase 1 enzymes (oxidation, reduction, and hydrolysis) and phase 2 enzymes (conjugation). Phase 1 enzymes expressed by the placenta include CYP1A1, CYP2E1, CYP3A4, CYP3A5, CYP3A7, CYP4B1, and CYP19 (aromatase). Drugs that undergo significant placental metabolism in pregnancy include dexamethasone and prednisone.[74] Remifentanil is metabolized by esterases highly expressed in the placenta, resulting in fetal remifentanil concentrations an order of magnitude less than maternal concentrations during remifentanil administration for labor analgesia and cesarean delivery (Table 3).[72]

Terminology regarding the ratio of maternal drug concentrations to that in the fetus is often confusing because several ratios are described with variable language. Maternal arterial blood from the uterine artery feeds the placenta. The abbreviation MA (maternal artery) refers to this concentration even though it may be measured from an arm vein, assuming that the arterial and venous concentrations in the mother's arm are at steady state. The umbilical vein (UV) takes the blood from the placenta to the fetus. The umbilical artery (UA) takes blood from the fetus back to the placenta. Drug measured in the UA represents the concentration measured after fetal metabolism and mixing and approximately represents the concentration of drug delivered to the fetal brain. If there is no fetal metabolism, then UA and UV are identical at steady state. The ratios UV/MA and UA/MA are often termed the fetal-maternal or fetal/maternal (F/M) ratio for simplicity. In this text, F/M will be used as the equivalent of UV/MA or UA/MA, as used, for example, in "Placental Transfer of Drugs and Perinatal Pharmacology" in the most recent version of *Shnider and Levinson's Anesthesia for Obstetrics*.[14] The term cord:maternal is also used for UA/MA in some texts including *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*.[37] Many of the ratios quoted in this text are collated from these textbooks, which serve as excellent references.

Neonates have significantly reduced glomerular filtration rate, decreased hepatic drug metabolism, and increased extracellular fluid (and therefore increased volume of distribution).[75,76] As a result, drugs that are metabolized in the liver or excreted by the kidneys (most drugs) would be expected to have significantly longer half-life and duration of activity in neonates relative to adults. In addition, decreased plasma protein binding can result in increased free-drug fraction and drug toxicity in the neonate. Doses well tolerated by adults may be relatively toxic to the fetus. For example, maternally administered amiodarone for refractory arrhythmia can result in iodine accumulation in the fetus, leading to hypothyroidism and even goiter that may require treatment at birth.[77] There are also physiologic effects specific to the fetus such as premature closure of the ductus arteriosus by nonsteroidal anti-inflammatory drugs (NSAIDs) that require consideration. The neonatologist and pediatric anesthesiologist must consider the potential consequences to the fetus of drugs given to the mother during pregnancy and parturition.

PHYSIOLOGIC CHANGES OF PREGNANCY AND PHARMACOKINETICS OF SPECIFIC DRUG CLASSES

Analgesics

Acetaminophen is commonly used in pregnancy for analgesia and the treatment of fever. Maternal absorption, metabolism, and clearance of oral acetaminophen is not changed in pregnancy.[78] Maternal clearance of a 2 g dose of IV acetaminophen was more rapid during cesarean delivery for preterm (<37 weeks) than term delivery, potentially suggesting differences in blood loss or fluid shifts.[79] A recent epidemiologic study suggested an association of acetaminophen with neurodevelopmental and behavioral problems in the offspring including a higher risk for attention deficit hyperactivity disorder and an increased risk of asthma-like syndromes.[80] This study considered repeated maternal dosing in pregnancy, and the findings likely do not apply to a single dose during delivery. Newborn infants are frequently given acetaminophen without observed negative consequences. However, the study does raise questions about an old drug that has long been considered safe in pregnancy.

NSAIDs may be prescribed in pregnancy both for chronic conditions such as inflammatory bowel disease and for obstetric indications such as tocolysis (indomethacin) and antiphospholipid antibody syndrome (aspirin). Pregnant women may also take these familiar over-the-counter medications that are part of many combination products without consulting their obstetric providers.[81] However, NSAIDs were classically categorized as categories C or D by the

Table 3. Opioids

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
Alfentanil	No major dosing changes anticipated	0.3	Excreted into breast milk at low concentrations	C	No change in volume of distribution or clearance	14, 37, 48, 49
Buprenorphine	Dose increase in third trimester. Decreased risk of neonatal withdrawal compared with methadone (adjusted odds ratio, 2.55)	Minimal data. Estimated F/M ratio was 6.3 in 1 patient	More data needed. Known to cross into breast milk. Values not reported. Poor oral bioavailability makes absorption during breastfeeding low	C	Increased metabolism to inactive metabolites via induction of CYP3A4	50–53
Codeine	Should not be used because of variable metabolism and excretion into breast milk	See morphine	See morphine	C	Prodrug metabolized by CYP2D6 that is induced in pregnancy and has extensive genetic variability	8, 54, 55
Fentanyl	Unknown	0.5–0.9	1.4–3. Low oral bioavailability in neonate	C	Peak maternal concentration 0.5 ng/mL with epidural dosing	14, 56–58
Hydrocodone	Unknown, more research needed	Unknown	Fully breastfed neonates received 1.6%–3.7% (range, 0.2%–9%) of the maternal weight-adjusted hydrocodone dose	C	Increased activity of hepatic CYP2D6 enzyme increases conversion to the more potent opiate, hydromorphone, can result in higher and more rapid peak effect	59–61
Hydromorphone	Unknown	Unknown	2.6. Estimated infant dose was 0.67% of the mother's weight-adjusted dose	C	Metabolized by CYP2D6	55, 59, 60
Meperidine	No change, caution with repeat dosing in breastfeeding	0.35–1.6	0.8–1.6. Long $t_{1/2}$ of meperidine and normeperidine in infants—no >1 dose is recommended in breastfeeding women	C	Increased metabolism (inactivation) is expected via induction of CYP3A4 in pregnancy. Likely counterbalanced by decreased clearance. No change in $t_{1/2}$	14, 48, 49, 51, 62
Methadone	Higher dose and shorter dosing interval required. Mean increased dose of 24 mg in methadone maintenance by third trimester, and many authors recommend splitting total daily dose into twice a day. Dose returns to normal by 6 wk postpartum	0.2. Withdrawal symptoms occur in 60%–90% of the infants exposed in utero to methadone	Average = 0.8, wide range of 0.05–1.2. Concentration in breast milk can help with symptoms neonatal abstinence syndrome	C	Increased clearance, largely due to induction of CYP3A4 and CYP2B6. Placental aromatase CYP19 also metabolizes methadone. Reduced elimination half-life of 8–20 h compared with the 24-h half-life in a nonpregnant patient	63–67
Morphine	May require increased dose and/or increased dosing interval	0.61–1. Undetectable in most infants 1–2 h after a single IV maternal dose	<1. Low oral bioavailability (26%) in infant. Receives 8%–12% maternal dose	C	Volume of distribution unchanged, clearance >70%, decreased half-life, glucuronide conjugation by UGT	14, 68–70
Oxycodone	May require a shorter dosing interval due to faster elimination half time	Maternal plasma: umbilical plasma ratio of 1	3.2	B	Increased clearance via increased GFR as well as induction of CYP3A4 and CYP2D6. May achieve a faster peak in active metabolite oxymorphone due to CYP2D6 induction. Shorter elimination half-time in laboring women (decreased from 3.8 to 2.6 h)	55, 71
Remifentanil	May require higher dose to achieve the same plasma concentration due to increased clearance	0.29–0.88. Extensive fetal and placental metabolism occurs, as evidenced by a large decrease from the UV:MA ratio of 0.88	Unknown. Low molecular weight and high lipid solubility suggest that it will be excreted into breast milk	C	Clearance more than doubles, likely due to larger blood plasma volume, increased cardiac output, and increased renal blood flow	14, 72, 73

FDA = Food and Drug Administration; F/M = fetal/maternal ratio; GFR = glomerular filtration rate; MA = maternal artery; PK/PD = pharmacokinetic/pharmacodynamic; UV = umbilical vein.

FDA because of concerns regarding increased risk of miscarriage and fetal teratogenicity in the first trimester and concerns for premature closure of the fetal ductus arteriosus in the third trimester.[82,83] Therefore, pharmacokinetic and pharmacodynamic studies of this drug class in pregnancy are largely lacking, but the existing data were recently reviewed.[81] Placental transfer of NSAIDs including aspirin, indomethacin, and naproxen has been demonstrated by studies of placental and fetal tissues of women who terminated pregnancy.

The use of prescription opioids during pregnancy has increased with significant regional variation in the United States.[84,85] Opioids are used for analgesia during pregnancy to prevent opioid withdrawal in chronic users and for labor analgesia. With the exception of remifentanil, all opioids are metabolized to inactive and occasionally active derivative compounds by the liver. Many opioids are metabolized by liver enzymes that have altered activity in pregnancy (Table 3). For the most part, opioids are dosed to effect. However, induction of metabolic enzymes in pregnancy can cause unexpected changes in drug duration and efficacy. Increased metabolism of a prodrug (codeine) may increase peak drug levels. Increased metabolism of the parent drug to inactive metabolites, as is the case for morphine, oxycodone, hydrocodone, hydromorphone, methadone, and buprenorphine, can result in unexpectedly low drug levels. This becomes particularly important in managing methadone and buprenorphine treatment during pregnancy. Methadone and buprenorphine, both metabolized by CYP3A4 and CYP2B6, respectively, are used to prevent opioid withdrawal syndrome. In patients who are not pregnant, methadone takes nearly a week to reach steady state with repeat dosing. During pregnancy, CYP2B6 is induced by increased estrogens leading to increased drug clearance.[86] Induction of CYP3A4 also results in reduced concentrations during pregnancy.[87] Because of these considerations, altered dosing regimens required in pregnancy are best managed by experts in their use.[50,63,64]

Systemic opioids as a drug class only offer marginal pain relief in labor, and their use is complicated by maternal, fetal, and neonatal side effects.[88] Remifentanil is unique among opioids in that it is metabolized by plasma and tissue esterases. Ultrarapid metabolism of remifentanil in the mother and extensive metabolism by the placenta and the fetus significantly reduce the possibility of respiratory depression and impaired transition in the neonate. This increased neonatal safety margin permits substantially higher doses to be used for labor analgesia compared with other systemic opioids.[72,89–92]

Sedative Hypnotics

For many years, thiopental was the primary drug used to induce general anesthesia in pregnant women. The pharmacokinetics of thiopental have been studied in detail in pregnancy.[93] Pregnant women have more rapid thiopental clearance because of increased liver blood flow, which decreases the elimination half-life.[94] All sedative hypnotic drugs cross the placenta (Table 4). The characteristics that allow them to cross the blood–brain barrier to induce hypnosis also favor placental transfer to the fetus.

Thiopental is no longer available in the United States and has been largely replaced by propofol for the induction of general anesthesia in healthy patients. Pharmacokinetic and pharmacodynamic changes of propofol in pregnancy have not been well studied, despite its nearly ubiquitous use for induction of general anesthesia. A few early studies evaluated the use of propofol for cesarean delivery but did not compare propofol in parturients with propofol in nonpregnant controls.[106,107,114] Studies of propofol transfer in perfused human placental cotyledons suggested that maternal concentration is highly dependent on albumin concentration.[115] As a result, free propofol concentration would be expected to be increased in pregnancy. Consistent with these expected pharmacokinetics, a case series using a target-controlled infusion of propofol and remifentanil for cesarean delivery under general anesthesia found that neonatal depression occurred in 6 of 10 babies delivered from women anesthetized with this technique.[114] Another study showed no change in the total propofol required for maternal hypnosis in patients early in pregnancy; however, free propofol concentration was not measured.[108] Other sedative hypnotic drugs have increased pharmacodynamic activity during pregnancy, possibly because of the neuronal effects of progesterone. No dosing changes are recommended based on the clinical experience,

Table 4. Sedative Hypnotic Drugs

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
Diazepam	Not recommended	1	0.2–2	D	No change in clearance	14, 95–98
Etomidate	Unknown	0.5–0.86	1.2, undetectable in 4 h	C	Unknown	14, 99, 100
Ketamine	Unknown	1.26	Unknown	NA	No human data; unchanged in pregnant ewe	14, 101
Midazolam	Not recommended during first trimester, may require dose increase for intended effect at term	0.15–0.66	0.15, cleared in 4 h	D	Peak plasma concentration is reduced, half-life unchanged CYP3A-induced hepatic metabolism increased	14, 102–105
Propofol	2 mg/kg resulted in less neonatal depression	0.7–1.3	Negligible	B	C_{50} for loss of consciousness unchanged first trimester	14, 106–111
Thiopental	No dose change	0.4–1.1	<1	NA	Volume of distribution and clearance increased resulting in lower plasma concentrations but more efficacious in pregnancy	14, 112, 113

FDA = Food and Drug Administration; F/M = fetal/maternal ratio; NA = not applicable; PK/PD = pharmacokinetic/pharmacodynamic.

but this is an area where more detailed pharmacokinetic and pharmacodynamic information is needed.

Two of the authors (PDF and SLS) attempted to address this shortcoming in propofol clinical pharmacology about 5 years ago by requesting an Investigational New Drug (IND) Application from the FDA to study propofol's pharmacokinetics in parturients who required cesarean delivery under general anesthesia because of placental invasion. The proposed study was simple: administer propofol when general anesthesia was indicated and obtain arterial blood samples to characterize the pharmacokinetics. The FDA imposed onerous requirements on the study before granting an investigator-initiated new drug application, including an analysis of propofol in breast milk that would require development of a completely new assay. Because of the demands placed by the FDA to grant an investigator IND, this study was never undertaken. This is an example of the barriers that academic investigators may encounter in attempting to better understand the pharmacokinetics of commonly used drugs in pregnancy.

The use of benzodiazepines in early pregnancy is limited by conflicting data concerning a potential increase in oral clefting when benzodiazepines are used during the first trimester.[116] Benzodiazepines are used for mild sedation and anxiolysis during cesarean delivery and other near-term procedures. Midazolam has been extensively studied as a typical drug metabolized by CYP3A4, a liver enzyme that is induced in pregnancy. Physiologically based pharmacokinetic models have been constructed based on known changes with the intention of predicting exposure changes induced by pregnancy for other compounds that are metabolized by CYP3A4 or renally excreted.[102] The peak concentration of midazolam is reduced after both oral and parenteral administration in pregnancy, but the half-life is unchanged. Prolonged use of benzodiazepines near term is contraindicated because of neonatal toxicity and withdrawal symptoms. The fetal–maternal ratio for most benzodiazepines with the exception of midazolam is close to 1 (Table 4), making midazolam the preferred drug when short-term use is required near term pregnancy.

Neuromuscular-Blocking Drugs

Succinylcholine and mivacurium are metabolized by plasma cholinesterase (pseudocholinesterase or butyrylcholinesterase). Maternal plasma cholinesterase activity is decreased about 30% from the 10th week of gestation until up to 6 weeks postpartum. However, decreased cholinesterase activity is not associated with clinically relevant prolongation of the neuromuscular blockade from succinylcholine or mivacurium in patients with normal baseline levels (Table 5). The larger volume of distribution of succinylcholine in pregnancy likely offsets any decreased cholinesterase activity, and normal nonpregnant doses are recommended for pregnant women and parturients. Very little succinylcholine crosses the placenta, and there is no pharmacodynamic effect in a fetus with normal pseudocholinesterase activity. However, even the small amount transferred can produce flaccidity in the setting where both the mother and the fetus produce atypical pseudocholinesterase.[117]

Nondepolarizing muscle relaxants are largely ionized at physiologic pH, so there is little transfer of nondepolarizing muscle relaxants across the placenta or into breast milk. When fetal muscle relaxation is desired for fetal surgery, muscle relaxants must be injected directly into the UV or fetal muscle.

Local Anesthetics

Local anesthetics are commonly used to provide labor or surgical analgesia during pregnancy. Local anesthetics may be administered for single-dose or continuous wound infiltration, perioperative IV infusions, peripheral nerve blocks, transverse abdominis plane blocks, or neuraxial blocks. Pregnancy does not increase the absorption or peak concentration of bupivacaine.[125] However, physiologic changes during pregnancy, in particular, decreased plasma protein binding, can increase the risk of local anesthetic toxicity when large doses of local anesthetics are administered to pregnant women (Table 6). Local anesthetics are highly protein bound, and the reduction in plasma protein that occurs in pregnancy will increase the free fraction

Table 5. Muscle Relaxants

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
Atracurium	Unchanged	0.12	Unknown, not orally absorbed by infant	C	VD, Vss, and Vc unchanged, clinical duration unchanged	14, 118, 119
Pancuronium	Unchanged	0.2–0.5	Unknown, not orally absorbed by infant	C	Faster clearance no change in VD	14, 120–122
Rocuronium	No change in initial dose, some studies suggest prolonged duration and therefore decreased redosing	0.1–0.6	Unknown, not orally absorbed by infant	C	PK unknown, onset unchanged, possible increased clinical duration of action	14, 123, 124
Succinylcholine	No change except avoid in women with atypical cholinesterase	Not detectable	Unknown, not orally absorbed by infant	C	Slightly prolonged recovery time postpartum Reduced cholinesterase not significant with 1 mg/kg dose, prolonged blockade may occur with larger doses	14, 119
Vecuronium	May require more frequent monitoring	0.1–0.5	Unknown, not orally absorbed by infant	C	VD, Vss, and Vc unchanged, terminal half-life reduced but clinical duration is prolonged	14, 121, 122

FDA = Food and Drug Administration; F/M = fetal/maternal ratio; PK/PD = pharmacokinetic/pharmacodynamic; Vc = central volume; VD = volume of distribution; Vss = steady-state volume.

Table 6. Local Anesthetic Drugs

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
2-Chloroprocaine	N/A, titrated to effect	Rapidly hydrolyzed by esterases, and only traces of this compound reach the fetus, even after overdose, suggesting safety for the fetus	Unknown	C	Unknown	14, 131
Bupivacaine	N/A, titrated to effect	0.3–0.7, 90% binding to maternal α1-acid glycoprotein that exceeds fetal protein binding (50%). Fetal acidosis will cause increased fetal accumulation and possible toxicity	0.3	C	No change in absorption or peak concentration. Some changes in metabolism—less 4′ hydroxylation, enhanced *N*-dealkylation	14, 125, 131–133
Lidocaine	N/A, titrated to effect	0.5–0.9, acidosis increases transfer to fetus	1	B	Unknown	14, 131–133
Mepivacaine	N/A, titrated to effect	0.5–0.7	Unknown	C	Unknown	14, 131
Prilocaine	N/A, titrated to effect	1	Unknown	B	Unknown	131
Ropivacaine	N/A, titrated to effect	0.3–0.7	0.25	B	Unknown	14, 134, 135

FDA = Food and Drug Administration; F/M = fetal/maternal ratio; NA = not applicable; PK/PD = pharmacokinetic/pharmacodynamic.

of local anesthetics. This effect is particularly important for hydrophilic drugs if the concentrations approach the upper limit of the therapeutic window. Transverse abdominis plane blocks, in particular, are associated with high local anesthetic absorption.[126] Case reports of maternal seizures have been reported after placement of transversus abdominal plane blocks for analgesia after cesarean delivery.[127–130]

Amide local anesthetics are primarily hepatically metabolized, and their metabolites are renally excreted. Toxic plasma concentrations may result from drug accumulation with large or repeated doses. Ester local anesthetics undergo hydrolysis by pseudocholinesterase present in plasma. Although ester local anesthetics have limited potential to accumulate, they may have higher than expected initial blood levels because of relative deficiency of pseudocholinesterase associated with pregnancy. Therefore, recommended "safe doses" outlined in drug package inserts for all local anesthetics may cause side effects in pregnant women.[126]

A study that measured ropivacaine blood concentrations after ultrasound-guided transverse abdominis plane blocks (2.5 mg/kg ropivacaine in 20 mL per side) in 30 women undergoing cesarean delivery found that concentrations of ropivacaine exceeded the potentially toxic threshold of 2.2 μg/mL in 12 patients and that 3 women described symptoms attributable to mild local anesthetic neurotoxicity (perioral tingling, slurred speech, tongue paresthesia).[126] There is also a suggestion of increased sensitivity to neuraxial local anesthetic doses in pregnancy, but it is not clear whether the changes are because of increased sensitivity of the nerves to local anesthetic blockade or changes in distribution because of engorgement of epidural vasculature.[136–139] It is not known whether the case reports of toxicity with doses at the top of the recommended range reflect a pharmacokinetic effect (increased drug concentration) only and/or reflect a pharmacodynamic effect (increased sensitivity to the same concentration). Thus, it is prudent in pregnancy to avoid the upper range of local anesthetic doses considered safe in other settings.

Fetal acidosis will increase the ionization of local anesthetics because they are all weak bases. As previously mentioned, local anesthetic drugs have the capacity to accumulate in an acidotic fetus.[140] Because of the potential for enhanced toxicity, lipid emulsion to treat local anesthetic overdose should be available whenever local anesthetics are administered to parturients.[141,142] Lipid emulsion should be administered to the mother at the first sign of local anesthetic toxicity. It is not known whether it crosses a human placenta; however, it does not cross the rabbit placenta intact.[143] It may need to be dosed to a rapidly delivered neonate separately if there are signs of local anesthetic-induced depression.

Antibiotics

Knowledge of pharmacokinetic and pharmacodynamic changes for antibiotics in pregnancy is particularly important because there is normally no clinical response to guide dose titration. Administration of prophylactic antibiotics, most commonly cefazolin, before skin incision reduces the incidence of surgical site infection, endometritis, and total surgical infectious morbidity.[144] Only free drug is assumed to have antibacterial activity. For antimicrobial agents to be effective, it is critical that the free drug concentration remains above the minimum inhibitory concentrations (MICs).[145] Changes in antibiotic pharmacokinetics during pregnancy include increased volume of distribution, increased renal clearance, and reduced protein binding. The reduction in protein binding is not sufficient to offset the decrease in free drug concentration because of a larger volume of distribution and increased clearance. The result is reduced free plasma concentration and antimicrobial efficacy of many antibiotics administered to pregnant women. When surgical antibiotic prophylaxis fails, the only measureable outcome is the incidence of surgical site infection or endometritis. These are potentially highly consequential, because maternal sepsis is a leading cause of maternal morbidity and mortality.[146]

Cefazolin, the most commonly used IV antibiotic in pregnancy, has been well studied (Table 7).[147–152]

Table 7. Antibiotic Drugs

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
Amoxicillin	Higher more frequent dosing	0.18 after 3 min	0.014, 0.013, and 0.043 at 1, 2, and 3 h	B	Increased clearance	154–156
Ampicillin	Higher more frequent dosing	0.3–0.7 at 1 h after dose, 1.1–10 2 at 6 h after dosing	0.2	B	Increased clearance in pregnancy	157, 158
Azithromycin	500 mg before cesarean delivery leads to sustained concentrations greater than MIC for *Ureaplasma*	0.2–0.4	Accumulates reaches steady state in 3 d	B	Clearance by hepatobiliary excretion may be reduced in pregnancy	159–162
Cefazolin	Higher dose to reliably keep plasma concentration above MIC	0.35–0.69	0.02	B	Clearance and volume of distribution are increased	149, 151, 152, 163
Cefepime	Higher dose or increased frequency may be required	0.23	Low concentration	B	Clearance and volume of distribution are increased	164
Cefoxitin	Higher dose or increased frequency may be required More studies needed	0.1–0.9	Minimal secretion	B	Clearance and volume of distribution are increased	157, 165
Ceftriaxone	More studies needed	Unknown	0.03–0.06	B	? Longer half-life in pregnancy	166
Ciprofloxacin	Unknown	Unmeasured but crosses placenta and concentrates in amniotic fluid	4.71	C	Unknown	167
Clindamycin	Increased dosing may be required depending on degree of protein binding More research needed	0.5	0.08–3.1	B	Decreased AUC/MIC ratio	167, 168
Ertapenem	Unknown	Low molecular weight, may pass	0.13–0.38	B	Unknown	37
Gentamicin	Increased frequency of dosing, may require measurement of plasma levels	0.34–0.44 were at 1–2 h	0.1 at 1 h and 0.4 at 7 h	D	Increased volume of distribution and increased clearance result in low peak concentrations	166, 169, 170
Meropenem	Unknown	Unknown	0.18	B	Unknown	171
Metronidazole	No dose adjustment required	1	1	B	Unchanged	167, 172
Moxifloxacin	Requires increased dosing	0.78	Unknown	C	Peak serum concentrations decreased, clearance increased, AUC 0.2 × nonpregnant values	173, 174
Piperacillin and tazobactam	Increased frequency of dosing	0.17–0.27	Unknown	B	Increased clearance and volume of distribution Concentration less than MIC at 4 h	175, 176
Sulfonamides	Likely reduced concentration due to dilution but not described	0.5 sulfasalazine 0.06 sulfisoxazole	Competes with bilirubin for albumin binding at birth	Sulfasalazine-B Sulfamethoxazole/trimethoprim-D Sulfamethoxazole-C	Unknown	37
Tetracyclines	Not tested Teratogenicity	Crosses and leads to dental discoloration	Crosses and leads to dental discoloration	D	Unknown	167, 177
Vancomycin	20 mg/kg q8h measurement of maternal plasma levels for sustained treatment	1 with steady state reached at 1–2 h	1	C	Increased volume of distribution, and clearance, unknown changes in half-life	178–180

AUC = area under the curve; FDA = Food and Drug Administration; F/M = fetal/maternal ratio; MIC = minimum inhibitory concentration; PK/PD = pharmacokinetic/pharmacodynamic.

Pregnancy increases the clearance of cefazolin likely because of increased renal excretion.[147,151,152] The increased volume of distribution for cefazolin in pregnancy in conjunction with increased clearance results in a requirement for both a larger initial dose and more frequent dosing to keep plasma concentrations above MIC during surgery.[152] Figure 2 (adapted from Elkomy et al.[152]) shows the probability of maintaining the plasma-free cefazolin concentration above 8 μg/mL (MIC) as a function of dose (1, 1.5, or 2 g) and time of administration in the mother (A) and the fetus (B).[152] A 2-g dose of cefazolin given 15 minutes before surgery should maintain adequate concentrations for a 1-hour procedure in approximately 100% of patients. However, a delay of 1 hour between the administration cefazolin and the surgery will not maintain adequate concentrations in >20% of patients. This is consistent with a recommendation for a 2-g dose of cefazolin for all pregnant patients regardless of weight. In addition, because of the more rapid clearance, the dosing interval for cefazolin should be 3 to 6 hours, not 8 hours.[151] Obesity decreases the tissue concentrations of cefazolin. Based on the adipose cefazolin concentrations reported by Pevzner et al.,[150] 3 g would be an appropriate cefazolin dose for parturients with a body mass index of 30 to 40 kg/m^2, and 4 g would be an appropriate cefazolin dose for parturients with body mass index >40 kg/m^2. Published guidelines have not kept up with advances in our understanding of pharmacokinetics. Despite good studies that recommend administration of 2 g cefazolin 15 minutes before skin incision, the American Congress of Obstetricians and Gynecologists currently recommends 1 g cefazolin be administered within 60 minutes at the start of the operation.[153]

Other cephalosporins are variable with respect to pharmacokinetic changes in pregnancy. Only about one-third of the dose of ceftriaxone is excreted unchanged in the urine and two-thirds by hepatic metabolism.[181] As a result of the reduced dependence on renal elimination, the pharmacokinetics of ceftriaxone are not significantly altered during pregnancy.[182]

Gentamicin, commonly used when enhanced Gram-negative coverage is required at cesarean delivery, has more rapid clearance in pregnant patients compared with nonpregnant control.[183] Larger doses are required to obtain adequate antibiotic concentrations, and the typical dosing interval should be 6 hours, not 8 hours.[183] A dose of 5 mg/kg given every 24 hours may provide better antibiotic coverage for chorioamnionitis with a sustained "postantibiotic effect" and no increase in maternal or fetal complications compared with multiple daily doses.[184]

Sulfonamides used immediately after delivery compete with bilirubin for albumin binding and can lead to kernicterus of the newborn. Although the potential for kernicterus should be considered, they should not be completely avoided peripartum.[37] Sulfonamides have important uses during the peripartum period for specific indications including ulcerative colitis, Crohn disease, and prophylaxis in the setting of human immunodeficiency virus infection. Most studies have demonstrated no adverse effects when used during gestation remote from delivery except for a single retrospective study that found an increase in congenital malformations in neonates of mothers who used sulfonamides during pregnancy.[37]

Antibiotics may be administered to the mother for the purpose of transfer to the fetus to decrease the incidence of neonatal sepsis. UV (blood from the placenta to the fetus reflecting blood concentration in the baby) to MA (reflecting blood concentration in the mother) concentration ratios are important to determine for drugs requiring transplacental efficacy. In our text and tables, this is referred to as the F/M ratio. Figure 2B (adapted from Elkomy et al.)[152] shows the probability of maintaining the fetal concentrations of cefazolin ≥8 μg/mL from a maternal dose of 1, 1.5, or 2 g of cefazolin as a function of the time before surgery. If the intent is to provide antibiotic coverage to the fetus, onset takes a significant amount of time. Even a dose of 2 g given 1.5 hours before surgery has only a 60% chance of providing

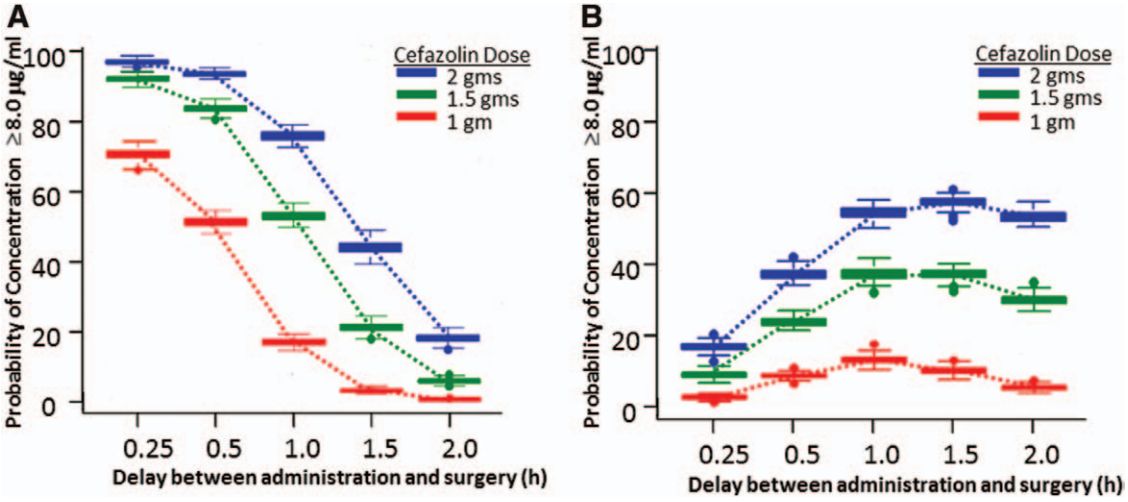

Figure 2. Probability of maintaining plasma concentration above minimum inhibitory concentration during surgery according to time delay between administration and surgery for 3 doses of cefazolin. A, Maternal concentrations. B, Fetal concentrations from uterine vein. Adapted from Elkomy et al.[152]

adequate coverage for the fetus at delivery. Higher doses will be required if fetal antimicrobrial coverage is a priority. Fetuses and neonates have significantly reduced metabolic capacity for many drugs, including antibiotics, which would be expected to extend the duration of antimicrobial coverage in the newborn.

Antihypertensive Drugs

The pharmacokinetics of antihypertensive drugs in pregnant women were reviewed in 2009.[20] By the end of the first trimester, maternal cardiac output increases approximately 35% above prepregnancy values and continues to increase to 50% above nonpregnant values by the end of the second trimester. Material cardiac output remains stable throughout the third trimester. At delivery, cardiac output can yet again double. Coincident with the increases in cardiac output and plasma volume, systemic blood pressure normally decreases secondary to a 20% reduction in systemic vascular resistance at term. Arterial blood pressure decreases approximately 20% by 20 weeks gestational age and then increases toward nonpregnant values because of further increases in plasma volume as the pregnancy reaches completion. Although blood pressure is reduced in normal pregnancy, antihypertensive drugs are commonly required to manage either underlying hypertension or hypertensive diseases associated with pregnancy including preeclampsia (Table 1).

β-Blockers are the mainstay of treatment of hypertensive diseases of pregnancy. The most commonly used β-blockers in pregnancy are labetalol, metoprolol, and atenolol. Increased volume of distribution and hepatic blood flow reduce peak concentrations and decrease appropriate dosing intervals for labetalol and metoprolol.

Labetalol is a mixed α- and β-adrenergic antagonist. The American College of Obstetricians and Gynecologists recommends labetalol as the first-line antihypertensive drug to treat blood pressure in the setting of preeclampsia.[185] The half-life of IV labetalol is 1.7 hours in the setting of pregnancy-induced hypertension at term, as opposed to 6 to 8 hours in nonpregnant women.[186] As such, IV labetalol may be an appropriate drug to treat acute hypertension in pregnancy but would have to be dosed too frequently to be effective for ongoing treatment. Larger bolus doses of labetalol are also required to treat hypertension in pregnant women compared with nonpregnant women.[185] The clearance of oral labetalol is increased 1.6-fold at term. Therefore, the dosing interval outlined should be shorter than recommended in the published guidelines.[20]

The effect of pregnancy on metabolism is not conserved among all β-blocking drugs. Similar to labetalol, increased clearance of metoprolol in pregnancy results in lower plasma concentrations in pregnant women compared with the same women postpartum.[9] In contrast to the reduced peak concentrations of labetalol and metoprolol in pregnancy, there is no difference in atenolol concentrations in pregnancy. Atenolol clearance is completely renal with no dependence on hepatic metabolism. Increased renal clearance is compensated for by increased oral absorption. Based on the absence of pharmacokinetic alteration, atenolol might be considered the preferred β-blocker for use in pregnancy. However, there are reports of intrauterine growth restriction when atenolol is used early in pregnancy, although separating drug treatment effect from severity of disease makes assessment of causation difficult.[187]

Magnesium sulfate is used commonly in preeclampsia/eclampsia for seizure prophylaxis and in preterm delivery for fetal neuroprotection. Minimum plasma magnesium sulfate concentrations of 4 mEq/L are suggested for seizure prophylaxis. Magnesium sulfate is commonly dosed IV but can be dosed IM in resource-poor settings. The 2 regimens are considered to have equivalent clinical efficacy.[139] Plasma concentrations peak at 15 minutes and are reliably maintained above 4 mEq/L at steady state after either a 4-g IV loading dose followed by 1 g/h or an IV push of 4 g over 20 minutes followed by 20 g by deep intramuscular injection.[188] However, there are a number of different treatment regimens that are used clinically, and there is uncertainty as to the optimal protocols for seizure prophylaxis, tocolysis, and fetal neuroprotection. Detailed pharmacokinetic and pharmacodynamic studies for magnesium sulfate are lacking. There are no comparison trials between pregnant and nonpregnant women, because magnesium at higher doses is typically only indicated in pregnant women.

Drugs Administered to the Mother for Fetal Treatment

Drugs with β-adrenergic blocking activity have been administered to the mother to treat fetal arrhythmias. Sotalol is a class III antiarrhythmic drug that acts largely through inhibition of potassium channels. Sotalol also has nonselective β-adrenergic blocking activity and prolongs both the PR and the QT interval. Sotalol has been used as first-line treatment of fetal tachycardia similar to digoxin and flecainide.[189,190] Proarrhythmic activity is a concern for the mother, and interaction with other drugs that prolong the QT interval requires surveillance. Sotalol is transferred effectively to the fetus with the mean F/M ratio of 1.[30] Betamethasone is administered to the mother to facilitate fetal lung maturation (see corticosteroids section).

Anticoagulants and Antiplatelet Drugs

Obtaining therapeutic anticoagulation in pregnancy can be challenging. Despite mild thrombocytopenia, pregnancy is a hypercoagulable state with increased fibrinogen and factor VII.[191] Factor XI, factor XIII, and antithrombin III are decreased, whereas factors II and V typically remain unchanged. These changes result in an approximately 20% decrease in prothrombin time and partial thromboplastin time in normal pregnancy. Hypercoagulability in pregnancy is a common cause of miscarriage, thrombophlebitis, and pulmonary embolism.

Treatment with anticoagulants is complex in the setting of pregnancy-associated hypercoagulability, increased liver blood flow caused by intravascular volume expansion, induction of liver enzymes, and increased renal clearance. Furthermore, it is imperative to normalize coagulation in the parturient to be able to offer neuraxial labor analgesia and avoid hemorrhage at delivery.

Warfarin is a highly effective anticoagulant that is being used in late pregnancy more frequently than in the past.[192]

However, as an uncharged, low-molecular-weight drug, warfarin readily crosses the placenta (Table 2). The use of warfarin between the 6th and 12th week of gestation is associated with a characteristic embryopathy associated with skeletal malformation and miscarriage. The skeletal malformations are because of defects in vitamin K-dependent osteocalcin carboxylation that is necessary for bone formation.[193] Previously, warfarin was considered absolutely contraindicated throughout pregnancy. Warfarin is now prescribed after the period of embryogenesis (after the first trimester), when consistent anticoagulation is necessary for the mother's well-being, such as in a pregnant woman with a mechanical heart valve.[194] Warfarin's pharmacokinetics have not been well studied in pregnancy because of its previous category X designation. With increased use in later pregnancy, more information would be valuable.

Heparin is a charged, high-molecular-weight molecule. As such, heparin does not readily cross the placenta and is not excreted into breast milk. The peak maternal plasma concentration of heparin is only 50% of concentrations in women who are not pregnant.[42] Although higher and more frequent doses of heparin are commonly used in pregnancy, the resulting reduction in factor Xa and activated partial thromboplastin time is highly variable, and therapeutic monitoring is often necessary.[43] Because activated partial thromboplastin time is prolonged in pregnancy, it is not entirely clear what target value is appropriate in pregnancy. Unfractionated heparin is often used as a short-acting, reversible bridge near term pregnancy to allow for discontinuation of longer-acting anticoagulants when delivery is anticipated to prevent intrapartum or postpartum hemorrhage.

Many new anticoagulatants have recently come to market including idrabiotaparinux, fondaparinux, otamixaban, RB006, dabigatran, AZD0837, rivaroxaban, apixaban, and edoxaban.[195] Other than enoxaparin, which is used commonly in pregnancy for thrombotic prophylaxis, these drugs have not been studied in parturients or pregnant women. Their package inserts uniformly state that they have not been studied in pregnancy, and they should only be used if the benefit outweighs the risk. Given the lack of data, it is surprising that some of these, including fondaparinux and apixaban, were considered category B under the old classification system for risk in pregnancy. Although enoxaparin has been studied for recurrent pregnancy loss, no large dose-finding studies have been performed in pregnancy. A variety of doses are used for prophylaxis and therapy of thrombosis. Given the importance of reliable thromboprophylaxis and its reversal in pregnancy, pharmacokinetic and pharmacodynamic studies of these drugs in pregnancy are needed.

Antinausea Drugs

Nausea and vomiting are common problems in pregnancy and during labor and delivery. Thalidomide remains one of the most extreme examples of the importance of evaluating drugs in human pregnancy. In the late 1950s, the treatment of morning sickness with thalidomide was responsible for malformed limbs in about 10,000 children. Animal models do not always predict human toxicity. The thalidomide experience demonstrates the risks when adequate human studies are not conducted, and doctors are not given proper guidance about the safety of drugs in pregnancy.

Table 8 shows the drugs commonly used to treat nausea and vomiting. Ondansetron is among the most effective and commonly used antiemetics. Ondansetron's pharmacokinetics are not affected by pregnancy, and plasma concentrations are not changed in pregnancy.[196] Ondansetron readily crosses the placenta with a F/M ratio of 0.41 at steady state.[197] Ondansetron has a significantly longer half-life in neonates compared with adults.[196] The use of ondansetron in the first trimester has been associated with a small increase in the risk for cleft lip and palate. More studies are needed to evaluate the risk versus benefit of ondansetron in pregnancy.[198]

Table 8. Drugs Commonly Used to Treat Nausea and Vomiting

Drug	Dose adjustment	F/M ratio	Breast milk/maternal plasma ratio	Former FDA category	PK/PD alteration	References
Betamethasone	Increased dose required for lung maturity in multiple gestations. 3 doses at 18-h intervals rather than 2 doses at 24-h intervals	0.3–0.5, more studies required	Unknown	C—concern for risk of cleft palate in T1	Increased volume of distribution, increased clearance, no change in half-life in singleton pregnancy Increased clearance proportional to number of gestations	199–201
Dexamethasone	Multiple gestation requires increased dose due to extensive placental metabolism	0.45	Unknown	C—concern for risk of cleft palate in first trimester	Clearance doubled in single gestation	199, 202
Doxylamine/ pyridoxine	No change first trimester of pregnancy	Unknown	Unknown	A	Clearance unchanged	203
Metoclopramide	Unknown	0.57–0.84	Highly variable	B	Unknown	204, 205
Ondansetron	Limited data, likely no change, more study needed	0.41	Unknown, low molecular weight likely excreted	B	No change in steady-state concentrations in first trimester	197
Scopolamine	Unknown	1	Excreted into breast milk, likely safe	C	Unknown	206, 207

FDA = Food and Drug Administration; F/M = fetal/maternal ratio; PK/PD = pharmacokinetic/pharmacodynamic.

Corticosteroids

Corticosteroids are commonly used to prevent nausea and vomiting and to enhance fetal lung maturity. The pharmacokinetics of steroids in pregnancy are unusual in that they are extensively metabolized by the placenta. The dose requirement is increased in the presence of multiple gestations. Because of increased placental metabolism, mothers carrying twins need greater steroid dosages than singletons and mothers carrying triplets more than mothers carrying twins.[199] This consideration is particularly important for dosing of betamethasone for lung maturity in multiple gestations. However, after delivery of the placenta, it is expected that the maternal dose requirements for steroids would abruptly decrease. Stress steroid prophylaxis may require an increased dose during vaginal delivery but no change during cesarean delivery because the placenta(s) will be quickly removed.

CONCLUSIONS

Pregnancy is associated with diverse physiologic changes that result in alterations of uptake, distribution, metabolism, and excretion of drugs.[208] Concern for adverse fetal outcomes has hampered clinical research on drugs administered in pregnancy. Despite an FDA mandate for the study of drugs in pregnancy, the pharmaceutical industry has not been willing to undertake these studies. Most of the high-quality studies in the literature were performed with academic funding. As shown in our example of propofol, even academicians attempting to study drugs in pregnancy may face unexpected regulatory obstacles.

Clinical choices about dosing and administration of drugs are mostly based on the experience and comfort of practitioners rather than on actual data.[5] Even when there are good pharmacologic data, for example, on reduced dosing interval for β-blockers in pregnancy and the higher dose requirements of cefazolin to attain effective antimicrobial levels, these findings have not made their way into clinical guidelines. Because β-blockers are a mainstay in the treatment of pregnancy-induced hypertension and preeclampsia, patients may be undertreated and their disease considered intractable when they are simply underdosed. Similarly, routine underdosing of cefazolin may contribute to the frequent incidence of peripartum infection.

All drugs commonly used in pregnancy should be subjected to rigorous pharmacokinetic study. When drugs have not been studied, there is little guidance for the clinician to determine whether the benefit outweighs the risk. When clinicians choose to administer drugs that have not been well studied in pregnancy (previous category B and C), significant consideration should be given to obtaining informed consent, recording patient characteristics, documenting drug dose and interval, measuring plasma drug levels, and publishing the experience as a case report. A few such case reports could become the basis of at least an initial effort to characterize the pharmacokinetics of unstudied drugs. These reports should be coalesced in new or existing clinical registries.[209] With better dosing guidelines for pregnant women, clinicians can improve treatment efficacy by avoiding underdosing and limiting overdosing with the associated side effects. Most critically, clinicians could provide better pharmacotherapy for optimal maternal and fetal well-being and outcomes.

DISCLOSURES

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RECUSE NOTE

Dr. Steven Shafer is Editor-in-Chief of *Anesthesia & Analgesia*, and Dr. Pamela Flood is married to Dr. Shafer. This manuscript was handled by Dr. James Bovill, Guest Editor-in-Chief, and Dr. Shafer was not involved in any way with the editorial process or decision.

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