Review Article

Principles of Anti-infective Dosing in Pregnancy

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ABSTRACT

Purpose: Anti-infectives are among the most commonly prescribed medications in pregnancy. However, detailed information on the pharmacokinetics and pharmacodynamics of these medications in pregnancy is limited, leading to uncertainty among clinicians regarding the tolerability and efficacy of treatments. The purposes of this review were to highlight key physiologic changes during pregnancy that influence drug behavior, and to discuss areas of active research related to anti-infective drugs in pregnancy.

Methods: A review of literature in PubMed was performed for topics related to physiologic changes of pregnancy, postcesarean surgical site infections, vaccines in pregnancy, and intrauterine infections. The literature was reviewed and pertinent sources were utilized for this article.

Findings: Physiologic changes during pregnancy may impact drug disposition and efficacy. Cefazolin regimens are the current prophylactic treatment of choice for postcesarean surgical site infections. Vaccines are provided in pregnancy for both maternal and neonatal benefit. Broad-spectrum antibiotics continue to be used as first-line therapy for intrauterine infections.

Implications: Continued efforts to broaden the knowledge base on anti-infective drug behavior in pregnancy will result in increased therapeutic options for this population. (*Clin Ther.* 2016;38:2006–2015) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: antibiotics, pharmacokinetics, pregnancy, vaccines.

INTRODUCTION

Few drugs used in pregnancy have been explicitly approved by the US Food and Drug Administration (FDA) for use specifically during pregnancy. Despite this fact, nearly 60% of women take medications during pregnancy in the United States.[1] Studies have found that pregnant women take an average of 2 to 5 medications throughout their pregnancy course.[2] Over the past 3 decades, antibiotics and vaccines have been consistently found among the 20 medications most commonly prescribed in the first trimester.[2] The widespread prescription of anti-infective medications in pregnancy has brought more attention to the relative paucity of tolerability and efficacy data in pregnant women compared with other patient populations. A study of health care providers' pregnancy-related medication inquiries to an academic, university-based drug information center over a decade identified infectious diseases as one of the most common indications for information requests.[3] Nearly 1 in 7 inquiries to the drug information center was related to anti-infective medications, with a primary focus on drug tolerability.[3]

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The process of drug approval is meant to demonstrate the tolerability and efficacy of new medications prior to widespread use. However, women have historically been underrepresented in this process, with the majority of testing occurring in men and animals. The rationale that data related to drug performance in men can be extrapolated to women has been challenged as our understanding of sex-related differences has increased. A study of intrasubject variability in bioequivalence trials revealed up to a 2- to 6-fold difference in variability in women compared to men.[4] In fact, $\sim 30\%$ of studies of bioequivalence would not have passed if drug performance between the sexes had been compared.[4] Accumulating data on these differences has led to calls for regulatory bodies such as the FDA and Health Canada require pharmaceutical developers to test new medications in the specific populations in which they are intended for use.[5]

Few medications have been studied in pregnant women during the drug-approval process, due to a myriad of tolerability and legal concerns. As a result, the development of tolerability data on drug use in pregnancy often occurs through postmarketing surveillance. In the interim, practitioners are left to extrapolate the anticipated behavior of a drug if they or the pregnant patient desires its use during gestation. Pharmacokinetic data on medication behavior, in particular, are sparse in the pregnant population, and are even less common for newly approved medications. In 2015, the FDA issued an updated Pregnancy and Lactation Labeling Rule[6] to improve the content and format of tolerability information on medications used in pregnancy. A major feature of the updated Pregnancy and Lactation Labeling Rule was to replace the pregnancy letter categories (A, B, C, D, and X) with descriptions of medication risks.

Clinical dosing of medications in pregnancy is based primarily on data from studies that have been performed in men and nonpregnant women, and does not account for the characteristics that make pregnant women a unique population to treat. The physiologic changes of pregnancy influence the behavior of most drugs during this phase of life. An understanding of these physiologic changes can help a practitioner to anticipate changes in the pharmacologic behavior of a medication. In turn, practitioners can modify drug dosing to elicit the desired pharmacodynamic effects. In this article, we review the physiologic changes of pregnancy that affect dosing of all medications in pregnancy, with a focus specifically on

recent areas of interest related to anti-infective drug selection or dosing in pregnancy. Our goal was to provide readers with a practical understanding of concepts that they can apply to their own practices and to the care of pregnant women.

MATERIALS AND METHODS

A search using PubMed was performed for articles published from January 1980 to July 2016 on topics related to physiologic changes during pregnancy, postcesarean surgical site infections (SSIs), vaccines in pregnancy, and intrauterine infections. The literature was reviewed and pertinent sources were utilized for this article.

RESULTS

Information from 46 articles from the PubMed search was used in this review. These sources were selected based upon pertinence to the selected topics with prioritization of more recent publications.

Physiologic Changes During Pregnancy

Pharmacokinetics describes the body's absorption, distribution, metabolism, and elimination (ADME) of a drug. Each part of this pathway can be affected by numerous physiologic changes that the body undergoes during pregnancy that may greatly affect dosing regimens. Absorption of the drug into the systemic circulation is dependent on the route of administration (oral, subcutaneous, intramuscular, intravenous, inhalation, transdermal, per vagina, or per rectum). Altered drug behavior due to changes in maternal physiology can influence drug bioavailability, which is the proportion of administered drug that reaches the systemic circulation in intact form. The oral route of administration is one of the most common with drugs taken during pregnancy, and the effects of drugs taken orally might be affected by several factors, including stomach pH, food, gut transit time, local gut metabolism, and uptake and efflux transport processes. Medications taken orally undergo a *first-pass effect*, consisting of metabolism by enzymes in the gastrointestinal lumen, gut flora, and liver. In the general population, the amount of intact drug reaching the systemic circulation after the first-pass effect is greatly reduced. In the pregnant state, there is decreased gastric acidity, which may increase the ionization of weak acids and may affect absorption. Additionally,

an increase in the orocecal transit time due to decreased intestinal mobility, an effect of the endogenous hormone progesterone, increases absorption.[7] Blood volume increases in pregnancy to ~40% to 45% above that in the nonpregnant state after 32 to 34 weeks.[8] Due to this change, hepatic blood flow is increased to 1.8 L/min.[9] This increased blood flow additionally increases the first-pass effect on oral medications. Due to the many variables that affect the absorption of oral medications, there is a wide variation in plasma levels thus leading to variable clinical and adverse effects.

The *distribution* of a medication refers to the reversible transfer of a drug from one location to another within the body. The volume of distribution (V_d = total drug in body/plasma concentration of drug), which is the theoretic volume necessary for maintaining the total drug at the current plasma concentration, is used as a measure of the extent of the distribution of a drug. If a drug is highly bound to tissue, the V_d will be very large. A large V_d means a lower plasma concentration due to a fraction of the drug localizing to target receptors within tissues (extravascular space). In cases of loss of a large amount of blood volume, as is typical for a delivery, drugs with a large V_d are more likely to remain in the body (greater extravascular distribution) than are drugs with a small V_d (primarily intravascular). An additional feature unique to pregnancy is transplacental transfer of medications to the fetal compartment (fetus, amniotic fluid, gestational tissues). The passage of a drug into the fetal compartment is reflected by a larger V_d than that in the nonpregnant state, primarily due to distribution into the amniotic fluid. An increased V_d may modify the efficacy of anti-infectives by decreasing drug at maternal target receptor sites while increasing fetal exposure.

The distribution of a drug is dependent on several factors, including the level of perfusion of tissue, plasma protein binding to the drug, lipid solubility, vascular permeability, and tissue binding. Many of these factors are altered in pregnancy, often leading to increased drug distribution. Additionally, pregnancy is a state of hypoalbuminemia, which increases the free fraction of drug and decreases drug at the receptor site.[8] The renal system also changes during pregnancy with increased activity of the renin–angiotensin–aldosterone system leading to increased water and sodium retention. Plasma volume expands by 1200 to 1600 ml compared with that in the nonpregnant state, beginning as early as 6 to 8 weeks' gestation and reaching a peak at ~32 weeks, with a total volume of 4700 to 5200 ml.[10] Several other changes to the cardiovascular system contribute to increased blood flow and perfusion of tissues. Cardiac output increases by 30% to 50% through increases in both stroke volume and heart rate, and regional blood flow is altered to favor perfusion of the pelvic organs.[11] Blood flow to the uterus, kidneys, skin, and mammary glands increases in pregnancy, while blood flow to muscles decreases.[9] These changes result in an increased V_d of most medications, with a preferential exposure of reproductive organs to the drug.

The *metabolism* of a drug describes the range of biochemical modifications performed by specialized enzymatic systems in order to facilitate the excretion of a xenobiotic. There are 3 phases of metabolism: phase 1, oxidation, reduction, and hydrolysis by cytochrome P450 (CYP) enzymes and flavin monooxygenases; phase 2, conjugation to polar compounds with sulfate, glucuronic acid, glycine, or glutathione; and phase 3, further metabolism and transport. The activation of metabolic enzymes is highly variable and is affected by a range of factors, such as race, ethnicity, age, concurrent medications, and pregnancy. The elevated hepatic blood flow in pregnancy of 1.8 L/min increases the exposure of xenobiotics to the metabolic enzymes, which promotes the first-pass metabolism of drugs. CYP enzyme activity is also altered as a result of the changing hormonal milieu of pregnancy, resulting in increased activity of some enzymes such as CYP34A, -2C9, -2D9 and decreased activity of others such as CYP1A2.[11] A detailed understanding of the enzymatic metabolism of a drug of interest is crucial to anticipating increases or decreases in drug concentration as a result of metabolism in pregnancy, and hence altered dosing requirements to achieve pharmacodynamics goals.

Elimination is the final step in the pathway of drugs in the body; it is the process by which a drug is excreted either in an unaltered form or after modification into metabolites. Routes of elimination are commonly through the kidney, liver, skin, lungs, feces, and glands (breast, lacrimal, salivary, sweat). Alterations in the elimination of a medication result in the accumulation of the parent drug or its metabolites. In pregnancy, the aforementioned cardiovascular

Table. Physiologic changes during pregnancy and their effects on drug pharmacokinetics (PK).

System	Changes During Pregnancy	Effects on PK
Cardiovascular	Plasma volume expansion Begins at 6–8 wk GA Peaks at 32 wk (4700–5200 mL) Increases 1200–1600 mL above that in nonpregnant women	1) Increased volume of distribution 2) Decreased concentration of drug at the receptor site
	Cardiac output increase 30%–50% 50% by 8 wk GA	1) Increased blood flow 2) Increased clearance of drug
	Increases in SV and HR SV in early pregnancy HR in late pregnancy Changes in regional blood flow	
	Increased to uterus, kidneys, skin, and mammary glands Decreased to skeletal muscle	
	Hepatic blood flow Constant during pregnancy 1.8 L/min	1) Increased blood flow 2) Increased metabolism 3) Increased clearance of drug
Respiratory	Decreased functional reserve capacity Increased respirations Lowered $PaCO_2$ Compensated respiratory alkalosis	1) Increased clearance of drug from lungs 2) Altered metabolism and systemic clearance
Metabolism	Hypoalbuminemia Increase in free fraction of drugs bound to albumin	1) Decreased drug at receptor site 2) Decreased drug effect
	Enzymatic activity N-methylation inhibited by progesterone	Altered metabolism of drugs
	P450 activity Increases in 34A, 2C9, 2D6 Decrease in 1A2	
Renal	Blood flow increased 50% Decreased renal vascular resistance GFR increased 50%	Increased clearance of drug
	Reduction in serum creatinine and urea Increased activity of RAAS Sodium and water retention	1) Increased volume of distribution 2) Decreased concentration of drug at receptor site
Gastrointestinal	Decreased gastric acidity	Altered absorption (K2)

(continued)

Table. (continued).

System	Changes During Pregnancy	Effects on PK
	Gastric emptying	Delayed peak concentration
	Delayed in laboring women	
	No difference between 1st and 3rd trimester in nonlaboring women	
	No difference from postpartum	
	Increased orocecal transit time in 3rd trimester	Increased absorption
	Progesterone effect	
	Pancreatic polypeptide inverse correlation	

GA = gestational age; GFR, glomerular filtration rate; HR = heart rate; RAAS = renin–angiotensin–aldosterone system; SV = stroke volume.

changes, including increased cardiac output (increased stroke volume and heart rate) and preferential regional blood flow, contribute to the increased clearance of a drug. Increased hepatic flood flow and renal blood flow due to decreased renal vascular resistance also contribute to enhanced elimination.[12] Elimination through the kidneys is the primary method of drug disposition, although elimination may also occur through the lungs. Pregnant women have increased respirations and a decreased functional reserve capacity, which lead to a lowered $PaCO_2$ and thus a compensated respiratory alkalosis.[10] These factors contribute to the increased clearance of inhalational drugs from the lungs. Another important contributor to elimination are drugs that are administered concurrently. Drug–drug interactions, or metabolic enzyme induction/inhibition, may affect the elimination rate of the drug of interest. A summary of physiologic changes of pregnancy is presented in the Table.

Surgical Site Infections

SSIs are a common cause of morbidity in patients who undergo any surgery, and cesarean sections are no exception. In the population of patients who undergo cesarean section, there are many risk factors for infection. Standard of care dictates the use of antibiotic prophylaxis, typically in the form of a single dose of IV cefazolin at the initiation of surgery, to decrease the risk for SSI.[13] A Cochrane review on the subject of prophylactic antibiotics at the time of cesarean section noted that the risk for endometritis was reduced by 76% in a group who underwent elective cesareans, and remained significant in a group who underwent emergent cesareans.[14] The most cost-effective regimen appears to be a single dose of cefazolin.[13,15,16] The standard cefazolin dose in pregnant women is 1 g, although a higher dose (2 g) is recommended for patients with a body mass index (BMI) of ≥ 30 kg/m^2 or a weight of >100 kg.[13,17]

As the pregnant population becomes increasingly obese, doses of prophylactic antibiotics at the time of cesarean delivery have come into question. Elkomy et al[18] assessed serum antibiotic levels after a 1-g cefazolin dose in pregnant women undergoing cesarean delivery. Using the data collected, the investigators created a pharmacokinetics model to assess cefazolin clearance in pregnancy, and thus the adequacy of dosing. The investigators concluded, based on their modeling, that due to increased cefazolin clearance in pregnancy, larger doses (than 1 g) were necessary to obtain the antibiotic effect seen in nonpregnant women. Pevzner et al[19] assessed the adequacy of a higher dose (2 g), comparing adipose and serum cefazolin concentrations in 3 groups of 10 patients with BMIs of <30 to 39.9, and >40 kg/m^2. In that population, a large percentage of patients in the higher-BMI groups did not attain a tissue concentration above the minimum inhibitory concentration for gram-negative rods, suggesting that a dose >2 g may be necessary in obese pregnant women. In a second phase of that study, Swank et al[20] gave 3 g of

cefazolin to a second cohort of 30 patients in the same BMI categories, then compared the serum and adipose levels. All of the patients in the higher-BMI classes who received 3 g attained tissue concentrations above the minimum inhibitory concentration. Based on these data and the comparison to the 2-g data, the investigators concluded that 2 g was an adequate dose in normal and overweight patients, while obese patients may need 3 g for adequate prophylaxis. During the interim between the 2 previous studies, Stitely et al[21] compared serum and adipose levels after the administration of a dose of 2 or 4 g of cefazolin for prophylaxis in patients with a BMI >35 m^2/kg. All of the patients in both groups, independent of BMI, attained tissue and serum levels above the minimum inhibitory concentration, leaving the investigators unable to conclude whether the higher dose was in fact protective. In a more recent, randomized, controlled trial, Maggio et al[22] compared adipose cefazolin levels in 57 patients receiving 2- or 3-g doses. All of the samples had cefazolin levels above the minimum inhibitory concentration. Thus, in that trial, the authors concluded that the data were not adequate to support the use of 3 g of cefazolin in the obese population.

However, the previously mentioned studies all were geared to assess tissue concentrations, not clinical outcomes. In 2015, Ahmadzia et al[23] conducted a retrospective cohort study to do just that. That study included 335 patients with a median weight of 140.6 kg, 175 of whom received a 2-g dose and 160 of whom received a 3-g dose. The difference in SSIs between the 2 groups was not significant. Thus, in that clinical study, the investigators concluded that a 3-g dose of cefazolin did not significantly reduce SSIs.

Based on the above data, while it appears that a single dose of a cephalosporin antibiotic is sufficient for obtaining adequate tissue concentrations and reducing SSI risk in most patients, a subset of patients may benefit from higher doses of antibiotics. More recently, the utility of dual-antibiotic regimens has been investigated to further reduce the prevalence of postcesarean infections. In particular, *Ureaplasma* and *Mycoplasma* spp are components of polymicrobial postcesarean infections that are not effectively treated with cephalosporins. Researchers have examined azithromycin as a secondary component of the antibiotic prophylactic regimen, finding myometrial tissue concentrations adequate for treating *Ureaplasma* spp infections and efficacy in the prevention of endometritis.[24,25] Efforts continue to identify and address the etiologies of postsurgical infections through the selection of effective antibiotics and stratification of dosing regimens in patients at highest risk for inadequate antibiotic tissue concentrations.

Vaccines

Pregnancy is a particularly vulnerable time for women to contract viral and bacterial diseases due to a general decrease in immunity, creating potential harm to both the mother and fetus. In addition, infants go unprotected during the first few months of life due to their immature immune system and inability to receive vaccines. Vaccination during pregnancy is an efficient way to offer protection to not only the mother but also the fetus/infant. It has long been established that immunoglobulin G antibodies are actively transported through the placenta, providing antibodies to the fetus.[26–28] This transplacental transport increases with gestational age, with peak transport occurring during the final 4 weeks of gestation.[28] Following delivery, these antibodies remain in the infant, offering the potential for passive immunity in the first months of life against diseases associated with significant morbidity and mortality.[26,27] However, the levels of antibodies in the fetus are directly related to the maternal levels, and vaccinations during pregnancy can increase antibodies in the fetus to levels adequate for protection.[28] For example, the recommended Tdap (tetanus, diphtheria, and pertussis) vaccine is given during the third trimester in an attempt to increase the levels when transplacental transport is at its greatest, therefore increasing the fetus' antibody levels.[28] In contrast, live attenuated vaccines are contraindicated in pregnancy due to the theoretic risk for transmission to the fetus, although studies have not confirmed this risk.[28–30] Currently, the only vaccines recommended in all pregnant women are the seasonal influenza and Tdap vaccines, which have not been associated with acute adverse outcomes in patients who received both.[31]

Influenza during pregnancy has been associated with a significant increase in poor outcomes, including increased rates of maternal hospitalizations, pneumonia, intensive care unit admissions, and mortality.[32–34] Influenza also has been associated with increased rates of pregnancy loss, stillbirth, neonatal death, preterm

birth, and low birth weight.[29,30,32] To help prevent these complications, the Centers for Disease Control and Prevention and the American Congress of Obstetricians and Gynecologists recommend that all pregnant women receive the yearly influenza vaccine regardless of gestational age.[35] Studies have reported that pregnant women who received the vaccine had a lower risk for preterm birth or infants small for gestational age, and a decreased risk for fetal death.[29,30,33] Additionally, vaccination has a longitudinal impact beyond the prenatal period as a result of trans-placental transfer of maternal antibodies to the fetus. Infants cannot receive the influenza vaccine until age 6 months, leaving them particularly vulnerable during the first few months of life.[29] Influenza is particularly dangerous to infants: The rate of hospitalization due to influenza is higher in infants aged <6 months than in any other group.[27,33] One study reported a 63% reduction in infant influenza and a 29% reduction in other febrile illnesses in infants of mothers who received the influenza vaccine during pregnancy.[33] Maternal vaccination was found to have a 91.5% likelihood of preventing infant hospitalization due to influenza.[27] The transplacental passage of immunoglobulin G antibodies is thought to be the key parameter explaining the success of maternal immunization for neonatal benefit. While the influenza vaccine offers significant benefits to pregnancy, improved infant outcomes, especially in pandemic years, can be of equal importance. While educating patients on these benefits, it is important to emphasize the maternal, fetal, and neonatal benefits.

Pertussis, more commonly known as whooping cough and caused by the bacteria *Bordetella pertussis,* is prevented by the DTap (diphtheria, tetanus, and pertussis) vaccine in infancy and later the Tdap in adolescence and adulthood. Pertussis is known to cause significant morbidity and mortality in infants, with this population being at the greatest risk.[26,28,36] In fact, newborns have rates of hospitalization and deaths higher than those of any other population.[37] This finding is in part due to infants not being protected, as they do not start their vaccinations until 2 months of life, and immunity not appearing until 6 months.[30,36] Although the prevalence of pertussis had been low for many years, it increased significantly in 2012, prompting the Centers for Disease Control and Prevention to recommend that all pregnant women be vaccinated during the perinatal period, specifically in the third

trimester.[29,30,32] Vaccination during pregnancy provides protection to the mother, as well as passive immunity to the infant, with antibodies remaining for up to 6 weeks of life.[26,32,36,37] A recent study from Belgium reported that infants of women who received vaccinations during the third trimester had significantly higher antibody levels at 8 weeks of life compared with infants of mothers who had no vaccine in the previous 10 years.[26] The practice of perinatal vaccination for pertussis has been widely implemented, and recent research suggests that the vaccine may be 91% effective in preventing pertussis in infants.[36] Further long-term studies are needed to assess the clinical impact of maternal vaccination during the third trimester on neonatal pertussis rates.

With the implementation of this vaccination strategy, however, there is a residual concern that the maternal antibodies may prevent the infant's immune system from appropriately responding to other immunizations, potentially decreasing the child's immunity later in life. Infants of vaccinated mothers have been reported to have lower levels of antibodies after the third vaccine in the series compared with infants of mothers who were not vaccinated, but no differences in clinical outcomes were observed.[26] The theory of potentially decreasing immunity with the current vaccination schedule is yet to be clinically proven, and further studies are needed. In the meantime, clinicians should weigh the potential benefit of preventing a dangerous and high-risk infection in infants against the theoretical risk for decreased immunity with future immunizations.

Intrauterine Infections

Chorioamnionitis is present in an estimated 3% to 5% of all pregnancies.[38] Although its diagnosis can be defined both clinically and histologically, most institutions use a modification of the Gibbs criteria, which includes fever ($>38°C$) and 1 or more of the following: maternal or fetal tachycardia, fundal tenderness, and/or foul-smelling, purulent vaginal discharge. The most commonly offending pathogens include *Escherichia coli,* group B streptococci, *Bacteroides* spp, and anaerobes.[39] This diverse group of bacteria led practitioners to use broad-spectrum antibiotics once the diagnosis had been established. There was, however, no clear consensus on whether to treat mothers intrapartum or postpartum. An initial study by Gibbs et al[40] reported that

intrapartum treatment of chorioamnionitis with broad-spectrum antibiotics was associated with decreased neonatal sepsis and improved neonatal and maternal outcomes. The antibiotic regimen included ampicillin 2 g IV q6h and gentamicin 1.5 mg/kg IVq8h. While this provided new insight into the management of chorioamnionitis, the ideal antibiotic (s) and dosing regimen was still unknown. Ampicillin and gentamicin had been historically used by most physicians due to their extensive gram-positive and gram-negative coverage. Gilstrap et al[41] validated this combination of antibiotics by comparing the cord blood levels of five different antibiotics—clindamycin, mezlocillin, ampicillin, cefoxitin, and gentamicin—in patients with clinical chorioamnionitis. They reported that ampicillin and gentamicin were associated with the highest cord blood–to–maternal blood ratios. These studies led to most institutions implementing a protocol of administering ampicillin 2 g IVq6h and gentamicin 1.5 mg/kg IVq8h, with the addition of clindamycin 900 mg for anaerobic coverage prior to cesarean delivery.[42]

In 2005, Locksmith et al[43] delved further into optimal gentamicin dosing and compared umbilical cord and maternal peak gentamicin concentrations between patients who received once-daily dosing (5.1 mg/kg/d) compared with TID dosing (120 mg followed by 80 mg q8h) for clinical chorioamnionitis. Interestingly, once-daily dosing was associated with fetal serum drug levels that were consistently >5 μg/mL, whereas conventional dosing led to serum levels in the range of 2 to 4 μg/mL. Due to concerns for kidney or 8th cranial nerve damage, though, most physicians have continued to follow conventional dosing. Surprisingly, there have been few studies to date that have compared conventional dosing to that of other broad-spectrum antibiotics. Recently, attention has been turned to ertapenem as an alternative to the conventional regimen of ampicillin/gentamicin/clindamycin due to its characteristics of a newer broad-spectrum agent requiring only once-daily dosing. However, evidence of the efficacy of ertapenem is conflicting and further studies are needed.[44,45] As bacterial resistance to antibiotics continues to evolve and newer antibiotics become available, there will be a need for additional trials to determine antibiotic regimens appropriate for the obstetric patient.

DISCUSSION

Anti-infective medications are commonly utilized in pregnant women despite limited formal testing of tolerability and efficacy. Clinicians must be aware of the physiologic changes during pregnancy that may modify the anticipated behavior of an anti-infective medication. These concepts can be used for rational modification of dosing regimens to elicit optimal pharmacodynamics effects. Current areas of interest related to anti-infective medication use in pregnancy include postcesarean infections, vaccines, and intrauterine infections. While not addressed in this article, a critical evaluation of therapeutic options for infections during pregnancy (pyelonephritis, pneumonia) may also result in dosing modifications to account for physiologic changes. These are some of the areas in which there are ongoing efforts to optimize drug selection or dosing regimens to in turn optimize clinical outcomes.

In the future, attention may be shifted to a personalized medicine approach to therapeutic interventions in obstetrics.[46] Specifically, research is needed to characterize the contribution of genetic polymorphisms in drug-metabolizing enzymes or transport proteins on the pharmacokinetics of anti-infective medications. The goals of these research efforts should be to improve identification and to optimize treatment in pregnant women at risk for suboptimal outcomes. Pregnant women are a special, understudied population that can benefit from continued efforts to improve anti-infective treatment regimens.

CONCLUSIONS

Physiologic changes during pregnancy may impact drug disposition and efficacy. Cefazolin regimens are the current prophylactic treatment of choice for postcesarean SSIs. Vaccines are provided in pregnancy for both maternal and neonatal benefit. Broad-spectrum antibiotics continue to be used as first-line therapy for intrauterine infections. Continued efforts to broaden the knowledge base on anti-infective drug behavior in pregnancy will result in increased therapeutic options for this population.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

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