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Physiologic Changes During Pregnancy and Impact on Small-Molecule Drugs, Biologic (Monoclonal Antibody) Disposition, and Response

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Abstract

Pregnancy is a unique physiological state that results in many changes in bodily function, including cellular, metabolic, and hormonal changes. These changes can have a significant impact on the way small-molecule drugs and monoclonal antibodies (biologics) function and are metabolized, including efficacy, safety, potency, and adverse effects. In this article, we review the various physiologic changes that occur during pregnancy and their effects on drug and biologic metabolism, including changes in the coagulation, gastrointestinal, renal, endocrine, hepatic, respiratory, and cardiovascular systems. Additionally, we discuss how these changes can affect the processes of drug and biologic absorption, distribution, metabolism, and elimination (pharmacokinetics), and how drugs and biologics interact with biological systems, including mechanisms of drug action and effect (pharmacodynamics) during pregnancy,as well as the potential for drug-induced toxicity and adverse effects in the mother and developing fetus. The article also examines the implications of these changes for the use of drugs and biologics during pregnancy, including consequences of suboptimal plasma drug concentrations, effect of pregnancy on the pharmacokinetics and pharmacodynamics of biologics, and the need for careful monitoring and individualized drug dosing. Overall, this article aims to provide a comprehensive understanding of the physiologic changes during pregnancy and their effects on drug and biologic metabolism to improve the safe and effective use of drugs.

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Conflicts of Interest

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Keywords

biologics; monoclonal antibodies; physiology; pharmacodynamics; pharmacokinetics; pregnancy

Pregnancy is associated with a number of physiologic changes.[1,2] These physiologic changes associated with pregnancy change during the course of gestation and can affect drug pharmacodynamics (PD) and pharmacokinetics (PK), resulting in decreased or increased drug disposition. Despite documented effects of pregnancy on drug disposition, medication usage during pregnancy continues to be very common.[3] However, PK, PD, and pharmacogenomic data for the majority of medications used during pregnancy remain unknown. Pregnancy studies can help determine the appropriate dose (PK) and response (PD) of drugs, but it is not always possible to extrapolate dosage and drug response recommendations for pregnant women from those for nonpregnant women.[4]

Unfortunately, lack of pregnancy-specific PK and PD studies due to a gap between initial licensure of a drug and the availability of pregnancy-specific pharmacologic data has led to delays in the deployment and use of several medications in pregnant women. As a result, many effective and well-tolerated medications that are widely prescribed to nonpregnant adults are not currently used in pregnant women. Understanding pregnancy physiology is important for pharmacologic research because it allows us to answer crucial questions about the effects of medications in pregnant women and how pregnancy modifies the PK and PD of drugs, and provide the needed physiologic data for better understanding of physiologically based PK modeling, with the ultimate goal of accelerating dose-finding and dose-response pharmacologic studies in pregnant women.

In this review, we summarize the processes of drug absorption, distribution, metabolism, and excretion; PD changes during pregnancy and its effect on drug disposition; system-specific changes affected by pregnancy; effect of physiologic changes on drug disposition, including dire consequences of suboptimal plasma drug concentrations; and effect of pregnancy on the PK and PD of monoclonal antibodies (biologics).

System-Specific Physiologic Changes During Pregnancy

Coagulation Changes

Due to the physiologic changes associated with pregnancy, hypercoagulability risk increases significantly (×5-10 times) compared to nonpregnant levels, continuing until ≈6-12 weeks postpartum. The risk of thrombosis continues (though minimally) until about 6 months postpartum when the risk becomes very minimal. Hypercoagulopathy during pregnancy is a direct consequence of increased (or decreased) activity and quantity of clotting factors. Several clotting factors are increased during pregnancy. For example, factors VIII, IX, and X are increased during pregnancy.[5] Up to 50% more fibrinogen is produced, while fibrinolytic activity is reduced. Protein S and antithrombin concentrations (free and total fractions) as well as functional activity decrease, shifting the balance in favor of thrombosis.[6] A summary of the coagulation changes that occur during pregnancy is presented in Table 1. Pregnancy has a direct effect on the 3 elements of the Virchow's triad[7]: hypercoagulability,

hemodynamic alterations (stasis of blood flow, turbulence), and endothelial dysfunction or injury that increase the risk of thrombosis during pregnancy.

The physiologic changes during pregnancy, dosage complexities of anticoagulants during pregnancy, and the lack of evidence to guide treatment decisions make it difficult to safely and efficiently balance the risks and benefits of anticoagulation in pregnant women. PK studies demonstrate that the dose of low-molecular-weight heparin (LMWH) should be modified during pregnancy to maintain anti-Xa concentrations in the therapeutic range levels due to increasing body mass index, changes in glomerular filtration rate (GFR), and increased activity of metabolic enzymes that occur during pregnancy.[8,9] Accordingly, a twice-daily LMWH dosing regimen is typically advised during pregnancy to make up for the increased renal clearance of LMWH that occurs in the second and third trimesters of pregnancy. No large-scale studies have determined the best dose of direct-acting oral anticoagulants for treating acute venous thromboembolism in pregnant women.

Cardiovascular Changes

During pregnancy, the cardiovascular system undergoes several remarkable changes to adapt to the increased cardiac demand in pregnancy. Changes in the cardiovascular system (mediated by increased estrogen concentrations during pregnancy) include changes in the heart and vascular systems. Pulse rate gradually rises over the course of pregnancy, peaking at 20%-25% in the third trimester of pregnancy (but typically not greater than 100 beats/min). Systemic and pulmonary vascular resistance start to decline steadily from 5 weeks of pregnancy onwards, plateauing from midpregnancy to term, with an overall drop of 35%-40%. Within 2 weeks after delivery, the resistance returns to normal. As a result, systolic and diastolic blood pressures, mean arterial pressure, and central systemic pressure all fall by 5-10 mm Hg in the first and early second trimesters of pregnancy. Progesterone's vasodilator action is responsible for the decline in pulmonary and peripheral resistance.

Cardiac output increases significantly throughout the first trimester and reaches ≈30%-50% higher than its baseline value at 24 weeks of gestation. Additionally, the left ventricular size, end-diastolic volume, and stroke volume increase above baseline values. Pregnancy may result in the physiological electrocardiogram changes that include left QRS axis deviation, atrial and ventricular ectopic beats, an inverted or flattened T wave (in leads II and V_1-V_3), sinus tachycardia, and a prominent Q wave in leads II, III, and aVF.[10] All of these changes that occur in the circulatory system may result in typical complaints such as palpitations, mild shortness of breath with exertion, and fainting, which occur in normal pregnancy. As such, these changes (including electrocardiographic changes) should be interpreted with caution in pregnancy. A summary of the cardiovascular changes that occur during pregnancy is presented in Table 2.

Renal Changes

Several renal changes occur during pregnancy that affect drug disposition. By the end of the first trimester, renal blood vessels undergo vasodilation, resulting in a 40%-50% increase in renal plasma flow and GFR. By the middle of the second trimester, renal plasma flow increases by 60%-80% and decreases to ≈50% in the third trimester of pregnancy compared

to prepregnancy values.[5] At 6 weeks' gestation, GFR begins to increase, reaching a 50% increase above nonpregnant levels by the end of the first trimester. Although some studies have shown that the increase in GFR is sustained until delivery, it is possible that GFR falls by ≈15%-20% throughout late pregnancy.[5] The increased renal blood flow and GFR reduces blood creatinine, urea, and uric acid concentrations. Creatinine falls from a mean of 0.7 mg/dL to a mean of 0.5 mg/dL during pregnancy. Thus, a creatinine concentration of ≥0.9 mg/dL might indicate renal impairment and necessitates evaluation.

While estimated GFR is used in determining renal function in nonpregnant adults and has been used extensively in estimating renal function in pregnant women, 1 study showed that estimated GFR may not be a reliable measure of renal function in pregnant women.[11] Pregnancy causes an increase in proteinuria, with daily maximums of ≈300 mg compared to 150 mg in nonpregnant adults.[12] The renal changes during pregnancy contribute significantly to the clearance and disposition of several drugs. A summary of the renal changes that occur during pregnancy is presented in Table 3.

Respiratory System Changes

There are significant alterations to the respiratory system, including the upper airway, the respiratory tract, and the respiratory mechanics, all of which are necessary to meet the increasing metabolic needs of pregnancy. Due to expanding uterus size, rising maternal metabolic rate (increase by ≈15%), and rising fetal consumption, pregnant women's oxygen needs increase by ≈30% above baseline. The diaphragm is raised ≈3-4 cm due to increasing uterine size. As a result, hypoxia, hyperventilation, and breathlessness are more common in pregnant women. By 1-2 weeks postpartum, the uterus returns to normal size.

There are also significant changes that occur in the lung volumes. A reduction of 20%-25% in residual volume, 10%-25% in total lung capacity, 15%-20% in expiratory reserve volume, and 10%-25% in functional residual capacity is typical. The respiratory capacity increases by 5%-10%, breathing rate by 1-2 breaths above normal, and tidal volume by 30%-50%. Because of these alterations, partial pressure of oxygen rises to promote oxygen transfer to the fetus. A summary of the respiratory changes that occur during pregnancy is shown in Table 4. The reduction in functional residual capacity brought on by the term uterus dislodging the diaphragm rebounds to normal levels. Other pregnancy-related abnormalities in respiratory physiology, such as larger tidal volumes, progressively return to normal over the course of 6-8 weeks after delivery. Notably, normal pregnancy physiology and the postpartum period should not cause respiratory rate to change.

Endocrine Changes

In addition to increases in estrogen and progesterone that happen in all normal pregnancies, there are several changes that occur in other hormones. For example, at the end of the first trimester, human chorionic gonadotropin concentrations reach their peak, which causes a temporary rise in free thyroxine and free triiodothyronine concentrations, as well as a decrease in thyroid-stimulating hormone concentrations, such that by 11-12 weeks of gestation, serum thyroid-stimulating hormone concentrations can drop to <0.1 mIU/L in a small percentage of pregnant women.[13] In addition, thyroid-binding globulin increases

≈3-fold above prepregnancy levels by midpregnancy.[14] Calcitonin concentrations appear unchanged in pregnant compared to nonpregnant adults. These changes lead to increased iodine and thyroxine requirements in pregnant women in the first and early second trimesters of pregnancy, and diagnosis of thyroid disorders should be made with caution in the first trimester of pregnancy. Pregnancy is said to be a diabetogenic state and a state of insulin resistance (50% reduction in insulin-mediated glucose metabolism from plasma).[15] As a result, there is a 200%-250% increased insulin secretion in an attempt to maintain euglycemia due to hyperglycemia caused primarily by cortisol and human chorionic gonadotropin.[15]

Pregnancy results in high renin and aldosterone concentrations in plasma, with increase in aldosterone and 24-hour urine aldosterone concentrations rising up to 8-fold above prepregnancy concentrations.[16] There are substantial increases in the concentration of lipids during pregnancy.[17] The trough of plasma lipids during pregnancy occur immediately after conception, increasing throughout pregnancy. Absolute cholesterol levels rise from ≈164.4 mg/dL at the beginning of pregnancy to ≈238.6 mg/dL and triglycerides from 92.6 mg/dL to 238.4 mg/dL relative to preconception levels.[18] The increase in lipid concentrations during pregnancy can be linked to pancreatitis, chylomicronemia, and cardiovascular complications and can make it difficult to diagnose metabolic syndrome during pregnancy.

Pharmacokinetic Changes During Pregnancy and Their Effect on Drug Disposition

Pregnancy-related physiological changes primarily account for the differences in PK profiles of drugs between pregnant and nonpregnant women.

Drug Absorption

As a result of progesterone-induced changes in gastric smooth muscle, gastric emptying is delayed and can have direct impact on drug absorption. For most orally administered medications, a number of factors, such as increased gastric and intestinal blood flow, delayed intestinal transit time, activity of intestinal drug transporters, and pH of the gastrointestinal tract, affect intestinal absorption.[19] The pH of the stomach rises during pregnancy to an alkaline range such that the absorption of basic drugs (eg, amphetamines, methadone) is decreased while the absorption of acidic drugs (eg, aspirin, phenytoin) increases (due to increased ionic dissociation) compared to the nonpregnant state. Despite these gastrointestinal associated changes in drug absorption, studies have suggested that the bioavailability and therapeutic impact of the majority of oral medications are generally unaffected by gastrointestinal changes during pregnancy, especially when drug dosing is repeated.[20]

For parenterally administered medications (intramuscular, intravenous, and subcutaneous), drug absorption increases during pregnancy as a direct consequence of increased muscle blood flow from increased cardiac output.[21] Increased blood flow also enhances the absorption of inhaled medications like anesthetics and muscle relaxants. Increased respiratory rate and pulmonary blood flow that occur during pregnancy enable faster

uptake of volatile anesthetics drugs during pregnancy, which shortens the time it takes for drug effects to begin. In addition, a drug's physicochemical properties, duration of exposure, lipid solubility, molecular size, protein binding, and drug transporters can affect drug absorption. Flip-flop (absorption-limited) kinetics (a phenomenon in which the rate of drug absorption lags behind the rate of drug elimination)[22] has been reported during pregnancy. When flip-flop kinetics exist, attainment of a drug's steady state would depend on the rate of drug absorption rather than rate of elimination. For example, orally administered artesunate undergoes extensive hydrolysis in the stomach, where it is absorbed as dihyroartemisinin.[23] In a PK study of artesunate/dihydroartemisinin in acute falciparum malaria during pregnancy,[24] plasma concentration of orally administered artesunate was ≈4 times lower than plasma concentrations following intravenous administration. In comparison to oral administration, its terminal elimination half-life was 3 times longer after intravenous administration. The 3 times prolonged terminal elimination half-life after oral administration was caused by flip-flop kinetics because the disposal of artesunate from plasma after oral administration is determined by its rate of absorption.[24]

Distribution

Following absorption, most drugs are distributed to various tissues in the body. The extent to which a drug is distributed within the body is defined by the volume of distribution (V_d), which reflects the apparent volume into which a medication is dispersed to achieve the same concentration as it does in plasma. Drugs with a low volume of distribution are dispersed within a volume similar to or lower than that of plasma, while drugs with a high volume of distribution have higher volumes compared to plasma. Pregnancy is associated with changes in V_d as a direct result of increased blood volume (by ≈50%), changes in plasma proteins, tissue binding, and body weight. Dilution of plasma proteins due to increased volume of distribution results in a decrease in available proteins in plasma and a decrease in protein binding.[25] With increasing maternal weight and fat stores that occur during pregnancy, the V_d of many drugs tends to increase. These changes in the V_d of drugs can lead to alterations to the loading doses and the peak-to-trough concentrations of drugs. For instance, buprenorphine, a partial opioid agonist used for medication-assisted therapy in women with substance use disorders during pregnancy, is very highly protein bound (96%) and extremely lipophilic. As a result, buprenorphine is widely distributed within body tissues following oral administration and absorption (V_d, 188-335 L).[26] Subsequently, due to buprenorphine's V_d properties, substantial differences in the PK of buprenorphine between pregnant and nonpregnant subjects in a PK dose-finding study demonstrated low plasma concentrations of buprenorphine throughout the second and third trimesters of pregnancy.[27] For a number of drugs used during pregnancy, similar variations in V_d and its potential to affect PK have been observed.[28–30] Just like drug absorption, a drug's physicochemical properties, lipophilicity, molecular size, protein binding, transporter function, and increased blood flow during pregnancy can affect the extent to which a drug is distributed.

Metabolism

While there are numerous sites for drug biotransformation and metabolism (liver, gastrointestinal tract, kidneys, skin, lungs, plasma), the liver is the primary site of drug metabolism. There are 2 major drug metabolism pathways in the liver: phase I drug

metabolism involves drug oxidation, reduction, and hydrolysis, predominantly by hepatic microsomal cytochrome P450 (CYP) enzymes, while phase II involves conjugation of the target to a polar molecule (including glucuronidation, sulfation, N-acetylation, catechol methylation, and glutathione addition). Pregnancy is known to affect phase I and II metabolism of several drugs. The clearances of drugs that are substrates for CYP1A2 and CYP2C19 decrease during pregnancy (due to decreased activity of this enzyme during pregnancy),[31] while the clearance of drugs that are substrates of other CYP metabolic enzymes increase during pregnancy. The effect of this was demonstrated by lower plasma concentration of cycloguanil, a CYP2C19-dependent metabolite of proguanil during pregnancy.[32] Similarly, increases in the plasma concentrations of caffeine[33] and clozapine in pregnancy (substrates of CYP1A2) have been demonstrated during pregnancy. It has been demonstrated that the activity of CYP1A2, as measured by caffeine clearance, decreases by ≈30% at 14-18 weeks of gestation, 50% at 24-28 weeks' gestation, and 65%-70% at 36-40 weeks of gestation.[34] Thus, CYP1A2 and CYP2C19 may potentially increase the toxicity of drugs they metabolize. The effects of other phase I and II drug enzymes like CYP3A4, CYP3A5, CYP2D6, uridine 5′-diphospho-glucuronosyltransferase (UGT) 1A4, UGT2B7, and CYP2E1 generally increase during pregnancy, leading to a decrease in plasma concentration of their substrates to low and sometimes subtherapeutic concentrations.[35]

Additionally, pregnancy affects hepatic clearance and hepatic extraction ratios by its influence on factors such as hepatic blood supply, hepatic biochemical processes (ie, intrinsic clearance), and drug protein binding.[5] Even in pregnancy, hepatic extraction ratios are affected differently on the basis of changes in blood flow and hepatic enzyme activity. Generally, drugs with low hepatic extraction ratios are regulated by changes in protein binding or hepatic enzyme activity, whereas changes in hepatic blood flow have a significant impact on hepatic clearances of drugs with high extraction ratio. Hepatic blood flow increases during pregnancy by ≈50%-60%, while protein binding decreases (with increased free fraction of drugs), and these have consequences on drug metabolism and disposition during pregnancy. For example, because medications with high extraction ratios are dependent on increased hepatic blood flow during pregnancy,[36] such medications as lidocaine, cyclosporine, methylprednisolone, and propranolol with high hepatic extraction, have higher hepatic clearance during pregnancy. In order to be excreted, hydrophobic drugs undergo metabolic change to become more polar (water soluble). However, drugs that are hydrophilic tend to be excreted without first undergoing metabolic modifications to their molecular structures, making them a more attractive therapeutic options, even during pregnancy.

Excretion

Although the biliary, hepatic, cutaneous, and pulmonary systems and feces are involved in drug excretion, the kidneys are the primary organ for drug elimination. GFR, active tubular secretion, tubular reabsorption, and renal metabolism are the primary mechanisms by which the kidneys excrete toxic metabolic intermediates of drugs. During pregnancy, the 30%-50% increase in renal blood flow, renal plasma flow, and GFR increases excretion of most drugs and their metabolites. In addition, the several renal transporters involved in the active carrier-mediated tubular secretion transport process undergo changes during

pregnancy that enhance their activity. For example, renal organic anionic transporter 1 and 3 expression have been predicted to increase by >2-fold during pregnancy (transporters that increase drug secretion into the renal tubules), a renal transporter–related change that can explain increased renal excretion of many drugs during pregnancy.[37] The activities of other transporters involved in active tubular secretion of drugs—adenosine triphosphate–binding cassette efflux transporters (multidrug-resistance proteins 2 and 4, P-glycoproteins [P-gps]), organic cationic transporters OCT and N), and multidrug and toxin extrusion proteins 1 and 2K)—increase during pregnancy.[5] Many medications' blood concentrations decline throughout the second and third trimesters of pregnancy due in large part to renal changes associated with normal pregnancy; many medications require dose adjustments during pregnancy to avoid subtherapeutic levels.[38–44]

Compounds with molecular weights >400 g/moL such as glucuronide-conjugated metabolites are primarily eliminated in bile, and biliary and hepatic excretion has also been demonstrated to increase during pregnancy. For example, morphine is mostly converted into morphine-6-glucuronide (molecular weight = 461.4 g/mol) and morphine-3-glucuronide through glucuronic acid conjugation.[45] About one-third of morphine metabolites are transported through the entero-hepatic circulation, and both metabolites accumulate and are eliminated into bile to a larger amount in pregnant women. Several factors affect drug excretion during pregnancy, including but not limited to a drug's physicochemical properties (pKa, molecular size, polarity), pharmacogenomics, first-pass metabolism, and other routes involved in the drug's distribution to various organs in the body.

Pharmacodynamic Changes During Pregnancy and Their Effect on Drug Disposition

During pregnancy, PD processes can be altered, and higher (or lower) doses of drugs might be required. Thus, understanding PD variables is critically important in the action of many drugs during pregnancy. The PD variables of interest in measuring dose-response during pregnancy include the maximum activity that can be produced by a drug during pregnancy (efficacy, E_{max}); the plasma drug concentration of a drug needed to produce 50%, 90%, or 95% maximum activity (EC_{50}, EC_{90}, or EC_{95}); minimum concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce a response (potency); and the ability to withstand the effects of a drug even at optimal or high doses (mechanism of resistance), and drug tolerance.

While the understanding of some aspects of pregnancy PD has undergone remarkable progress (for example, use of viral load and CD4+ changes as PD markers in HIV in response to antiretroviral therapy), several areas, such as our understanding of therapeutic drug actions in the fetus (fetal therapeutics), drug action across the fetoplacental unit, mechanisms of adverse drug reactions, mechanism of action of drugs to cause teratogenicity in the developing fetus (congenital malformations), and some areas of maternal drug action, are still poorly understood and are areas of active research.

PD changes during pregnancy can result in increased or decreased response of drugs. For example, a drug with simple, reversible direct graded effect (no biophase distribution or

transduction processes) would achieve a concentration-effect curve where the drug attains an E_{max} of 100% at high drug concentrations and similar EC_{50} in pregnant and nonpregnant individuals. However, due to changes that occur during pregnancy, these responses could be different. An example of a drug with a simple direct graded effect on receptors is heparin. During pregnancy, the E_{max} and EC_{50} of heparin are decreased as a direct result of lower plasma heparin concentrations, resulting in lower E_{max} and EC_{50} in pregnancy compared to nonpregnant controls.[46] These findings have significant ramifications for pregnant women's dose and monitoring of heparin during pregnancy.

Maternal drug actions can be altered during pregnancy as a result of hormonal changes. For example, adrenergic receptor changes increase the probability of postural hypotension (due to depressed baroreceptor gain and sensitivity), predisposing pregnant women to orthostatic hypotensive syndrome during pregnancy.[47] Similarly, there is increased sensitivity to inhaled, local, and intravenous anesthetics (due to decreased minimum alveolar concentration) during pregnancy. In some drugs, a time delay in E_{max} and EC_{50} relative to plasma concentrations, resulting in 2 different responses to a single drug concentration (anticlockwise hysteresis loop), can occur and has been observed in pregnancy.[48] Mechanisms of drug resistance, drug tolerance, drug-transporter action, drug-receptor modulations, and drug-drug interactions in pregnant women are areas of active PD research. The effects of these PD properties on pregnancy are currently unknown, and more data are critically needed.

Physiologic Changes During Pregnancy Can Substantially Affect Drug Disposition and Response

As described, physiologic changes during pregnancy can affect how a drug is available and affect not only the safety profile of a determined drug but also its efficacy. Therefore, dose adjustments of medications during pregnancy are sometimes required, adapting recommended doses and/or dosing intervals, especially those used for chronic or life-threatening conditions (eg, antiepileptic drugs, antidepressants, anti-infectives), when the suspension of the medication during pregnancy is not a feasible option.[49] In the remaining sections of this article, we summarize how the physiologic changes during pregnancy can affect disposition, response, and dosing of select antiretrovirals, antihypertensives, anticoagulants, and antibiotics.

Antiretroviral Drugs

PK boosting regimens of antiretroviral therapies, like ritonavir and cobicistat, are widely used to enhance patient exposure to a second protease inhibitor, preventing resistance and allowing a better patientcentric approach, improving adherence with fewer pills.[35,50] Cobicistat, a second-generation PK enhancer frequently used in HIV treatment and approved in the United States in 2014 as fixed-dose combinations, is an excellent example of how pregnancy can alter the efficacy of a drug and ultimately expose the mother and fetus to unnecessary risk. In 2018, the US Food and Drug Administration advised against cobicistat-boosted regimens during pregnancy due to lower plasma drug exposure observed in clinical PK studies of cobicistat fixed-dose combinations. The product labels for cobicistat in

combination with atazanavir or darunavir, as well as for elvitegravir/cobicistat/emtricitabine/tenofovir, were subsequently updated to indicate that these products combined are not recommended for use during pregnancy.

Cobicistat was developed as an analog to ritonavir but without an anti-HIV activity, both strongly inhibiting intestinal and hepatic CYP3A activity. Cobicistat also inhibits the intestinal efflux transporter P-gp, which increases absorption of P-gp substrates such as tenofovir alafenamide and increases serum creatinine, without affecting renal function, due to altered proximal tubular secretion of creatinine through inhibition of drug transporters. A study assessing elvitegravir/cobicistat PK in 30 pregnant women compared second-trimester, third-trimester, and postpartum parameters was published in 2018, suggesting that elvitegravir exposure was considerably lower during pregnancy while in combination with cobicistat.[51] Elvitegravir area under the plasma concentration–time curve from time 0 to 24 hours was 24% lower in the second trimester compared to postpartum and 44% lower in the third trimester compared to postpartum; cobicistat area under the plasma concentration–time curve from time 0 to 24 hours was 44% lower in the second trimester compared to postpartum and 59% lower in the third trimester compared to postpartum.[51]

Other case studies have corroborated these findings of decreased elvitegravir exposure in pregnant individuals.[52,53] Similar studies were also performed with the cobicistat in combination with darunavir and atazanavir,[53] finding similar low plasma concentrations, especially during the second and third trimesters. Cobicistat fixed-dose combinations are not currently recommended for use during pregnancy due to low plasma concentrations of these regimens during the second and third trimesters of pregnancy. Darunavir and cobicistat concentrations were reduced by ≈80%-90% in the second and third trimesters of pregnancy compared to postpartum. Comparably, second- and third-trimester concentrations of elvitegravir/cobicistat were also lower by ≈50%-60% compared to postpartum.[35,54] Reduced efficacy of certain antiretroviral drugs, when associated with cobicistat, can generate a higher risk for pregnant individuals and fetuses, enhancing the chance for viro-logic failure, vertical transmission, and other adverse health consequences, including the possible development of drug resistance. Interestingly, the pregnancy-related effect on darunavir/ritonavir concentrations is less than those observed with darunavir/cobicistat (Table 5), and darunavir/ritonavir remains a boosted-protease-inhibitor–based viable treatment option for HIV-infected pregnant individuals.

Unfortunately, pregnant women are usually excluded from clinical trials, and the majority of the data collected from this population typically come many years after a drug is on the market. Cobicistat-containing products, for example, were commercially available and widely used in nonpregnant individuals living with HIV for an average of 6-8 years before PK and safety studies in pregnancy became available. Over 19.2 million women of reproductive potential are living with HIV worldwide, raising this issue into a public health concern and demanding more studies on antiretrovirals in pregnant individuals.

Other Drugs Frequently Used During Pregnancy

Many other examples of drugs requiring dose adjustments during pregnancy can be found in the literature. Table 6 shows some frequently used medications during pregnancy that

may require dose adjustments based on PK/PD variations, such as antihypertensives, anticoagulants, and antibiotics.

Frequently used antihypertensives, like clonidine, labetalol, metoprolol, and nifedipine, may need to have the dose increased or a shorter dosing interval during pregnancy due to, along with other reasons, increased renal clearance, increased half-life, or increased activity of hepatic blood flow and induction of specific enzymes like UGT1A1, CYPD2D6, or CYP3A4.[55,56] The 2020 American College of Cardiology/American Heart Association hypertension guidelines recommend transitioning pregnant patients with chronic hypertension to methyldopa, nifedipine, or labetalol.[57,58] For the chronic treatment of moderately elevated blood pressure during pregnancy (140/90 to 160/110 mm Hg), if treatment is indicated, both the American College of Obstetricians and Gynecologists and American College of Cardiology/American Heart Association recommend oral labetalol, slow-release nifedipine, or methyldopa for use during pregnancy. However, studies have suggested higher oral clearance and lower plasma concentrations of labetalol and nifedipine after oral administration during pregnancy, most likely due to increased maternal hepatic UGT1A1- and CYP3A4-mediated activity, and decreased bioavailability secondary to enhanced first-pass metabolism.[59] These pregnancy-related changes in the PK/PD of labetalol and nifedipine concentrations may require a dose increase and/or more frequent dosing.

Increased volume of distribution and hepatic blood flow reduce peak concentrations and decrease appropriate dosing intervals for certain β-blockers during pregnancy as labetalol and metoprolol. For example, studies show that the half-life of intravenous labetalol is 1.7 hours in the setting of pregnancy-induced hypertension at term compared to 6-8 hours in nonpregnant women, making it appropriate to treat acute hypertension in pregnant individuals but not effective as an ongoing treatment. Also, higher doses are often required.[60] For oral labetalol, the clearance is also increased 1.6-fold at term. Oral nifedipine use during pregnancy has also been evaluated in different studies on patients receiving hypertension or preterm labor treatment.[60] Nifedipine undergoes rapid absorption after oral administration, is highly protein bound (92%-98%), and the half-life varies with the formulation. It also undergoes substantial hepatic and intestinal first-pass metabolism that results in oral bioavailability of ≈50% and is an intermediate hepatic extraction ratio drug primarily cleared via hepatic metabolism (CYP3A4 and, to a lesser degree, CYP3A5).[61]

Based on limited available studies, no human or preclinical data suggest that the PK of methyldopa alters during pregnancy.[61,62] Methyldopa is not bound to plasma proteins and has an oral bioavailability of 25%-50%.

Effect of Pregnancy on the PK and PD of Monoclonal Antibodies

Therapeutic monoclonal antibodies (mAbs) are large-molecular-size (≈150 KDa) immunoglobulin G (IgG) generated from a single B-cell clone. These antibodies are engineered to recognize unique epitopes or binding site on a single antigen. The mAb binds to its targets located either as soluble form in the circulation or on cell membrane and blocks the function of the soluble/cell surface receptors or kills the target

cells through triggering antibody-dependent cellular toxicity (ADCC) and/or complement-dependent cytotoxicity (CDC).[63] Currently, mAbs are used for the treatment of allograft rejections in transplantation, asthma, autoimmune disorders, cancers, hypercholesterolemia, inflammatory bowel disorders, osteoporosis, viral infections, and others.[64]

The mAb has a Y-shaped structure with 2 identical heavy chains and 2 identical light chains linked through covalent disulfide bonds. Each heavy or light chain consists of variable (VH and VL) and constant (CH and CL) domains. Each mAb has 2 regions: (1) fragment antigen-binding (Fab) region (2 identical arms) and (2) fragment crystallizable (Fc) region (tail region). Each Fab is composed of variable (VH and VL) and constant (CH and CL) domains. The variable region of Fab binds to the antigen. The Fc region interacts with a variety of receptors (eg, Fcγ receptors in the immune cells) and components of the complement system (C1q receptor) and triggers ADCC and CDC. The Fc region also interacts with neonatal Fc receptor (FcRn), which facilitates the recycling of mAbs and thereby prolongs the half-life of mAbs.[63,65]

The extent of evidence that supports the safe and effective use of mAbs in pregnancy is limited. The binding of mAbs with FcRn has been reported to facilitate the transfer of mAbs across the placenta, which may pose safety risks to the fetus.[66] Despite having this challenge, the emerging case reports and clinical studies reported in the literature suggest that use of mAbs in pregnant patients is steadily increasing over a decade.[67] We performed the systematic review of clinical studies, case reports, and reviews published in PubMed using the key words “monoclonal antibodies,” “pregnancy,” “PK,” and “PD” to identify mAbs used in pregnant patients. Table 7 represents the features of mAbs used in pregnancy.

Factors Affecting the Disposition of mAbs

The PK and PD of mAbs are dependent on product- and patient-related factors. The product-related factors include molecular weight, charge, and structural modifications of certain residues (eg, glycosylation), dosage (dose and dosing interval), and route of administration. Patient-related factors include target antigens (soluble or membrane bound, turnover kinetics, target-mediated disposition, and target shedding), FcRN, disease state (eg, cancer and inflammatory disorders), genetic variation (on FcRN and FcγR), and immunogenicity.

Product-Related Factors

Molecular weight.—The kidney glomeruli can filter small proteins with molecular weight <30-50 KDa.[68] Given that mAbs have a large molecular weight (≈150 KDa), the renal excretion of intact mAbs through glomerular filtration is unlikely unless there is impairment in the renal function.[69]

Charge.—The interaction of mAbs with blood, interstitial fluid, and tissue components may depend on their charge.[70] Reducing the isoelectric point by >1 unit is associated with a lower plasma clearance and tissue accumulation of the negatively charged mAbs. Increasing the isoelectric point by >1 unit is associated with a higher plasma clearance and distribution to the tissues and a lower subcutaneous bioavailability of the positively charged mAbs.[71]

Structural modifications.—The glycosylation of the amino acid residue (Asn297) in the Fc region has been reported to modulate the affinity of the Fc region to the FcγR or C1q and thus alters the mAbs ability to trigger the ADCC or CDC. The absence of fucose sugar linkage in the N-acetylglucosamine glycan at the amino acid Asn297 of the Fc region increased the binding affinity of trastuzumab to FcγR IIIa and augmented ADCC. This results in a reduction in the half-life and an improved efficacy of nonfucosylated trastuzumab compared to the approved trastuzumab with fucosylated and nonfucosylated forms.[72] Although the structural modification of mAb is intended to improve the biological activities of mAbs, this may enhance the risks of nonspecific binding of mAbs and reduce their half-lives by increasing the clearance.[73,74] Due to the exchange of the Fab region of the mAb with endogenous IgG in the circulation, the stability and efficacy of the mAb are reduced. The mutation of serine residue to a proline in position 228 in the hinge region improved the stability of IgG4 subtype mAbs.[75,76]

Dosage and Route of Administration

The target-mediated drug disposition (TMDD) plays a significant role in the disposition of mAbs. It is a dose-dependent saturable phenomenon responsible for the nonlinear PK characteristics of mAbs.[77] The contribution of TMDD to mAb clearance is dose dependent and significant at low concentrations of mAb. However, at high concentrations, TMDD gets saturated, and the clearance follows a first-order process.[78] The rate and extent of absorption of mAbs depend on the site of injection. The mAbs are commonly administered through intravenous infusion. Some mAbs are administered via subcutaneous injection and intramuscular injection. The oral administration of mAbs is limited by low permeability and stability in the gastrointestinal tract. Following SC or IM injection, the absorption of mAbs into the systemic circulation occurs through convective transport in the interstitial space, uptake into the lymphatic system and draining into the systemic blood vessels. The mAbs administered through SC route undergo presystemic elimination by peptidases in the interstitial fluid, endocytosis, and lysosomal degradation in the endothelial cells of the lymphatic vessels and phagocytosis by immune cells.[79] The blood flow to the injection site may also impact the absorption of mAbs following IM or SC injection.[80]

Patient-Related Factors

Target antigens.—The extent of expression, binding affinity, internalization rate, and turnover kinetics of target antigen significantly account for the dose-dependent TMDD clearance of mAbs and thereby influencing the PK and PD of mAbs. Given the clearance of the soluble form of target antigens is not dependent on the TMDD phenomesnon, the PK of mAbs is different between the soluble form and the membrane-associated form of target antigens.[81] The membrane-associated receptors often endure a target-shedding process where the extracellular domain of the receptor is cleaved and released into the circulation. The cleaved antigen in the circulation is more easily accessible by the mAb than the membrane-associated antigen. Therefore, the mAbs bind to the shed antigen in the circulation, which limits the availability of mAbs for the membrane-associated antigen. This affects the disposition and biological effects of mAbs (eg, CD52 receptor), a target for alemtuzumab.[82]

Neonatal Fc receptor.—The binding of mAbs to FcRn protects the mAbs from proteolytic degradation and facilitates the recycling of mAbs to plasma and thus reduces the clearance and prolongs the half-life of mAbs.[83,84] FcRN is expressed ubiquitously in different tissues in humans including spleen, lymph node, liver, lung, kidney, intestines, colon, small bowel, skin, brain, adipose, muscle, and heart.[85] The wide range of expression of FcRN facilitates the tissue distribution of mAbs into multiple tissues. In general, the therapeutic mAbs are expected to increase the total IgG level by 1%-2%, and they are not likely to saturate the FcRN recycling pathway in humans.[86]

Disease State

The disease states including cancer and chronic inflammatory conditions have been reported to affect the catabolism of many proteins and the whole-body protein turnover, which affects the PK/PD of mAbs.[87] The systemic exposure to trastuzumab was 30%-40% lower in patients with human epidermal growth factor receptor 2 (HER2)-positive advanced gastric or gastroesophageal junction cancer compared with patients with HER2-positive metastatic breast cancer.[88] The clearance of infliximab was higher in patients with Crohn disease and ulcerative colitis (0.37-0.41 L/day) compared to patients with rheumatoid arthritis (RA; 0.26-0.27 L/day) and ankylosing spondylitis.[89] The time-dependent changes in inflammatory conditions and protein turnover affect the clearance of mAbs. Patients with partial or complete response showed the time-dependent decrease in clearance of nivolumab and pembrolizumab over time. However, patients with progressive disease showed a minimal change in clearance.[90]

Genetic Polymorphism

The genetic polymorphism in genes encoding for FcRN and FcγR affects the PK/PD of mAbs. Compared to the homozygous genotype, the systemic exposures to infliximab and adalimumab were reduced by 14% and 24%, respectively, in patients with inflammatory bowel disease with heterozygous genotype for variable number of tandem repeats for FcRN. This is due to the reduced expression of FcRN and increased clearance of mAbs.[91] Similarly, the genetic polymorphism (exchange of phenylalanine to valine at position 158) in the gene encoding FcγR IIIa increases the binding affinity of IgG1 to FcγR, improves ADCC, and has higher objective response rates and longer progression-free survival for trastuzumab in HER2 overexpressing in patients with breast cancer,[92] cetuximab in colorectal cancer,[93] and rituximab in B-cell lymphoma.[94] In addition to the PD effects, the homozygous for phenylalanine/phenylalanine genotype for FcγR IIIa reduced the clearance for infliximab.[95]

Immunogenicity

Therapeutic mAbs may trigger an immune response in patients, resulting in the formation of antidrug antibodies (ADAs). The immunogenicity of mAbs may be due to the extent of nonhuman sequence, patient genotype, duration of therapy, and route of administration. The fully rodent or chimeric mAbs or humanized mAbs are more immunogenic than fully human mAbs.[96] The formation of aggregates at the injection site causes the SC route of administration to be more immunogenic than intravenous (IV) or IM administration. Given

that the binding affinity of ADAs has been reported to mature over time, the probability of immunogenicity increases with a longer duration of mAb therapy. Although all ADAs may not affect the PK/PD of mAbs, some ADAs may increase the clearance and reduce the systemic exposure of the mAb (eg, infliximab in patients with RA). The disposition of mAb by ADA is a result of interaction of ADAs with mAb to form ADA-mAb immune complex, which triggers binding of the FcγR IIa on platelets, internalization, and lysosomal degradation by phagocytes.[97]

In addition to the above factors, patient covariates such as age, sex, body weight/body surface area, and albumin have been reported to contribute for the interindividual variability in the rate and extent of absorption of mAbs in humans.[98–100]

Impact of Pregnancy on the PK of mAbs

The complex physiological changes during pregnancy may affect the PK of mAbs in pregnant subjects. The paucity of clinical PK studies in pregnant women limits our understanding on how the pregnancy impacts the absorption, distribution, and elimination of mAbs. We reviewed the literature reports of PK of mAbs in pregnancy and summarize how pregnancy may impact the absorption, distribution, and elimination of mAbs in pregnant subjects.

Absorption.—The absorption of mAbs into the systemic circulation depends on the site of administration, lymphatic flow, and blood flow at the injection site. Most mAbs are administered through IV infusion. Given that the bioavailability of mAbs following IV administration is 100%, the pregnancy is not anticipated to affect the absorption of intravenously administered mAbs. The biophysical properties (large molecular weight and hydrophilicity) and gastrointestinal degradation limit the permeability and stability of mAbs in the gastrointestinal tract. Therefore, the mAbs are not administered via the oral route. The bioavailability of subcutaneously or intramuscularly administered mAbs depends on the proteolytic degradation at the injection site, extent of uptake into the lymphatic system, and draining to the systemic circulation. The activity of proteolytic enzymes is higher in the third trimester of pregnancy compared to the postpartum period.[101] When the fluid pressure in the interstitial space is higher, the lymphatic system drains them out to maintain homeostasis. However, the fluid overload during pregnancy could exceed the capacity of the lymphatic drainage system, resulting in edema in pregnant subjects.[2] Pregnancy-associated increase in activity of proteolytic enzymes and limited capacity of the lymphatic drainage system could minimize the bioavailability of subcutaneously administered mAbs despite increase in blood flow. Following SC administration, adalimumab concentrations are lower in pregnancy compared to the prepregnancy state (prepregnancy vs pregnancy: ≈18 μg/mL vs 10 μg/mL[102]; ≈10 μg/mL vs 6 μg/mL).[103]

Distribution.—The large molecular weight and hydrophilic properties of mAbs allow the distribution of mAbs primarily in the plasma and extracellular fluids,[100] and the FcRN binding facilitates the limited distribution to the tissues. As the pregnancy progresses, the plasma volume increases by ≈40%, and body weight increases by 11.5-16 kg.[104–106] Also, pregnancy alters the immunological system in a complex manner, and its impact

on the PK is unclear. Because the mAbs are mainly distributed within the plasma and extracellular fluids, the pregnancy-induced changes are not expected to significantly alter the distribution of mAbs. Given that volume of distribution of infliximab increases with increasing body weight, the weight-based dosing is used for infliximab administration in nonpregnant patients with inflammatory bowel disease.[106] However, following IV injection, a gestational age-dependent increase in dose-normalized median plasma concentrations of infliximab in prepregnancy and the first, second, and third trimesters of pregnancy were 7.3, 8.5, and 15 versus 13 mg/mL/kg, respectively, in pregnant women with inflammatory bowel disease.[107] This possibly could be due to reduced clearance of infliximab associated with lower inflammatory disease activity during pregnancy compared to prepregnancy rather than alteration of volume of distribution.

As the pregnancy progresses, the expression of FcRN increases in the placenta, most importantly in the third trimester of pregnancy. FcRN has been reported to facilitate the transfer of endogenous IgG from mother to fetus.[4] Given that the Fc region of mAb binds to FcRN, mAbs can cross the placenta to the fetus. When infliximab, adalimumab, and certolizumab were stopped at the gestational ages of 18.4 weeks, 19 weeks, and 37 weeks, the umbilical cord blood levels were detected in 57%, 48%, and 5.9% of pregnant patients with RA, respectively. The median umbilical cord blood levels (median cord to maternal concentration ratio) of infliximab, adalimumab, and certolizumab were 0.4 μg/mL (0.012), 0.5 μg/mL (0.062), and 0.3 μg/mL (0.010), respectively. Because certolizumab does not contain the Fc region, very low detectability (5.9% of pregnant patients with RA) was observed. Overall, low levels of antitumor necrosis factor-alpha mAbs were detected in cord blood compared to maternal blood.[108]

Elimination.—The mAbs are primarily catabolized by proteolytic enzymes to peptides and amino acids.[100] The hepatic CYP enzymes do not account for the disposition of mAbs. The renal excretion of mAbs through glomerular filtration is limited due to the large size.[74] The TMDD plays a major role in the elimination of mAbs from the systemic circulation. Following binding of mAb to the target antigen, the antigen-bound mAb binds to Fcγ receptors in the effector cells. Subsequently, the reticuloendothelial system clears the immune complex from the body. Binding of mAbs to FcRN in the endothelial cells will transiently clear the mAbs in the circulation and facilitate the uptake by endothelial cells through endocytosis. The FcRN binding prevents the lysosomal degradation of mAbs and recycles the mAbs to cell membranes. The FcRN binding determines the half-life of mAbs.[81,109]

Pregnancy increases the activity of proteolytic enzymes compared to the postpartum period. This increase in proteolytic activity may increase the clearance of mAbs. Compared to prepregnancy, the levels of adalimumab and vedolizumab were decreased during pregnancy.[102,103] The immunological changes during pregnancy may alter the formation of ADAs against mAbs, which may affect the clearance of mAbs.[110] The higher clearance of antitumor necrosis factor-alpha mAbs (adalimumab, certolizumab, and infliximab) has been reported in patients with ADAs.[111,112] However, Grišić et al reported a slight decrease in infliximab clearance (≈15%) during pregnancy.[107] This possibly could be due to the reduced inflammatory state observed during pregnancy. Because the inflammatory state affects the

protein turnover, the lower inflammatory state is associated with lower protein turnover, resulting in lower clearance of mAbs.[90]

Conclusion

Systematically evaluating the impact of pregnancy on the PK/PD of drugs, including biologics, can provide important dosing guidance to physicians wishing to prescribe these agents to patients during pregnancy. The paucity of safety, PK, and efficacy data in mother and fetus limits our understanding on the extent of PK/PD changes and need for dose adjustment in the pregnant population. Therefore, additional clinical studies are warranted to support optimal medications during pregnancy.

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Data Availability Statement

All data in this manuscript is available publically.

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Table 1.

Hematologic Changes During Normal Pregnancy

Blood Clotting Factor	Pregnancy-Associated Changes
Protein C	No change
Protein S	Decreased by ≈50% compared to prepregnancy values
Antithrombin III	Decreased by ≈20% compared to prepregnancy values
Plasminogen activator 1	Increased
Plasminogen activator 2	Increased
Prothrombin time	No change
Activated partial thromboplastin time	No change
Platelets	Decreased by ≈20% compared to prepregnancy values
Von Willebrand factor	Increased by >100% compared to prepregnancy values
Fibrinogen	Increased by >100% compared to prepregnancy values
Prothrombin	Increased
Tissue thromboplastin	Increased
Factor IV	No change
Factor V	No change
Factor VII	Increased by >1000% compared to prepregnancy values
Factor VIII	Increased by >100% compared to prepregnancy values
Factor IX	Increased by >100% compared to prepregnancy values
Factor X	Increased by >100% compared to prepregnancy values
Factor XI	Values vary during pregnancy (can increase or decrease)
Factor XII	Increased by >100% compared to prepregnancy values
Factor XIII	Decreased by ≈50% compared to prepregnancy values

Table 2.

Cardiovascular-Associated Changes During Pregnancy

Covariate	Pregnancy-Associated Changes
Systolic blood pressure	Decreases by ≈10% compared to prepregnancy levels
Diastolic blood pressure	Decreases by ≈20% compared to prepregnancy levels
Pulse pressure	Decreases by ≈10% compared to prepregnancy levels
Maternal heart rate	Increases by ≈20% compared to prepregnancy levels
Maternal oxygen consumption	Increases by ≈30% compared to prepregnancy levels
Cardiac output	Increases by ≈50% compared to prepregnancy levels
Stroke volume	Increases by ≈30% compared to prepregnancy levels
Systemic vascular resistance	Decreases by ≈20% compared to prepregnancy levels
Pulmonary vascular resistance	Decreases by ≈30% compared to prepregnancy levels
Central venous pressure	No change
Pulmonary capillary wedge pressure	No change
Colloid osmotic pressure	Decreases by ≈15% compared to prepregnancy levels
Red blood cell volume	Increases by ≈20% compared to prepregnancy levels
Plasma volume	Increases by ≈40% compared to prepregnancy levels

Table 3.

Renal-Associated Changes During Pregnancy

Covariate	Pregnancy-Associated Changes
Serum creatinine	Decreases between 16%-23% in compared to prepregnancy levels
Renal osmolality	Decreases by ≈10 mOsm of water compared to prepregnancy levels
Blood urea nitrogen concentrations	Decreases by ≈10 mg/dL compared to prepregnancy levels
Electrolytes (serum)	
Sodium	Decreases to 130-135 mmol/L
Bicarbonate	Decreases to 18-22 mmol/L
Potassium	Unchanged
Calcium (ionized)	Unchanged
Magnesium	Unchanged
Chloride	Unchanged
Phosphorus	Unchanged
Renal blood flow	Increases by ≈80% compared to prepregnancy levels
Renal protein excretion	Increases
pH	Increases
Renal aldosterone action	Increases
Renin-angiotensin action	Increases
Serum uric acid	Decreases to 130-135 mmol/L
Glomerular filtration rate	Increases by ≈50% compared to prepregnancy levels

Table 4.

Respiratory-Associated Changes During Pregnancy

Covariate	Pregnancy-Associated Changes
Vital capacity	No change
Tidal volume	Increases by ≈40% compared to prepregnancy levels
Residual volume	Decreases by ≈20% compared to prepregnancy levels
Respiratory rate	No change
Minute ventilation	Increases by ≈40% compared to prepregnancy levels
Inspiratory reserve volume	Increases by ≈10% compared to prepregnancy levels
Expiratory reserve volume	Decreases by ≈30% compared to prepregnancy levels
FEV_1 (forced expiratory volume in 1 s)	No change
FEV_1/Forced vital capacity	No change
Functional residual capacity	Decreases by ≈20% compared to prepregnancy levels
Inspiratory capacity	Increases by ≈20% compared to prepregnancy levels
Total lung capacity	Decreases by ≈5% compared to prepregnancy levels

Table 5.

Summary of Pharmacokinetic Studies of Darunavir, Ritonavir, and Cobicistat During Pregnancy and Postpartum

Darunavir/Ritonavir Drug Regimen Used During Pregnancy	Antiretroviral drug	AUC_{0-24} (mg • h/L) Second Trimester	AUC_{0-24} (mg • h/L) Third Trimester	AUC_{0-24} (mg • h/L) Postpartum	GMR – Second Trimester Compared to Postpartum	GMR – Third Trimester Compared to Postpartum	Mean AUC_{0-24} Decrease in the Third Trimester of Pregnancy Compared to Postpartum, %
Darunavir/ritonavir 600/100 mg once daily (n = 30)[113]	Darunavir	45.8	45.9	61.7	0.74	0.74	−26
	Ritonavir	3.9	3.8	5.6	0.72	0.73	−27
Darunavir/ritonavir 800/100 mg once daily (n = 34)[113]	Darunavir	64.6	63.5	103.9	0.62	0.61	−39
	Ritonavir	3.7	3.7	8.2	0.65	0.67	−37
Darunavir/ritonavir 800/100 mg twice daily (n = 24)[39]	Darunavir	55.1	51.8	79.6	0.62	0.64	−26
	Ritonavir	3.2	4.8	6.7	0.88	0.65	−25
Darunavir/cobicistat 800/150 mg once daily (n = 29)[114]	Darunavir	50.0	42.1	95.6	0.47	0.44	−56
	Cobicistat	4.5	3.9	8.5	0.50	0.44	−56

AUC_{0-24}, area under the plasma concentration–time curve from time 0 to 24 hours; GMR, geometric mean ratio.

Table 6.

Drugs Commonly Used in Pregnancy Requiring Dose Adjustments (Estimates From the Literature)

Antihypertensives Drug	Dose Adjustment	PK/PD Alteration
Labetalol[60,115,116]	Increased dose or more frequent dosing may be needed	Oral labetalol clearance increased with pregnancy (1.4× at 12 wk, 1.6× at term); increased hepatic UGT1A1-mediated metabolism[56,59]
Clonidine[61]	Increased dose/shorter dosing interval may be needed	Renal clearance increased by 2×; half-life significantly decreased
Nifedipine[117–121]	Increased dose/shorter dosing interval may be needed	Oral clearance 4× higher half-life decreased by 50%; mechanism increased hepatic blood flow and CYP3A4 induction
Metoprolol[122]	Increased dose or more frequent dosing may be needed	Oral clearance 4× greater in third trimester; peak serum concentrations 12%-55%; mechanism increased hepatic blood flow and CYP2D6 induction
Anticoagulants		
Acetylsalicylic acid[123–125]	Unknown, possibly increased dose requirement based on PK	Slower uptake, lower peak plasma concentration after single dose
Heparin[46,126,127]	Increased doses and/ or more frequent intervals may be needed	Peak plasma concentration 50% that of nonpregnant controls; reduced efficacy in pregnancy; ACCP recommends 10,000 U every 12 h or monitoring anti-Xa levels
Antibiotic drugs		
Amoxicillin[128,129]	Increased dose/shorter dosing interval may be needed	Increased clearance
Ampicillin[130]	Increased dose/shorter dosing interval may be needed	Increased clearance
Cefazolin[131]	Increased dose/shorter dosing interval may be needed (keep plasma concentrations above the MIC)	Increased clearance and volume of distribution

ACCP, American College of Chest Physicians; CYP, cytochrome P450; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; UGT, uridine 5′-diphospho-glucuronosyltransferase.

These recommended dose adjustments of antibiotics, anticoagulants, and antibiotics used in pregnant women were obtained from an extensive review of the literature.

Table 7.

Monoclonal Antibodies Used in Pregnancy

Name	Structure	Route of Administration	Indication	Clinical Considerations in Pregnancy
Anti-TNFα				
Adalimumab	Human anti-TNFα IgG1	SC injection	RA, JIA, PsA, AS, CD, UC, Ps, HS, UV	Placental transfer increases as pregnancy progresses and may affect the immune response in fetus. Risk-benefits should be considered prior to use
Infliximab	Chimeric murine-human anti-TNFα IgG1	IV injection	CD, UC, RA, AS, PsA, Ps	Placental transfer during the third trimester of pregnancy may affect the immune response and increase the risk of infections in fetus
Certolizumab	Humanized PEGylated Fab of anti-TNFα IgG1	SC injection	CD, RA, PsA, AS, NAS, Ps	Placental transfer is negligible or very minimal. Fetal risk is anticipated to be minimal
Golimumab	Human anti-TNFα IgG1	SC injection	RA, PsA, AS, UC	Crosses the placenta and may affect the immune response in fetus
Anti-IL receptor				
Tocilizumab	Humanized anti-IL-6 receptor IgG1	IV infusion or SC injection	RA, GCA, SSc-ILD, PJIA, SJIA, CRS	Placental transfer increases as pregnancy progresses. Risk-benefits should be considered prior to use
Canakinumab	Human anti-IL-1β receptor IgG1	SC injection	PFS, Still disease	Placental transfer increases as pregnancy progresses. Risk-benefits should be considered prior to use
Anti-complement C5				
Eculizumab	Humanized anti-complement C IgG2	IV infusion	PNH, aHUS, gMG in adults who are AchR antibody positive, NMOSD in adults who are AQP4 antibody positive	Placental transfer is minimal. Fetal risk is anticipated to be minimal
Anti-integrin				
Vedolizumab	Humanized anti-$\alpha4\beta7$-integrin IgG1	IV infusion	CD, UC	Placental transfer is minimal. Fetal risk is anticipated to be minimal
Natalizumab	Humanized anti-α4-integrin IgG4	IV infusion	CD, MS	Placental transfer increases as pregnancy progresses. Risk-benefits should be considered prior to use
Anti–B cell				
Belimumab	Human anti-BLyS IgG1	IV infusion: pediatric patients (≥5 years); SC injection: adults (≥ 18 years)	SLE and adjunct therapy for lupus nephritis	Placental transfer increases as pregnancy progresses. Risk-benefits should be considered prior to use
Anti-immunoglobulin				
Omalizumab	Humanized anti-IgE IgG1	SC injection	Asthma, nasal polyps, chronic spontaneous urticaria	Placental transfer increases as pregnancy progresses. Risk-benefits should be considered prior to use

AchR, acetylcholine receptor; aHUS, atypical hemolytic uremic syndrome; AQP4, aquaporin-4; AS, ankylosing spondylitis; BLyS, B-lymphocyte stimulator; CD, Crohn disease; CRNP, chronic rhinosinusitis with nasal polyposis; CRS, cytokine release syndrome; GCA,giant cell arteritis; gMG, generalized myasthenia gravis; HS, hidradenitis suppurativa; IgG, immunoglobulin G; IL, interleukin; IV, intravenous; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; NAS, nonradiographic spondyloarthritis;NMOSD,neuromyelitis optica spectrum disorder;PFS,periodic fever syndrome;PJIA,polyarticular juvenile idiopathic arthritis;PNH,paroxysmal nocturnal hemoglobinuria; Ps,plaque psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC,subcutaneous; SJIA,systemic

juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; SSc-ILD,systemic sclerosis–associated interstitial lung disease; TNFα, tumor necrosis factor-α; UC, ulcerative colitis; UV, uveitis. The clinical recommendations considering the risk-benefit of monoclonal antibodies in pregnant women were obtained from an extensive review of the literature.