Review Article

Clinical Therapeutics in Pregnancy

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Most drugs are not tested for use during pregnancy, consequently, labeling, which may include information about fetal safety, includes nothing about dosing, efficacy, or maternal safety. Yet these are concerns of health care providers considering treatment of disease during pregnancy. Therefore, the practitioner treats the pregnant woman with the same dose recommended for use in adults (typically men) or may decide not to treat the disease at all. However, is the choice of not treating a woman during pregnancy better than dealing with the challenges which accompany treatment? This paper, which summarizes metabolic and physiologic changes induced by pregnancy, illustrates that standard adult dosing is likely to be incorrect during pregnancy.

1. Introduction

Clinically, efforts have focused on minimizing the consumption of drugs during pregnancy to avoid possible adverse fetal effects. However, 50–80% of pregnant women use prescription or nonprescription (over-the-counter or herbal) drugs during pregnancy [1, 2]. One investigation found that 83% of pregnant women received at least one prescription drug [3], with analgesics, tranquilizers, antihistamines, antiemetics, hypoglycemics, antiasthmatics, antiepileptics, antibiotics, and diuretics most widely used [3]. Many of these drugs have not been adequately studied for pharmacokinetics (PK), pharmacodynamics (PD), efficacy, or maternal safety during pregnancy and consequently are used off-label [4, 5].

The optimal dose of a drug used during pregnancy should maximize therapeutic efficacy while minimizing the risk of maternal, fetal, and placental toxicity. With pregnancy being a dynamic state exhibiting numerous physiologic and metabolic changes (see Table 1), assuming that PK, PD, and efficacy are the same as the adult male or nonpregnant female should be considered erroneous [6]. For example, cefatrizine, a cephalosporin antibiotic, is eliminated by renal mechanisms and not metabolized. Pregnancy reduces the antibiotic's oral availability by 43%, serum concentration by 45%, and extends its elimination half-life by one hour [7].

Beyond changes in cardiovascular, pulmonary, gastrointestinal, renal, and hepatic function during pregnancy [8], there are also changes in the expression and activity of transport proteins and enzyme systems, such as cytochrome P450 (CYP) enzymes leading to PK alterations which may change the metabolic profile of a drug.

The presence of the fetal-placental unit further distinguishes the pregnant state from a nonpregnant adult, and offers significant complexity to determining a drug's safety profile [9–11]. Developmental toxicity (death, structural malformations, functional abnormalities, growth restriction, or premature birth) is a concern throughout gestation [12], and certain drugs or exposures may interfere with the development and function of the placenta [13]. The placenta may change the metabolic profile of a drug during pregnancy, for example, the placenta may be responsible for new metabolites, not observed in the nonpregnant adult, as recently observed for glyburide [14].

Furthermore, while adverse drug reactions are more frequent and more severe in women, the mechanism of which remains unknown [15, 16], little is known about maternal adverse drug effects during pregnancy. This has led the FDA to launch the Medication Exposure in Pregnancy Risk Evaluation Program which is intended to focus on the maternal and fetal safety of medications during pregnancy [17].

Table 1: Pregnancy-induced physiologic changes during near term.

System [ref.]	Parameter	Non pregnant	Pregnant
Cardiovascular [18, 19]	Cardiac output (L/min)	4.0	7.0
	Heart rate (beats per min)	70	90
	Stroke volume (mL)	65	85
	Plasma volume (L)	2.6	3.5
	Colloid osmotic pressure (mmHg)	22.0	18.2
	Total peripheral arterial resistance (dyne s cm^{-5})	1530	1210
Respiratory [20]	Total lung capacity (mL)	4225	4080
	Residual volume (mL)	965	770
	Tidal volume (mL)	485	680
	Minute O_2 uptake	201	265
Liver [21]	Portal vein blood flow (L/min)	1.25	1.92
	Hepatic artery blood flow (L/min)	0.57	1.06*
Renal [22]	Glomerular filtration rate (mL/min)	97	144
	Creatinine (mg/dL)	0.7	0.5

* Difference was not statistically significant.

At a time when precise information on dosing, efficacy, and safety are needed, data is sparse or unavailable. In many instances, each pregnant woman becomes an individual experimental subject when it comes to dosing, efficacy, and safety, leaving the concerned practitioner to prescribe medication without sufficient information or to withhold medications because of the lack of fetal safety data. In addition, for a comprehensive understanding of drug effects during pregnancy, research should expand to include the multiple inactive ingredients (excipients) present in formulations, a topic which has been ignored. In this review we summarize the current understanding of PK and PD changes during pregnancy. While our understanding of these changes is improving, we also draw attention to data gaps, research needs and issues of concern for practitioners.

2. Physiologic Changes of Pregnancy

Pregnancy is a complex state during which changes in physiology of the maternal organism (see Table 1) have evolved to enhance development and growth of the placenta and fetus [8, 23]. These changes also alter maternal disposition of drugs and the effect of a drug on the mother, placenta, and fetus [24, 25].

2.1. Cardiovascular Changes during Pregnancy. In 1973, Pirani et al. assessed cardiovascular changes during pregnancy and found that, on average, a woman's cardiac output increases early in pregnancy then plateaus at 16 weeks of gestation at around 7 L/min where it remains until delivery

[26, 27]. Stroke volume also increases to a maximum of 85 mL at around 20 weeks of gestation and remains close to that level until delivery. Pregnancy is also a time of gradual increase in maternal heart rate, reaching 90 beats per minute at rest during the third trimester [26]. Finally, the same authors describe a gradual increase in plasma volume reaching over 3.5 L at 38 weeks of gestation.

Along with physiologic changes, pathophysiology is altered during pregnancy. The hypertensive disorders, recently reviewed by Lindheimer and Sibai, are an example of diseases altered during pregnancy [28, 29]. Chronic hypertension is distinguished from gestational hypertension by the time of diagnosis [30, 31]. The former is defined as elevated blood pressure occurring earlier than 20 weeks of gestation, compared to blood pressure elevations which occur beyond 20 weeks for gestational hypertension.

Hypertension during pregnancy can signal the development of preeclampsia [32], a pregnancy-specific condition, which involves the development of hypertension and proteinuria over the last half of pregnancy. The severe form of the disease presents with hemoconcentration, thrombocytopenia, liver dysfunction, and seizures in some cases. The clinical significance of the different hypertensive disorders is evident with the choice of therapy; antihypertensive medications are typically used in gestational and chronic hypertension, but not in preeclampsia, where magnesium sulfate is used acutely, and in the majority of cases the treatment is delivery.

While appropriate dosing with antihypertensives is critical during pregnancy, few have been evaluated for PK or PD in pregnancy [33]. Hogstedt and Rane studied the PK of metoprolol in 5 pregnant women with postpartum followup [34]. The study concluded that there was a substantial increase in hepatic metabolism during pregnancy, which resulted in increased clearance. The same authors expanded their work on the drug, looking at its PD properties. In their study, metoprolol had four-times and twice the effect on heart rate and systolic blood pressure, respectively, during pregnancy as compared to the postpartum period. The authors concluded that the altered cardiovascular response to metoprolol during pregnancy may be due to increased sensitivity or altered function of the beta-adrenergic system [35]. The net effect of these investigations, however, illustrate that both PK and PD are not fixed during pregnancy and may be substantially different. In support of these observations, recent studies of the PK and PD of atenolol during pregnancy demonstrate increased renal clearance; however, the effect on PD remains to be fully characterized [36].

2.2. Pulmonary Changes during Pregnancy. Anatomic and physiologic changes in pregnancy affect pulmonary function with a decrease in functional residual capacity and ~30% increase in minute ventilation (see Table 1). This change results in hyperventilation in 60–70% of normal pregnancies, along with the sensation of dyspnea [49]. These changes are most evident in pregnant woman with asthma.

The prevalence of asthma complicating pregnancy has increased [50], and it is now estimated that it affects 8% of pregnant women [51]. Gluck investigated this disease

during pregnancy, observing that asthma improves in 1/3 of cases, worsens in 1/3, and remains unchanged in the last 1/3 [49]. Changes in estrogen and progesterone are thought to improve the disease while elevation of the diaphragm, increased pulmonary vascular permeability, and increased gastroesophageal reflux have been associated with worsening asthma [49].

Asthma during pregnancy has been linked to preterm birth, low birth weight, congenital malformations, and perinatal death [49]. Along with increased risk of adverse outcomes in poorly controlled disease, the importance of diagnosis and treatment are emphasized. Adherence to treatment with inhaled corticosteroids has been reported to be poor in many studies. Women with asthma have been reported to decrease their use of inhaled corticosteroids during pregnancy, compared to their use in the 20 weeks before their last menstrual period [52]; this may be due to concern regarding the safety of inhaled corticosteroids during pregnancy [53]. Moreover, a substantial proportion of asthmatic exacerbations during pregnancy have been associated with nonadherence to treatment with inhaled corticosteroids [54].

Reports of higher risk of preeclampsia and prematurity with inhaled corticosteroids compared to nonsteroidal asthma medication have made adherence even more difficult [55, 56]. A study on treatment of acute asthma in emergency departments across the United States included 551 women (51 pregnant and 500 not pregnant) [56]. Both groups had similar duration of symptoms and peak expiratory flow rates [56]. However, there was a significant difference in treatment. Pregnant women were less likely to be given systemic corticosteroids (44 versus 66%) in the emergency department than nonpregnant women. This finding could not be attributed to a concern about steroid exposure in the first trimester, because corticosteroids were used almost equally in all trimesters: 53, 40, and 50% during the first, second, third trimesters, respectively [49]. Among those patients who were admitted, pregnant women had lower final peak expiratory flow rate in the emergency department and had longer hospital stays (3 versus 2 d). This inadequate treatment may partially explain continued asthma symptoms at 2 wk follow-ups in pregnant patients (three times more often than symptoms in nonpregnant patients; $P = .002$) [49]. Only 41% of pregnant asthmatics seen in emergency departments were being treated with inhaled corticosteroids when they presented with severe disease [56], which is suggestive of reluctance to treat asthma appropriately during pregnancy.

Many aspects of pulmonary pharmacology during pregnancy remain unknown. One study has looked at inhalation anesthetics and found that the minimum alveolar concentration of isoflurane was reduced by 28% in pregnant women at 8–12 weeks' gestation compared with that of nonpregnant controls [57]. The pharmacokinetics of the majority of inhaled drugs and those used to treat pulmonary conditions during pregnancy have yet to be determined, but this small observational study suggests that pulmonary function changes during pregnancy influence both PK and PD.

2.3. Liver Physiology. Hepatic blood flow has been reported to increase up to 160% during pregnancy, following the increase in cardiac output [22]. Using Doppler ultrasonography, Nakai et al. have reported on the increase in hepatic perfusion during the third trimester compared to nonpregnant level. The study examined the hepatic arterial and portal venous blood flow in healthy pregnant women. The authors found that hepatic arterial blood flow did not increase significantly during pregnancy. They concluded that the major determinant of the increase in the hepatic perfusion was increased portal venous return [21, 58]. A change in hepatic flow influences the disposition of drugs which are highly extracted by the liver. Theoretically, an increase in hepatic flow could increase hepatic extraction of drugs from portal venous or arterial blood and result in lower bioavailability or increased clearance, respectively. Nevertheless, data on drugs with high extraction ratios showed variable changes in PK properties, suggesting the presence of additional hepatic and gastrointestinal mechanisms of drug disposition which are altered during pregnancy [59].

Plasma protein binding of drugs, which generally decreases during pregnancy, has important implications for drug disposition and action. It is therefore possible that an increased free fraction of the drug is responsible in part for changes in its clearance. During pregnancy, both albumin and alpha 1-acid glycoprotein (AAG) concentrations are reduced, likely due to a dilutional effect of increased plasma volume, as well as increased urinary albumin excretion [59–61].

Furthermore, maternal and fetal plasma differ in their concentrations of both albumin and AAG which can influence a drug's plasma concentration in maternal and fetal circulations. Albumin is more concentrated in fetal plasma, and AAG is at 37% of the maternal concentration in term babies [62]. Such a difference in albumin and AAG concentrations can significantly alter the concentration and relative distribution of drugs between maternal and fetal plasma. For example, the unbound fraction (free fraction) of indinavir and saquinavir have been found to be higher in umbilical cord than maternal plasma [63]. These findings were in part explained by the lower concentration of AAG in fetal blood. Further decreasing fetal exposure to these drugs is the fetal to maternal efflux of these drugs by placental P-gp, which further lowers the concentration of the drugs in the fetal circulation [63, 64].

The transport proteins, responsible for influx or efflux of many different substances into organs like the kidney, placenta, gut, or liver play an important role in drug delivery as well as drug-drug interactions, and they are discussed in more detail below [65, 66].

2.4. Renal Physiology during Pregnancy. An early change in pregnancy is systemic vasodilation which is thought to be mediated by progesterone and relaxin [8, 70]. Dilation of renal vasculature with an increase in glomerular filtration rate (GFR) and effective renal plasma flow (RPF) also occurs [71]. Both RPF and GFR are increased, with RPF increasing up to 1.8-fold, and GFR increasing up to 1.6-fold compared with prepregnancy or postpartum values [8, 72].

TABLE 2: Pregnancy-induced pharmacokinetic changes for selected drugs.

Drug	Half-life	Clearance	Protein binding (%)	Bioavailability	Time during pregnancy change noted	Reference
Cefatrizine	Decreased (1.5 h)	Increases	60	43%	19–24 weeks	[7]
Amoxicillin	Decreased (1.2 h)	Increases		95%	Delivery second and third Trimester and postpartum	[37, 38]
Cefuroxime	Decreased (44 min)	Increases		30–50%	Delivery	[39]
Zidovudine	Unchanged (1.1 h)	Increases	<25	63%	Delivery	[40]
Lamivudine	Unchanged (6 h)	No change	10–50	55%	38 to Delivery	[41]
Saquinavir	Unchanged (9–15 h)		98%		Delivery	[40]
Lopinavir	Unchanged (5-6 h)	Decreases	99%	37%	30–36 weeks	[42]
Nelfinavir	Unchanged (3–5 h)		98%		2nd and 3rd trimester	[43]
Ritonavir	Unchanged (3–5 h)		99%		Delivery	[40]
Glyburide	Unchanged (4 h)	Increases	98%	Decreases	28–38 weeks	[44]
Digoxin	Decreased (38 h)	Increases	33%	60%	3rd trimester	[45, 46]
Midazolam	Unchanged (2.5 h)	Increases	30%	24%	28–32 weeks	[46]
Lamotrigine	15–24 h	Increases	98%	55%	Throughout pregnancy	[47]
Caffeine	Increased (10.5 h)	Decreases			36–40 weeks	[48]

Despite increased GFR and renal blood flow among pregnant women, differences have been noted in the clearance of drugs which are predominantly eliminated by renal mechanisms. Lithium is almost completely eliminated by renal mechanisms. Women using lithium during the third trimester demonstrated a doubling of clearance compared to prepregnancy [73]. In comparison, the clearance of atenolol, also eliminated predominantly by renal mechanisms, was only increased by 12% across pregnancy [36]. Similarly, the clearance of digoxin, which undergoes 80% renal excretion, was increased by 20–30% during the third trimester when compared to postpartum [45, 46]. Such variations in drug clearances restrict any generalization about the effect of pregnancy on renally eliminated drugs. Specific evaluation is needed to determine whether changes in clearance are due to GFR, tubular secretion or reabsorption, or other physiologic or metabolic processes. Table 2 summarizes pregnancy-induced PK changes in the drugs listed above.

3. Drug Transporters

Previously, drug-drug interactions were thought to involve the phase I or phase II enzymes. Over the past two decades, a number of important human drug transporters that are expressed at the apical or basal side of epithelial cells in various tissues, including the placenta [66], have been described [74, 75]. Given the role of transport proteins in the transfer of drugs into or out of cells, the impact on drug-drug interactions that these transport proteins can play in achieving therapeutic goals in pregnancy remains ill-defined (Table 3).

Like the enzymes involved in phase I and phase II metabolism of drugs, it is possible that drugs can interact at transport proteins by induction, inhibition, agonistic, or antagonist actions. For example, ritonavir is often used in combination with other protease inhibitors to compete with cellular elimination because it competes with P-gp (see Table 3 and subsequent discussion of protease inhibitors). A similar phenomenon occurs with coadministration of drugs which are substrates interacting with other drug transporters [76]. Also, numerous polymorphisms have been identified in transporter genes [76, 77]. However, many challenges remain in the understanding of the clinical relevance of these genetic variations in transporters for drug disposition and drug-drug interactions across the course of pregnancy, especially in the context of placental transport from and into the fetal compartment [66].

In addition to genetic variation, changes to drug transporters can ensue when physiologic changes occur. Just like the cytochrome P450 enzymes' activity or amount is altered in pregnancy, it is postulated that such changes also involve drug transporters but have yet to be described in detail [78, 79]. Most of the studies on drug transporters during pregnancy have focused on placental transporters [80–87].

Hebert et al. assessed the PK and PD of glyburide in women with gestational diabetes. They observed that plasma concentrations of glyburide during pregnancy were about half that observed in nonpregnant women with type 2 diabetes. In addition, beta cell responsiveness was lower in women with type 2 diabetes than other pregnant women. The lower plasma concentrations of glyburide observed during pregnancy were attributed to increased intestinal and/or hepatic metabolism [44]. The increased levels of unbound glyburide metabolites supported the authors' conclusions.

The placenta performs many functions that affect both mother and fetus. It produces and secretes hormones which affect the maternal endocrine state [88]. It assists in fetal growth and development by transporting nutrients towards the fetal side and transporting products of fetal metabolism for excretion by the mother [74, 75].

The placenta is a selective transporter for multiple compounds [74]. The selective nature of the transport activity is mediated by the polarized nature of syncytiotrophoblast,

TABLE 3: Major ABC drug efflux transporters, their placental localization, and substrates.

Transporter	Gene	Placental localization	Gestational-age-dependent regulation	Substrate	Inhibitor	Inducer
P-gp	ABCB1	Apical, syncytiotrophoblast	Yes	Digoxin, fexofenadine, indinavir, vincristine, colchicines, topotecan, paclitaxel, talinolol, loperamide	Ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, elacridar, azithromycin, valspodar	Rifampin, St. John's wort
MRP1	ABCC1	Basolateral, syncytiotrophoblast predominantly at fetal blood endothelia	Yes	Adriamycin, topotecan, cisplatinum, methotrexate, etoposide, vincristine	Probenecid, sulfinpyrazone, indomethacin, glibenclamide, agosterol A, verapamil, cyclosporin A, genistein, quercetin, RU486, budesonide, agosterol A	
MRP2	ABCC2	Apical, syncytiotrophoblast	Yes	Vincristine, etoposide, doxorubicin, epirubicin, methotrexate, irinotecan, ampicillin, ceftriaxone, pravastatin, temocaprilat, grepafloxacin, BQ-12, saquinavir, ritonavir, indinavir, ^{99}mTc-Sestamibi	Probenecid, sulfinpyrazone, benzbromarone, MK571	Sulfinpyrazone
MRP3	ABCC3	Basolateral, syncytiotrophoblast predominantly at fetal blood endothelia	Unknown	Etoposide, methotrexate, tenoposide, acetaminophen	Probenecid, sulfinpyrazone, benzbromarone, MK571	
MRP4	ABCC4	Unknown	Unknown	Azidothymidine monophosphate, lamivudine, ganciclovir, 6-mercaptopurine, 6-thioguanine, methotrexate	Probenecid, benzbromarone, sulfinpyrazone, MK571, dipyridamole	
MRP5	ABCC5	Preferentially basolateral, syncytiotrophoblast, and fetal vessels	Yes		Benzbromarone, sulfinpyrazone, MK571, dipyridamole	Sildenafil
MRP6	ABCC6	Unknown	Unknown	Conjugated organic anions		
MRP7	ABCC10	Uknown	Unknown	Organic anions		
BCRP	ABCG2	Apical syncytiotrophoblast	Yes	Daunorubicin, doxorubicin, topotecan, rosuvastatin, AZT, lamivudine	Elacridar, acridone carboxamide, fumitremorgin C	
OCT3	SLC22A3	Basal syncytiotrophoblast	Cimetidine	Desipramine, phenoxybenzamine, quinine		
OCTN1	SLC22A4	Apical syncytiotrophoblast	Quinidine, verapamil			

References: [67–69].

the functional cells of the placenta, with support of polarity provided by transport proteins [66]. The plasma membrane of these cells consists of a brush border membrane that faces the maternal side, and a basal membrane that faces the fetal side. On the maternal side, blood flows directly from the uterine vasculature through intervillous spaces to the syncytiotrophoblast without an intervening capillary network. In contrast, the fetal vessels form a capillary network within the placental villi on the fetal side.

Compounds transported between mother and fetus, must cross the syncytiotrophoblast, through the stroma of the villi, across the basement membrane and endothelium of placental capillaries before entering fetal circulation. The placenta facilitates this process as a result of differential expression of various transporters [89–92]. Transporters are expressed to serve specific functions by transporting endogenous compounds (such as cytokines, nucleoside analogs, and steroid hormones); however, exogenous compounds with similar structures may also interact with these transporters. Expression of placental drug transporters is under developmental control and depends on gestational age [67], with expression increasing, for some transporters, with advancing gestational age. Such a pattern of expression indicates that fetal exposure changes with gestational age [93–95]. It has also been shown that placental transporter expression is altered by maternal disease in rodent models [78, 79].

Protease inhibitors, an important drug class used in highly active antiretroviral therapy in HIV-infected individuals, have a low and variable oral availability [96]. This means that patients have to take the drugs more frequently and at higher doses which can lead to poor adherence and associated low and variable drug plasma concentrations. It has been shown that when saquinavir is coadministered with ritonavir, both protease inhibitors, its oral availability increases dramatically [97]. Two mechanisms have been proposed to explain this finding. It has been demonstrated that inhibition of the metabolizing CYP3A4 and other cytochrome P450 isoforms by ritonavir is a major factor in the dramatically increased saquinavir bioavailability [98]. In addition, ritonavir has been reported to be a P-gp inhibitor and saquinavir a substrate [99–101]. When saquinavir and ritonavir are coadministered, ritonavir inhibits P-gp function, resulting in increased saquinavir bioavailability. Another drug acted upon by P-gp is lopinavir, a protease inhibitor that had become standard therapy for HIV during pregnancy. Studies have shown that pregnancy results in reduced lopinavir levels when compared to postpartum [42], doubling of the dose is needed during pregnancy to reach therapeutic concentrations, a phenomenon that disappears within 2 weeks postpartum [102]. These findings stress the need for tight dosing and close monitoring to avoid subtherapeutic levels as well as toxicity.

Another example where drug transporters have significant clinical implications is treatment of fetal tachycardia. While transplacental pharmacotherapy for the condition is available, it remains a challenging task to maximize fetal drug exposure, while minimizing drug exposure of the mother. Despite some challenges, digoxin is commonly used as an initial monotherapy [103]. Digoxin's clearance increases during pregnancy leading to lower steady-state serum concentrations [46, 104]. These changes have been attributed to an increase in renal clearance of the drug, due partly to an increased glomerular filtration during pregnancy, but also to increased P-gp transport of the drug. P-gp is responsible for the increased secretion of digoxin across the apical membrane of the renal tubular epithelium [105, 106]. In addition, P-gp is expressed on the maternal surface of the placenta and acts to further decrease fetal exposure to the drug, complicating treatment of fetal arrhythmias. These pharmacokinetic changes require an increase in the dose or a change in the dosing interval used during pregnancy to maintain therapeutic concentrations [104]. The need for increased digoxin during pregnancy carries an underlying risk for increased maternal digoxin toxicity. Despite the lengthy history of the drug, its toxicity is severe and well defined, with a 41% rate of mortality and a 47% rate of life-threatening arrhythmia in individuals who suffer from it. The risk for women is intensified by data suggesting that women are at increased risk for digoxin toxicity when compared to men across all age groups [11].

With the accumulating evidence on drug transporters, there is little doubt that their expression and regulation play a critical role in modulating the exposure of the mother, placenta, and fetus to potentially harmful drugs, endogenous toxic compounds, and potentially beneficial drugs such as retrovirals. Currently there is a need to develop new strategies for PK studies in pregnancy which recognizes the critical role of transport proteins. In addition, further development of models for understanding the regulation of placental transporters by inhibitors and inducer compounds could prove valuable in improving fetal drug availability and decreasing toxicity.

4. Drug Metabolism

4.1. Phase I Metabolism. The cytochrome P450 (CYP) system is the predominant oxidative enzyme system involved in human drug metabolism and plays a critical role in drug disposition [121]. A number of recent studies have evaluated the changes affecting drug metabolism during pregnancy (see Table 4 for summaries of some of these studies).

4.1.1. CYP3A. CYP3A is the most abundant P450 enzyme in the liver and gut, and results in 30% of the enzyme complex's activity. It has a broad spectrum of substrates, and is involved in some way in the metabolism of more than half of the currently known drugs [107, 121].

Midazolam is a selective substrate for the enzyme. One study measured a doubling in oral midazolam clearance during pregnancy as compared to postpartum, leading to a decrease in drug bioavailability [46]. In addition, other research on CYP3A substrates has suggested that its activity is increased during pregnancy. N-demethylation of dextromethorphan, a substrate used as a probe for the enzyme, has been reported to increase by 35–38% during pregnancy [121]. Similarly, nelfinavir was reported to have a 25–33% increase in apparent oral clearance in pregnancy [108, 109].

TABLE 4: Pregnancy-induced enzyme-specific changes.

Enzyme	Pregnancy-induced change	Potential substrates in obstetrics	Possible clinical consequences	Ref.
CYP3A4	Increased	Nifedipine, methadone, indinavir	Significantly lower trough levels of methadone during pregnancy associated with symptoms of withdrawal. Increase daily dose by 5–10 mg or administer in more frequent doses to avoid withdrawal	[107–110]
CYP2D6	Increased	Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, citalopram	Increased metabolism of fluoxetine desmethylcitalopram, lower plasma levels of the drug are associated with recurring symptoms of depression	[107, 111]
CYP1A2	Decreased	Theophylline, clozapine, olanzapine, ondansetron, cyclobenzaprine	Increase in theophylline half-life during pregnancy requiring dose reductions to avoid toxicity	[107, 112–114]
UGT1A4	Increased	Lamotrigine	Significant decrease in lamotrigine concentration resulting in loss of seizure control, recommended to measure plasma lamotrigine concentrations during each trimester and adjusting dose as needed	[115–117]
UGT1A1	Increased	Acetaminophen	Increased acetaminophen glucuronidation resulting in decreased half-life, clinical consequences are unknown	[118]
NAT2	Decreased	Caffeine	Decreased metabolism of caffeine Clinical consequences are unknown	[114, 119, 120]

Because CYP3A is involved in the metabolism of many drugs, the findings have implications for medication dosing in pregnancy [107, 121]. Those with a narrow therapeutic window may fall below clinically effective concentrations. Also, medication started during pregnancy might reach toxic concentrations if continued during the postpartum period. More information is needed about this enzyme. The enzyme's expression and activity during pregnancy have yet to be fully described, and it has multiple substrates that overlap with the P-glycoprotein transporter, which itself is affected during pregnancy.

4.1.2. CYP2D6. CYP2D6 is the second most common enzyme in the CYP family [107]. The individual status of CYP2D6 activity can be assessed with several drugs such as metoprolol and dextromethorphan. Low activity of the enzyme (the poor metabolizer (PM) phenotype) is an autosomal recessive trait that affects approximately 7% of Caucasians and 1% of Orientals [122]. The opposite phenotype, called ultrarapid metabolism, also exists and is caused by gene amplification [122]. With standard medication dosing, the poor metabolizer has very high concentrations of the parent drug and the ultrarapid metabolizer very low plasma concentrations. CYP2D6 activity, assessed with dextromethorphan O-demethylation, was found to gradually increase throughout pregnancy as compared with the postpartum period, interpreted by some investigators as induction during the third compared to the first trimester [111, 121].

4.1.3. CYP1A2. Many studies have reported decreased CYP1A2 activity during pregnancy [48, 107, 112, 113, 121, 123]. Caffeine (a substrate frequently used to measure CYP1A2 activity) has its half-life increased from 3.4 h in nonpregnant patients to 8.3 h during pregnancy, with values returning to prepregnant levels shortly after delivery [112, 114, 119]. A study by Brazier et al. showed a normalization of caffeine clearance within four days after delivery, compared to a 65% reduction during the third trimester [114]. CYP1A2 activity decreases gradually with advancing gestational age. Tracy et al. reported a reduction in caffeine clearance of 33%, 48%, and 65% for each trimester compared with postpartum [121].

Theophylline, also metabolized by CYP1A2, has decreased clearance during the third trimester of pregnancy with half-life estimated at 13 h compared to 9.5 h postpartum [124]. This change has been attributed to a reduction in nonrenal intrinsic clearance and calls for a decrease in theophylline doses used in later stages of pregnancy.

A more comprehensive understanding of the regulation of the enzyme and the changes affecting its numerous substrates is needed. With the current evidence, it may be necessary to decrease the dose of CYP1A2 substrates when used during late pregnancy to avoid toxicity.

4.2. Phase II Metabolism

4.2.1. Uridine 5′-Diphosphate Glucuronosyltransferase (UGT).
Approximately 1.1 million women with epilepsy are of child-bearing age in the United States and give birth to over 20,000 babies each year [125]. Pregnancy in women with epilepsy is accompanied by increased maternal risks from seizure occurrence and potential adverse developmental outcomes related to certain antiepileptic drugs [115, 116]

Lamotrigine is an antiepileptic drug whose metabolism is significantly altered during pregnancy. It is a UGT substrate (see Table 4), and approximately 90% of its metabolism is through N-glucuronidation by UGT1A4 in the liver [118]. One study reported a 360% increase in lamotrigine clearance between prepregnancy and the third trimester [118]. In addition, a study of pregnant women on lamotrigine monotherapy reported a significant 27% decrease in the ratio of serum concentration-to-dose during the first trimester and 66% decrease in the third trimester, compared to postpartum [47]. Five of the eleven women suffered seizures while enrolled in this study and required an increased dose in order to achieve seizure control. Lamotrigine metabolism returned to nonpregnant levels within 3 weeks after delivery and required a dose readjustment to avoid toxicity [47].

Other UGTs also undergo increased activity. The clearance of acetaminophen is 58% higher during pregnancy, secondary to a 75% increase in glucuronidation activity of UGT1A1 and -1A6 during pregnancy [126]. Similar findings have been reported for oxazepam. The drug, metabolized by UGT2B7, was found to have a two- to threefold increase in clearance in pregnant women compared to clearance rates in men and nonpregnant women [127].

Current data suggests a possible hormonal regulation of UGTs. When taken with oral contraceptives, both lamotrigine and acetaminophen demonstrate decreased maximum concentration and concentration-to-dose ratio [120], thought to be mediated by estrogen [128]. Studies in mice describe a possible role for prolactin in UGT induction [129]. Such findings suggest the need for continued drug monitoring while a woman is lactating.

4.2.2. N-Acetyltransferase.
Sulfamethoxazole, commonly used during pregnancy, is a substrate of N-acetyltransferase (NAT). Studies involving sulfamethoxazole and other substrates of NAT suggested a decreased activity of the enzyme during pregnancy [129]. NAT might also be under hormonal regulation, since women on oral contraceptives experience decreased NAT2 activity [130]. More studies are needed to better determine changes affecting drugs metabolized by NAT and the regulation it undergoes.

5. Ethics of Drug Studies in Pregnant Women

Current medication labeling typically only reports on fetal safety issues with respect to the use of the medication, and typically provides no information on PK, PD, or efficacy during pregnancy. Unfortunately, it follows that if a drug is not studied for a condition unique to pregnancy (e.g., preterm labor, asthma during pregnancy), treatment during pregnancy is not considered an indication for regulatory purposes (i.e., use of the drug is considered off-label). Such illustrative use of medications during pregnancy was the focus of a Cochrane report by Webb et al. The authors noted the absence of any objective trial-based evidence to guide the treatment of psychosis during pregnancy [131]. Treatment was based on personal clinical judgment, which raises "important clinical and ethical concerns for the current use of antipsychotic drugs for women during pregnancy" [131].

McCullough et al. approached the complex matter of maternal and fetal patients and developed a framework for pharmacologic studies in pregnant women. The authors defined the previable fetus as a patient only when the pregnant woman confers this dependent moral status on it, which she has the freedom to do [132]. The viable fetus was defined as a patient by virtue of both its ability to survive ex utero and access to medical technology which makes this possible [133]. In research that is designed to benefit the pregnant patient, the ethical concept of the fetus as a patient requires the pregnant woman to consider the health-related interests of the fetus against her own legitimate interest in participating in research which may improve her own health [134]. Conversely, a study designed to determine if an intervention benefits the fetus (e.g., fetal surgery) would require that the pregnant subjects take only reasonable risks to their own health [134].

This framework allows women the right to withhold the moral status of being a patient from a previable fetus. This adds an additional ethical consideration to a pregnancy that is complicated by an adverse fetal event attributed to the pharmacologic agent being studied. Such an adverse fetal event pertains to the legal liability of the investigator, the funder, and the sponsoring organization. Preventing unnecessary liability to these parties would count as self-interest. McCullough et. al suggest that when studies follow the beneficence-based obligation, they would offer a balanced protection to the study personnel as well as the fetal patient [132]. Their paper lists four criteria for drug studies during pregnancy that, when satisfied, would not violate any beneficence-based obligations to the fetal patient. These criteria prioritize the use of drugs that are predicted to alter the course of a pregnant woman's condition, as well as having previous animal or human studies that do not report "documented death or documented serious, far-reaching, and irreversible injury of any major organ system to the fetal or maternal patient." In addition, the criteria stress the need for data demonstrating minimized risk to the fetal patient [132]. Though this list does not exclude drugs lacking any previous animal or human safety and/or teratogenic studies, it does discourage the prioritization of studies for such agents [132].

A different dimension to the ethics of drug studies during pregnancy involves study design. Less risk would be associated with a retrospective study. However, such a study would offer limitations to standardizations of patient characteristics and drug use. Although difficult, the optimal drug study design would be a double-blind placebo or active agent controlled trial. Some situations limit the use of such a design. Yonkers states "it is neither ethical nor

practical to randomly assign depressed pregnant women to antidepressant agents compared with placebo" [135]. Other authors support such a position. Brody explains "the more serious the disease process and the less likely that the established therapy will produce bad side effects, the more problematic is a placebo-controlled trial" [136]. It is plausible to understand how such a situation would inhibit the use of placebo but allow for controlled randomized trials to compare different agents.

6. Conclusion

Pregnancy alters the disposition and effect of drugs and consequently can change efficacy and appropriate use of the medication. In the setting of prescribed drugs, simply describing pregnant women as a special population is a mistaken oversimplification. In current practice, each pregnant woman is a study population of one every time she is treated with a medication which has not been previously studied in pregnancy to define PK, PD, or efficacy. However, drugs continue to be used during pregnancy with incomplete data on the maternal consequences of use in pregnancy. In addition, pregnancy has yet to lead to consideration of drug dose alterations, with changes occurring in a case-by-case fashion. This review has described physiological and metabolic changes which increase or decrease drug clearance, metabolism, and efficacy. Given the paucity of understanding about pregnancy-related changes in PK, PD, and efficacy, it is necessary at the present time to specifically study drugs intended to be used in pregnancy. As this database grows it may be possible to simulate expected changes to anticipate improvements in study design and clinical therapeutics.

Conflict of Interests

The authors have no financial interests or potential conflicts of interests to disclose. This paper was prepared in part by D. R. Mattison as an employee of the US Government making this a "work of the US Government" and therefore copyright is nontransferrable.

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