LEADING ARTICLE

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Pregnancy-Induced Changes in Pharmacokinetics

A Mechanistic-Based Approach

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Abstract

Observational studies have documented that women take a variety of medications during pregnancy. It is well known that pregnancy can induce changes in the plasma concentrations of some drugs. The use of mechanistic-based approaches to drug interactions has significantly increased our ability to predict clinically significant drug interactions and improve clinical care. This same method can also be used to improve our understanding regarding the effect of pregnancy on pharmacokinetics of drugs.

Limited studies suggest bioavailability of drugs is not altered during pregnancy. Increased plasma volume and protein binding changes can alter the apparent volume of distribution (V_d) of drugs. Through changes in V_d and clearance, pregnancy can cause increases or decreases in the terminal elimination half-life of drugs. Depending on whether a drug is excreted unchanged by the kidneys or which metabolic isoenzyme is involved in the metabolism of a drug can determine whether or not a change in dosage is needed during pregnancy. The renal excretion of unchanged drugs is increased during pregnancy. The metabolism of drugs catalysed by select cytochrome P450 (CYP) isoenzymes (i.e. CYP3A4, CYP2D6 and CYP2C9) and uridine diphosphate glucuronosyltransferase (UGT) isoenzymes (i.e. UGT1A4 and UGT2B7) are increased during pregnancy. Dosages of drugs predominantly metabolised by these isoenzymes or excreted by the kidneys unchanged may need to be increased during pregnancy in order to avoid loss of efficacy. In contrast, CYP1A2 and CYP2C19 activity is decreased during pregnancy, suggesting that dosage reductions may be needed to minimise potential toxicity of their substrates.

There are limitations to the available data. This analysis is based primarily on observational studies, many including small numbers of women. For some isoenzymes, the effect of pregnancy on only one drug has been evaluated. The full-time course of pharmacokinetic changes during pregnancy is often not studied. The effect of pregnancy on transport proteins is unknown. Drugs eliminated by non-CYP or non-UGT pathways or multiple pathways will need to be evaluated individually. In conclusion, by evaluating the pharmacokinetic data of a

variety of drugs during pregnancy and using a mechanistic-based approach, we can start to predict the effect of pregnancy for a large number of clinically used drugs. However, because of the limitations, more clinical, evidence-based studies are needed to fully elucidate the effects of pregnancy on the pharmacokinetics of drugs.

Observational studies have documented that women take a variety of medications during pregnancy, including prescription, over-the-counter (OTC) and herbal medications.[1-3] Many women with chronic diseases (i.e. asthma, diabetes mellitus, hypertension, epilepsy, depression and other mood disorders) continue taking medication during pregnancy. Women can develop acute illnesses or pregnancy-induced complications that necessitate drug therapy. It is well known that pregnancy can induce changes in the plasma concentrations of some drugs. However, for the large majority of drugs used during pregnancy, there is little or no information available regarding whether pregnant women have altered pharmacokinetics or dosage requirements. For drugs with clear clinical endpoints, those undergoing routine therapeutic drug monitoring and/or those with a wide therapeutic index, these pharmacokinetic changes are less relevant. However, the majority of the drugs do not fit any of these categories.

The use of mechanistic-based approaches to drug interactions has significantly increased our ability to predict clinically significant drug interactions and improve clinical care.[4-7] This same method can also be used to improve our understanding regarding the effect of pregnancy on the pharmacokinetics of drugs. The purpose of this review is to evaluate the literature regarding pregnancy-induced changes, with a primary emphasis on drugs with well described pharmacokinetics in the nonpregnant population. Only drugs that are predominantly eliminated either unchanged by renal excretion or metabolised by one primary isoenzyme were included in the analysis. As this review will not provide a complete overview of all reported pregnancy-induced changes on pharmacokinetics, the interested reader is directed to several excellent comprehensive reviews in the literature for specific drug classes and/or diseases.[8-15]

1. Absorption

There are many physiological changes that occur during pregnancy that could theoretically alter drug absorption, including a reduction in intestinal motility and an increase in gastric pH owing to a reduction in gastric secretions.[9] There are little data documenting that any of these changes significantly alter drug absorption. Six pregnant women were given the β-adrenoceptor antagonist sotalol by intravenous and oral routes during their third trimester and 6 weeks postpartum. Bioavailability was 85–90% and did not differ during pregnancy and postpartum.[16] Similar studies of the β-lactam antibacterials were performed in women diagnosed with asymptomatic urinary tract infections. The women received both intravenous and oral doses of ampicillin (n = 6),[17] cephradine (n = 12)[18] and cefazolin (n = 6)[18] during the second or third trimester and at least 6 weeks postpartum. For all three β-lactam antibacterials there was no difference in bioavailability during pregnancy compared with postpartum.

2. Distribution

Theoretically, the increased plasma volume and changes in protein binding during pregnancy could increase the apparent volume of distribution (V_d), resulting in a decrease in initial concentrations (C_0)

achieved after a loading dose, and decrease in peak plasma concentrations (C_{max}) after multiple-dose administration. For example, an increase in V_d will result in an increased terminal elimination half-life ($t_{½\beta}$) if clearance of the drug is decreased or is unchanged. An increase in both clearance and V_d can result in an increase, decrease or no change in $t_{½\beta}$ depending on which increase is the largest (see tables I, II, III, IV and V for specific examples). The effect of pregnancy on $t_{½\beta}$ could result in changes in the duration of effect; however, clinically important effects on C_0, C_{max} or $t_{½\beta}$ have not been identified.

Albumin concentrations decrease during the second trimester and continue to decline throughout pregnancy, reaching concentrations approximately 70–80% of normal values at time of delivery.[60] Benet and Hoener[61] determined that protein binding effects are only clinically significant for two different types of highly protein bound drugs that are predominantly eliminated by hepatic elimination. First are the low extraction ratio drugs where doses are monitored using total plasma concentration. In this case, total plasma concentrations will underestimate unbound or active plasma concentrations of these drugs. This has been clearly shown for both phenytoin (see section 3.3)[31,33] and valproic acid (valproate sodium)[33] in pregnant women with epilepsy. For valproic acid, mean total plasma concentrations decreased 50% by the third trimester despite only a 29% decrease in unbound plasma concentrations. Adjusting dosages based on total plasma concentrations would result in higher doses of valproic acid than needed to maintain therapeutic unbound concentrations. As the teratogenicity of valproic acid and phenytoin has been found to be dose-dependent,[62,63] minimising unnecessary dosage increases is desirable.

Second are the high extraction ratio drugs with a narrow therapeutic window and administered by non-oral routes. In this case, the area under the plasma concentration-time curve (AUC) of unbound

Table I. Effect of pregnancy on drugs (caffeine as an example) metabolised by cytochrome P450 1A2

Study	Study design	Results during pregnancy compared with postpartum or nonpregnant controls
Knutti et al.[19]	13–38gw (n = 57) and 1mo postpartum compared with males and nonpregnant women (n = 25)	Longer $t_{½\beta}$ (8.3 vs 3.4h), returned to baseline within 1mo
Aldridge et al.[20]	First trimester (n = 8), seven of eight patients also studied during the second and third trimesters (11, 17, 24, 32 and 28gw) and 1mo postpartum	CL was 100%, 68%, 54%, 57% and 36%, respectively, of the CL postpartum; $t_{½\beta}$ was 5.3, 9.9, 12.6, 10 and 18.1h, respectively, compared with 5.5h postpartum
Bologa et al.[21]	30–38gw and 6–8wk postpartum (n = 7)	MR ↓ 59%
Tsutsumi et al.[22]	8–16gw, 20–28gw and 32–38gw, and 1mo postpartum (n = 12, nonsmoking)	MR ↓ 35%, 50% and 52%, respectively†

CL = clearance; **gw** = gestational weeks; **MR** = metabolic ratio of caffeine metabolites; $t_{½\beta}$ = terminal elimination half-life; ↓ indicates decrease; † $p < 0.05$ vs postpartum.

Table II. Effect of pregnancy on drugs metabolised by cytochrome P450 (CYP) 2D6

Study	Drug (route of administration)	Study design	Results during pregnancy compared with postpartum or historical controls
Wadelius et al.[23]	Dextromethorphan	Third trimester and 7–11wk postpartum genotyped for CY2D6. Six homozygous EM, seven heterozygous EM and four PM	MR ↓ 53%† indicating an ↑ in CYP2D6 activity in EM MR ↑ 63% in PM indicating a ↓ in CYP2D6 activity (MR 1.9–3.1 during pregnancy vs 1.3–2.0 postpartum) [NS]
Hogstedt et al.[24,25]	Metoprolol (PO/IV)	Third trimester and 3–6mo postpartum (n = 10)	CL ↑ 390% with PO administration (range 2- to 13-fold)† No change in protein binding CL ↑ 112% after IV administration (NS)
Heikkinen et al.[26]	Fluoxetine (PO)	Third trimester and postpartum (n = 5) compared with historical controls	Norfluoxetine to fluoxetine ratio ↑ 2.4-fold†† Low trough concentrations of parent and metabolite during pregnancy
Wisner et al.[27]	Nortriptyline (PO)	Third trimester and 6wk postpartum (n = 5)	Mean CL ↑ 100% (range 42–206%)

CL = clearance; **EM** = extensive metabolisers; **gw** = gestational weeks; **IV** = intravenous; **MR** = metabolic ratio; **NS** = statistically nonsignificant; **PM** = poor metabolisers; **PO** = oral; ↓ indicates decrease; ↑ indicates increase; **†** $p < 0.05$ vs postpartum; **††** $p < 0.05$ vs controls.

drug can be significantly increased when albumin level is decreased during pregnancy, and can result in increased pharmacological effect. Some of these agents may be administered during labour and delivery (i.e. alfentanil, fentanyl and midazolam). The effect of pregnancy on their pharmacokinetics and pharmacodynamics has not been evaluated.

3. Metabolism

Alterations in drug clearance during pregnancy can significantly affect steady-state concentrations of drugs. Based on pharmacokinetic models of hepatic elimination,[64] hepatic clearance is dependent on protein binding, activity of the metabolic enzymes and liver blood flow. The activity of the enzymes is dependent on genetic, physiological and environmental effects. The most common families of metabolic enzymes involved in drug metabolism are cytochrome P450 (CYP), uridine diphosphate glucuronosyltransferase (UGT) and *N*-acetyltransferase (NAT). CYPs are a multi-gene superfamily of enzymes primarily found in the liver, but also found, to a lesser extent, in the gastrointestinal tract, lungs and kidneys. The individual isoenzymes are composed of three major families (CYP1, CYP2 and CYP3) with specific isoenzymes involved in the hepatic metabolism of most drugs.[65] UGTs are a group of isoenzymes located in the hepatic endoplasmic reticulum and consist of two major subfamilies, UGT1 and UGT2.[66] The UGT1 subfamily catalyse the conjugation of a variety of xenobiotics, phenols and bilirubin, but generally do not catalyse steroid conjugation.[67,68] UGT2 isoenzymes primarily catalyse steroid and bile acid glucuronidation, but also drugs.

3.1 Cytochrome P450 (CYP) 1A2

CYP1A2 is inducible by cigarette smoking[69] and the inducibility is under genetic control, specifically *CYP1A2**1F.[70] The effect of the *CYP1A2**1F mutation on CYP1A2 inducibility during the first

Table III. Effect of pregnancy on drugs metabolised by cytochrome P450 (CYP) 3A

Study	Drug (route of administration)	Study design	Results during pregnancy compared with postpartum or historical controls
Ohkita and Goto[28]	NA[a]	Third trimester, 1wk and 3mo postpartum (n = 9)	Urinary ratio ↑ 183% and 266% during the third trimester compared with 1wk and 3mo postpartum, respectively
Kosel et al.[29]	NA[b]	Second or third trimester compared with post-partum (n = 5)	Urinary ratio ↑ 39–167% in four of five patients
Prevost et al.[30]	Nifedipine (PO)	Third trimester (n = 15) compared with historical controls	CL ↑ 30%
Tomson et al.[31,32]	Carbamazepine (PO)	First, second and third trimesters, 10wk and postpartum (n = 50)	No change in total or unbound carbamazepine
Yerby et al.[33]	Carbamazepine (PO)	First, second and third trimesters, 8wk and postpartum (n = 22)	↓ in total concentrations by 14%, 17% and 18%, respectively† No change in unbound carbamazepine Significant ↓ in both total and unbound carbamazepine at delivery
Wilson et al.[34]	Midazolam (IV)	Third trimester – awaiting elective caesarean section (n = 18), third trimester – in active labour (n = 10) compared with nonpregnant women undergoing other gynaecological procedures (n = 20)	Caesarean section patients had higher CL and lower midazolam concentrations No difference in pregnant women in active labour
Acosta et al.[35]	Saquinavir (PO)	27–34gw (n = 4) compared with historical controls	Median CL ↑ 27% (NS)
Acosta et al.[36]	Saquinavir (PO)	14–31gw and postpartum (n = 12) also receiving ritonavir, a potent CYP3A4 inhibitor	No significant ↑ in mean or median CL during pregnancy
Acosta et al.[36]	Ritonavir (PO)	14–31gw and postpartum (n = 12)	C_{max} ↑ 44%† and C_{min} ↓ 40%†
Kosel et al.[29]	Indinavir (PO)	Second and third trimesters (n = 4) and postpartum (n = 2)	CL ↑ 615% and 175%, respectively
Stek et al.[37]	Lopinavir (PO)	Third trimester and 6–12wk postpartum (n = 12); also receiving ritonavir	CL ↑ 149%†

a Measured 24-hour urinary 6β-hydroxycortisol : 17-hydroxycorticosteroid ratio.

b Measured 24-hour urinary 6β-hydroxycortisol : cortisol ratio.

CL = clearance; **C_{max}** = peak plasma concentration; **C_{min}** = minimum plasma concentration; **gw** = gestational weeks; **IV** = intravenous; **NA** = not applicable; **NS** = statistically nonsignificant; **PO** = oral; ↓ indicates decrease; ↑ indicates increase; **†** $p < 0.05$ vs postpartum.

Table IV. Effect of pregnancy on drugs metabolised by uridine diphosphate glucuronosyltransferase-dependent glucuronidation

Study	Drug (route of administration)	Study design	Results during pregnancy compared with postpartum or nonpregnant controls
Pennell et al.[38]	Lamotrigine (PO) monotherapy	Pre-pregnancy, first, second and third trimesters, and varied times postpartum	CL ↑ 213%, 281% and 333%, respectively†
De Haan et al.[39]	Lamotrigine (PO) monotherapy	Pre-pregnancy, 10wk intervals and varied times postpartum	CL ↑ 122%, 200%, 250%, 208%, respectively
Tran et al.[40]	Lamotrigine (PO) polytherapy with enzyme inducers	First, second and third trimesters and pre-pregnancy (n = 12)	CL ↑ 65% in the first trimester, 90% in the second and third trimesters†
Ohman et al.[41]	Lamotrigine (PO) monotherapy or polytherapy with enzyme inducers	Pre-pregnancy, at delivery and 2–3wk postpartum (n = 9)	Median CL ↑ 65% (range 0–630%). Two patients treated with carbamazepine or phenytoin had no change
Watts et al.[42]	Zidovudine (PO)	19–39gw and postpartum (n = 3)	C_{max} ↓ 10% and CL ↑ 47%
O'Sullivan et al.[43]	Zidovudine (PO)	Third trimester (n = 8) and delivery (n = 9) compared with nonpregnant controls	No effect on pharmacokinetics
Gerdin et al.[44]	Morphine (IM)	Delivery (n = 13) compared with healthy controls (n = 6)	CL ↑ 70% and $t_{½\beta}$ ↓ 43%
Tomson et al.[45]	Oxazepam (PO)	Delivery (n = 8) compared with nonpregnant controls (n = 20)	CL ↑ 160% and $t_{½\beta}$ ↓ (5–8h compared with 6–19h in nonpregnant controls)

CL = clearance; C_{max} = peak plasma concentration; **gw** = gestational weeks; **IM** = intramuscular; **PO** = oral; $t_{½\beta}$ = terminal elimination half-life; ↓ indicates decrease; ↑ indicates increase; † $p < 0.05$ vs postpartum.

trimester of pregnancy was studied in 904 Swedish women, including 164 current smokers.[71] Subjects were genotyped for *CYP1A2* alleles and also phenotyped using caffeine as a probe. Unlike healthy nonpregnant subjects where *CYP1A2**1F resulted in higher CYP1A2 inducibility by smoking,[72] the investigators found no effect of *CYP1A2* genotype on inducibility of CYP1A2 isoenzyme in pregnant women.

Approximately 90% of the metabolism of caffeine is catalysed by CYP1A2 isoenzyme.[73] As shown in table I, the $t_{½\beta}$ of caffeine is significantly longer in pregnant women than postpartum women and nonpregnant controls, returning to nonpregnant values by 1 month postpartum.[19,20] The oral clearance of caffeine was significantly decreased by 17–32 weeks gestation compared with 1 month postpartum, suggesting decreased CYP1A2 activity.[20] A more specific probe for CYP1A2 is the urinary 5-acetylamino-6-amino-3-methyluracil (AAMU) + 1-methylxanthine (1X) + 1-methyl-uric acid (1U) **:** 1,7-dimethyl-uric acid (17U) metabolic ratio after caffeine administration. Two studies have evaluated the effect of pregnancy on the caffeine urinary metabolic ratio.[21,22] Tsutsumi et al.[22] evaluated the ratio throughout all three trimesters and postpartum and found a significant decrease in CYP1A2 activity starting in the first trimester compared with postpartum. Bologa et al.[21] also found a significant decrease in CYP1A2 activity in women studied during the third trimester compared with postpartum.

Theophylline is classically characterised as a CYP1A2 substrate with minor metabolism by CYP2E1 and CYP3A4. Two studies found a nonsignificant trend towards a decrease in unbound clearance during the third trimester compared with postpartum.[74,75] Despite being a minor pathway, the increase in CYP3A4 activity (see section 3.6) during pregnancy may have offset the decrease in CYP1A2. There are no studies evaluating the effect

Table V. Effect of pregnancy on drugs eliminated unchanged by the kidneys

Study	Drug (route of administration)	Study design	Results during pregnancy compared with postpartum or nonpregnant controls
Chamberlain et al.[46]	Ampicillin (IV)	Third trimester and 6wk postpartum (n = 22)	CL ↑ 22% and $t_{1/2\beta}$ ↓ 20% (NS)
Philipson[17]	Ampicillin (IV/PO)	9–33gw and 3–12mo postpartum (n = 26)	CL and CL_R ↑ 50%†; $t_{1/2\beta}$ ↓ 12%†
Assael et al.[47]	Ampicillin (IM)	21–40gw (n = 14) and healthy controls (n = 6)	CL ↑ 79%††
Philipson and Stiernstedt[48]	Cefuroxime (IV)	11–35gw, at delivery and postpartum after termination of breastfeeding and resumption of normal menses (n = 7)	CL ↑ 42%, CL_R ↑ 37%† and $t_{1/2\beta}$ ↓ 24%
Nathorst-Boos et al.[49]	Ceftazidime (IV)	First and third trimesters, and postpartum after termination of breastfeeding (n = 12)	CL ↑ 38% and 65%, respectively
Philipson et al.[18]	Cephradine (PO/IV)	Second trimester and postpartum after termination of breastfeeding and resumption of normal menses (n = 12)	CL ↑ 39%† and $t_{1/2\beta}$ ↓ 26%†
Philipson et al.[18]	Cefazolin (IV)	Second trimester and postpartum after termination of breastfeeding and resumption of normal menses (n = 6)	CL ↑ 31%† and $t_{1/2\beta}$ ↓ 35%†
Heikkila and Erkkola[50]	Piperacillin (IV)	At delivery (n = 8) and healthy controls (n = 5)	CL ↑ 184%†† and no difference in $t_{1/2\beta}$
Heikkila et al.[51]	Mecillinam (IV)	First trimester (n = 10) compared with at term (n = 10), and healthy subjects (12)	No difference in CL; $t_{1/2\beta}$ ↑ 77% and 42%, respectively
Heikkila et al.[51]	Pivmecillinam (PO)	10–32gw (n = 6) compared with healthy controls (n = 6)	No difference in CL or $t_{1/2\beta}$
Hurst et al.[52]	Atenolol (PO)	Third trimester and 6wk postpartum (n = 10)	No difference in CL
Thorley et al.[53]	Atenolol (PO)	22–38gw (n = 11) compared with historical controls	No difference in $t_{1/2\beta}$
Hebert et al.[54]	Atenolol (PO)	Second and third trimesters and 3mo postpartum (n = 17)	CL_R ↑ 38% and 36%†; $t_{1/2\beta}$ ↓ 12% and 11%†, respectively; no difference in CL
O'Hare et al.[16]	Sotalol (PO/IV)	Third trimester and 6wk postpartum (n = 6)	CL ↑ 60%† and $t_{1/2\beta}$ ↓ 29% after IV administration; no effect on $t_{1/2\beta}$ after PO administration
Luxford and Kellaway[55]	Digoxin (PO)	Third trimester and 6–12wk postpartum (n = 15)	CL_R ↑ 21%†
Schou et al.[56]	Lithium (PO)	Third trimester and 6–7wk postpartum (n = 4)	CL ↑ 100%
Ensom and Stephenson[57]	Dalteparin sodium (SC)	Pre-pregnancy, and first, second and third trimesters (n = 9)	CL ↑ 100% in first, second and third trimesters†††
Blomback et al.[58]	Dalteparin sodium (SC)	32–35gw (n = 15) compared with historical controls (n = 12)	CL ↑ 64%
Casele et al.[59]	Enoxaparin sodium (SC)	First and third trimesters, and 6–8wk postpartum (n = 13)	CL ↑ 46% and 17%, respectively†

CL = clearance; **CL_R** = renal clearance; **gw** = gestational weeks; **IM** = intramuscular; **IV** = intravenous; **NS** = statistically nonsignificant; **PO** = oral; **SC** = subcutaneous; **$t_{1/2\beta}$** = terminal elimination half-life; ↓ indicates decrease; ↑ indicates increase; **†** $p < 0.05$ vs postpartum; **††** $p < 0.05$ vs nonpregnant controls; **†††** $p < 0.05$ vs pre-pregnancy.

of pregnancy on CYP2E1 metabolism. Two drugs that are used to treat schizophrenia and other psychiatric disorders (clozapine and olanzapine) are predominantly metabolised by CYP1A2. Neither drug has been studied during pregnancy. The caffeine data suggest that drugs metabolised by CYP1A2 will have increased unbound plasma concentrations and possibly increased pharmacological effects during pregnancy if dosages are not reduced. The decrease in CYP1A2 activity occurs early in pregnancy, suggesting a need for an approximately one-third decrease in dose initially, with a further one-half and two-thirds decrease of the pre-pregnancy dose for the second and third trimesters, respectively. *CYP1A2* genotype and smoking could be confounding factors in the effect of pregnancy on CYP1A2 activity.

3.2 CYP2A6

Nicotine is a high extraction ratio drug primarily metabolised by CYP2A6, with 70–80% converted to cotinine.[76] Cotinine is also extensively metabolised by CYP2A6. The metabolic clearance (formation clearance) to cotinine is a specific marker of CYP2A6 and is independent of hepatic blood flow.[77] Ten healthy women received single intravenous infusions of nicotine and cotinine at 16–37 gestational weeks and postpartum. The clearance of nicotine and cotinine were 60% and 140% higher, respectively, during pregnancy. The $t_{1/2}\beta$ was decreased by 50%. The CYP2A6-dependent formation clearance of cotinine was increased, on average, by 54% during the second and third trimesters of pregnancy.[78] The increase in CYP2A6 activity during the second to third trimester of pregnancy suggests that pregnant women may need higher dosages of nicotine replacement therapy during pregnancy.[78] The time course of change in CYP2A6 has not been investigated. Pregnant women were only studied in the second or third trimester, not both, and no data are available for early pregnancy. CYP2A6 contributes, to a lesser extent, to the metabolism of several other drugs.[79]

3.3 CYP2C9

Phenytoin is primarily metabolised by CYP2C9 (major pathway) and CYP2C19 (minor pathway).[80] Both CYP2C9 and CYP2C19 are polymorphically distributed. Genetic mutations in *CYP2C9* result in significantly greater impairment of phenytoin clearance than those of *CYP2C19*.[81] Owing to the routine monitoring of phenytoin concentrations, there is a significant amount of information known regarding the effects of pregnancy.[31-33,82-85] Thus, the largest amount of data regarding CYP2C9 in pregnancy evolves from phenytoin. Phenytoin apparent clearance increases during pregnancy, resulting in a decrease in both unbound and total plasma concentrations. Total plasma concentrations decrease significantly more (approximately 50–60%) than unbound (or active) plasma concentrations (approximately 20%) owing to a concurrent decrease in albumin level.[31-33] Thirty-six women with epilepsy treated with phenytoin were studied prior to pregnancy and during the first, second and third trimesters. Total plasma clearance increased immediately during the first trimester, and continued to increase in the second and third trimesters, while intrinsic or unbound plasma clearance only increased significantly during the third trimester. This suggests that dosage adjustment is only needed during the third trimester in order to maintain therapeutic unbound concentrations.[32] As with valproic acid, adjusting dosages based on total plasma concentrations would result in significantly higher dosages of phenytoin than needed. Unlike valproic acid, unbound phenytoin plasma concentrations can be routinely monitored and should be used to adjust dosages. As the teratogenicity of phenytoin has been found to be dose-dependent,[62,63] minimising unnecessary dosage increases is desirable. Major drug interactions with phenytoin have been associated with CYP2C9,

with only minor interactions associated with CYP2C19.[86] Other drugs, such as *S*-warfarin, the active isomer of racemic warfarin, that are predominantly metabolised by CYP2C9, exhibit the same inhibition spectrum as phenytoin.[86] Therefore, phenytoin should be a good marker of the effect of pregnancy on other CYP2C9 substrates. Other CYP2C9 drugs include losartan, several NSAIDs, celecoxib and the oral antidiabetic agents, glipizide and glibenclamide (glyburide). An increase in CYP2C9 activity during the third trimester will result in a decrease in plasma concentrations of other CYP2C9 substrate drugs by at least 20%. Theoretically, women who are poor metabolisers of CYP2C9 substrates should not demonstrate a pregnancy-induced effect on the clearance of CYP2C9 substrate drugs. As there is evidence that CYP2C19 activity is decreased during pregnancy (see section 3.4) and phenytoin is metabolised by both CYP2C9 (increased during pregnancy) and CYP2C19 (decreased during pregnancy), the effect on drugs that are only metabolised by CYP2C9 may be significantly greater than the effect of pregnancy on phenytoin.

3.4 CYP2C19

CYP2C19 catalyses the metabolism of proguanil to its active metabolite cycloguanil.[87,88] A study of 44 women during the third trimester and 60 days postpartum found a significant decrease in cycloguanil plasma concentrations during pregnancy, with a 63% higher proguanil **:** cycloguanil ratio.[89] The inhibitory effect of pregnancy on formation of the active metabolite was only found in the 30 women who were CYP2C19 extensive metabolisers, based on the postpartum metabolic ratio. The metabolic ratio has been shown to co-segregate with the CYP2C19-dependent mephenytoin polymorphism.[90] The result of this study was consistent with the 50% decrease in CYP2C19-dependent clearance found by the same investigators in a population study of 24 pregnant women studied ranging from 20–36 gestational weeks.[91] Proguanil is moderately protein bound (75%) and a pregnancy-induced decrease in albumin would result in an apparent increase in total clearance, not decrease. The studies with proguanil demonstrating a significant decrease in CYP2C19 activity during the late second and third trimester would suggest that plasma concentrations of other CYP2C19 substrates may increase during pregnancy if dosages are not adjusted. The proton pump inhibitors omeprazole, lansoprazole and pantoprazole, are primarily metabolised by CYP2C19. The effect of pregnancy has not been studied with these commonly used drugs. The effect of pregnancy should only occur in extensive metabolisers (homozygous and heterozygous) and not in poor metabolisers of CYP2C19 who have already decreased CYP2C19 activity.

3.5 CYP2D6

CYP2D6 is responsible for the metabolism of over 40 drugs, including many antidepressants, antiarrhythmics, analgesics and β-adrenoceptor antagonists, many commonly used during pregnancy.[92] As shown in table II, the metabolic ratio of dextromethorphan, a probe of CYP2D6, was evaluated during the third trimester and postpartum in women genotyped for *CYP2D6*.[23] The metabolic ratio was significantly reduced (53%), indicating increased CYP2D6 activity during the third trimester among the homozygous and heterozygous extensive metabolisers. An opposite trend was found in a limited number of women genotyped as poor metabolisers, suggesting a possible decrease in CYP2D6 activity during pregnancy.

The oral clearance of metoprolol, a high extraction ratio drug, was increased 4- to 5-fold during the third trimester of pregnancy compared with postpartum.[24,25] There was no difference in plasma protein binding or clearance after intravenous administration. Fluoxetine, its active metabolite norfluoxetine,

and nortriptyline are substrates of CYP2D6. The mean norfluoxetine to fluoxetine ratio was higher during the third trimester compared with postpartum. Plasma trough fluoxetine and norfluoxetine concentrations during the entire pregnancy were low compared with historical controls.[26] A similar decrease in nortriptyline plasma concentrations was found in women during the third trimester compared with postpartum.[27]

In conclusion, increased clearance due to increased CYP2D6 activity during pregnancy will result in decreased plasma drug concentrations and possibly loss of effect. At this time, there is only sufficient data during the third trimester, suggesting that doses of CYP2D6 substrate drugs may need to be increased as much as 2-fold. Unfortunately, very little is known regarding the effects that occur during the first and second trimesters. Fluoxetine and norfluoxetine are highly protein bound. Therefore, the low plasma trough concentrations reported throughout pregnancy also reflect decreased albumin level. Unbound plasma concentrations have not been determined.

3.6 CYP3A4

CYP3A is the most abundant CYP in the human liver and the gastrointestinal tract, and accounts for approximately 30% of total hepatic CYP.[93] It has the broadest substrate specificity and is involved in the metabolism of >50% of all drugs.[65] The urinary excretion of cortisol and its metabolites has been used as a nonspecific probe of CYP3A4 activity, primarily as a marker of induction. As shown in table III, the 6β-hydroxycortisol : cortisol ratio[28] and the 6β-hydroxycortisol : 17-hydroxycorticosteroid ratio were significantly increased during the second and third trimesters compared with postpartum.[29] The oral clearance of nifedipine was 4-fold higher during the third trimester compared with historical controls.[30] As nifedipine is highly protein bound (>90%) and the unbound clearance was not determined, the decreased albumin concentrations would have also contributed to the overall effect on total clearance. Total plasma concentrations of carbamazepine are decreased in pregnant women, with no effect on unbound plasma concentrations due to a decrease in protein binding.[31,33] Carbamazepine auto-induces its own metabolism and the lack of effect of pregnancy on unbound plasma clearance may be explained by the induction of CYP3A that has already occurred prior to pregnancy.

The protease inhibitors (PIs), saquinavir, ritonavir, indinavir and lopinavir, are eliminated by CYP3A4 and the drug transporter P-glycoprotein (P-gp). In mice, P-gp activity was no different in pregnant mice compared with nonpregnant mice;[94] however, there are no corresponding human studies. The studies evaluating the effect of pregnancy on the pharmacokinetics of the PIs in women with HIV infection are difficult to interpret as the women are often receiving multiple drugs, many of which are CYP3A4 inducers and/or inhibitors. The range of oral clearances of saquinavir was considerably higher during 27–34 gestational weeks than the values previously found in a nonpregnant adult population.[35,36] Similar results have been found for ritonavir, with plasma peak and trough concentrations significantly decreased during pregnancy compared with postpartum, which is consistent with an increased CYP3A4 metabolism and/or protein binding changes.[36] The AUC of oral indinavir was significantly lower during pregnancy than found with historical AUCs in nonpregnant women.[29] The effect of pregnancy on the pharmacokinetics of lopinavir was studied in women who were receiving lopinavir plus ritonavir during the third trimester and postpartum at 6–12 weeks. The average oral clearance increased during the third trimester.[37]

The studies of CYP3A4-metabolised drugs suggest that CYP3A4 activity is increased during pregnancy. As with the other CYPs, the studies are

limited by small sample size in the context of large intersubject variability; unbound plasma concentrations were not measured. As with CYP2D6, the time course of the effects throughout pregnancy has also not been studied. Therefore, it is unclear as to when dosages need to be adjusted and how much adjustment is needed. Many CYP3A4 substrates are also substrates of P-gp, and the effect of pregnancy on P-gp is not known.

3.7 Uridine Diphosphate Glucuronosyltransferases

Lamotrigine, an antiepileptic drug, is metabolised to glucuronide conjugates catalysed by UGT1A4. UGT1A4 catalyses the formation of quaternary ammonium-linked glucuronide with other substrates, including imipramine, amitriptyline, doxepin, promethazine and cyproheptadine.[95] The effect of pregnancy on the pharmacokinetics of lamotrigine has been reported in patients receiving lamotrigine monotherapy[38,39] or lamotrigine with other antiepileptic drugs, including enzyme inducers.[40,41] None of the studies evaluated unbound lamotrigine plasma concentrations. Lamotrigine is only moderately protein bound (55%), and pregnancy-induced decreases in albumin should provide only a minor contribution to changes in total clearance. As shown in table IV, pregnancy results in significant increases in clearance, starting as early as the first trimester. The increase in clearance is greater in patients receiving lamotrigine as monotherapy compared with those receiving lamotrigine polytherapy with enzyme inducing drugs (i.e. phenytoin, carbamazepine, phenobarbital [phenobarbitone]). Baseline oral clearance of lamotrigine in nonpregnant women receiving lamotrigine plus enzyme inducers is already 2- to 3-fold higher than in patients receiving monotherapy. The amount of the increase in dosage required to maintain similar pre-pregnancy lamotrigine plasma concentrations in a women receiving lamotrigine plus enzyme-inducing drugs pre-pregnancy will be less than in a women on lamotrigine monotherapy. Lamotrigine oral clearance returns to pre-pregnancy baseline by 2–3 weeks postpartum.[39,41]

Zidovudine[96] and morphine[97] are metabolised to a glucuronide conjugate by UGT2B7. For zidovudine, one study found an increased clearance in three women during the second and third trimesters and postpartum.[42] An additional study failed to find a difference using a nonpregnant population as a control.[43,98] Given the large intersubject variability in zidovudine pharmacokinetics, the studies were underpowered to demonstrate a significant effect. The clearance of morphine, a high extraction ratio drug, at the time of delivery was higher and the $t_{1/2}\beta$ shorter when compared with nonpregnant women.[44] Oxazepam is administered as a racemic mixture; *S*-oxazepam is metabolised by UGT2B15, while *R*-oxazepam is metabolised by UGT2B7 and UGT1A9.[99] At the time of delivery, oxazepam oral clearance was higher and the range of $t_{1/2}\beta$ was significantly shorter[45] than reported in 20 nonpregnant females.[100] In conclusion, of the UGT substrates evaluated, the effect of pregnancy on UGT1A4 has been well characterised, with limited data on UGT2B7.

3.8 *N*-acetyltransferase 2

Using the urinary ratio of metabolites of caffeine as a specific probe for NAT2 (AAMU : AAMU + 1X + 1U),[101] 12 nonsmoking women were studied during all three trimesters of pregnancy and 1 month postpartum. The metabolic ratio was decreased by an average of 12% only during the first trimester compared with postpartum, with no significant difference during the second and third trimesters.[22] Therefore, limited data using one probe suggest a small and possibly not clinically significant decrease in NAT2 activity during the first trimester. Substrates predominantly metabolised by NAT2 in-

clude isoniazid, procainamide, sulfasalazine, dapsone and various sulfonamides.

3.9 Proposed Mechanism of Effects of Pregnancy on the Metabolic Enzymes

3.9.1 Maternal Effects

The observational studies presented suggest that pregnancy has differential effects on the metabolic enzymes. Specifically, pregnancy increases the activity of CYP3A4, CYP2D6, CYP2C9, CYP2A6, UGT1A4 and UGT2B7, while it decreases the activity of CYP1A2 and CYP2C19. The activity of the CYP and UGT families, as well as several of the drug transporters, are regulated by a variety of nuclear receptors, including pregnane X receptor (PXR), constitutive androstane receptor (CAR), hepatic nuclear factors and the aromatic hydrocarbon receptor (AhR).[102-105] PXR and CAR regulate the expression of CYP2A, CYP2B, CYP2C and CYP3A.[103] CYP1A2 is predominately regulated by AhR.[105] Regulation of the specific UGT isoenzymes is not as well understood. PXR and CAR regulate the induction of UGT1A1 and UGT1A6.[104] AhR also has been shown to be involved in the induction of UGT1A6 and UGT1A9.[104]

Using a pregnant mouse model, Masuyama et al.[106] found that the expression of CYP3A and PXR messenger RNA (mRNA) in the liver and placenta increased 20-fold during the prenatal period. In addition, progesterone activates the PXR receptor *in vitro*.[106] Progesterone activation of the PXR receptor could be responsible for increasing the activity of CYP3A4, CYP2C9 and CYP2A6. The activity of CYP2D6 is not induced by any of the classic inducer drugs (phenobarbital, rifampicin (rifampin), β-napththoflavone), which act via CAR, PXR or AhR.[107] Therefore, the effect of pregnancy on CYP2D6 is not attributed to PXR activation.

There is evidence to suggest that increased estrogen during pregnancy may be responsible for the decrease in CYP2C19 and CYP1A2 activity as well as the increase in UGT activity. Oral contraceptives (OCs) inhibit CYP2C19 activity as shown by increased mephenytoin *S*/*R* ratio and omeprazole metabolism in women taking OCs compared with no concurrent OC use.[108] A follow-up study found that ethinylestradiol, but not levonorgestrel, was responsible for the inhibition of CYP2C19-mediated omeprazole metabolism.[109] The OC did not affect CYP2D6 activity using dextromethorphan as a probe.[110,111] However, women had slightly higher CYP2D6 activity (20%) than males, suggesting that CYP2D6 activity is hormonal regulated.[110] OC use increased the clearance (and decreased plasma concentrations) of lamotrigine,[112] several benzodiazepines that are predominantly glucuronidated, including oxazepam, lorazepam and temazepam,[113,114] and the analgesic, paracetamol (acetaminophen).[115]

The activity of CYP1A2-mediated metabolism of caffeine is inhibited by OCs containing ethinylestradiol with either levonorgestrel or gestodene[116] and hormone replacement therapy with estradiol.[117] A case report describes a women with a 2-fold increase in her clozapine plasma concentrations when an OC containing ethinylestradiol and norethisterone was added.[118] OCs decreased the clearance of theophylline by 50%.[119]

3.9.2 Fetal and Placental Effects

Both CYP and UGT isoenzymes are present in the fetus at very low levels compared with pregnant women. CYP3A7 is the predominant CYP, with low levels of CYP3A4 expression in the fetal liver.[120] CYP2C9 and CYP2C19 activity in fetus is at 1–2% of mature activity during the first trimester and reaches approximately 30% of adult values at the time of birth.[121] In a recent review of drug transfer and metabolism by the placenta, Syme et al.[122] described the presence of CYP1A1, CYP2E1, CYP3A4, CYP3A5, CYP3A7 and CYP4B1 at the level of mRNA, protein and enzyme activity early in

the first trimester. Hakkola et al.[123,124] demonstrated that the mRNA, but not protein, of several of the CYPs have been detected in the full-term placenta; however, the mRNA levels are extremely low compared with the maternal liver. The intrinsic clearance of 4-methylumbelliferone, a nonspecific substrate for several UGTs (UGT1A, UG2B7, UGT2B11, UGT2B17), ranged from 7.5% to 43% in 25 full-term placentas compared with estimates in the adult female liver.[125] It is unlikely that fetal or placental metabolism contributes significantly to the changes in CYP-catalysed drug metabolism in pregnant women. However, placental contribution to UGT-dependent metabolism may occur to a limited extent.

3.10 Hepatic Blood Flow

Using Doppler ultrasonagraphy, Nakai et al.[126] reported that total liver blood flow (Q) increased significantly after 28 weeks gestation. In contrast, Robson et al.[127] found no change in apparent liver blood flow during pregnancy using indocyanine green as a marker. Based on pharmacokinetic models of hepatic elimination,[64] an increased total liver blood flow would result in an increased clearance and decreased AUC after non-oral administration. Several high extraction ratio drugs (nicotine, cotinine, midazolam, metoprolol, morphine) have been studied during pregnancy. The clearance of nicotine and cotinine[78] (section 3.2), midazolam[34] (table III) and morphine[44] (table IV) are higher during pregnancy. The clearance of intravenous metoprolol (table II) was highly variable, with no significant change during the third trimester of pregnancy compared with postpartum.[24,25] Therefore, there is some evidence that increased total liver blood flow, in addition to decreased protein binding, may result in increased clearance and decreased concentrations of high extraction ratio drugs.

4. Renal Excretion

Renal excretion of drugs is dependent on glomerular filtration rate (GFR), active tubular secretion and/or reabsorption. In healthy women studied during each trimester and 8–12 weeks postpartum, GFR was increased approximately 50% by the first trimester and continued to increased throughout pregnancy compared with postpartum values.[128] In a series of 25 healthy women, Dunlop[129] found an 80% increase in effective renal plasma flow by the second trimester, which decreased during the third trimester.[129] Serial weekly 24-hour creatinine clearances were obtained in ten healthy pregnant women during the third trimester. A decrease in GFR during the last 3 weeks of pregnancy was found, reaching postpartum values by the last week of pregnancy.[130]

Tubular secretion and reabsorption are dependent on saturable membrane transport proteins. These include members of the organic anion transporters, organic cation transporters, P-gp, multidrug resistant-associated protein and peptide transporters (PEPT1 and PEPT2), and others.[131] There is very little known regarding the effect of pregnancy on tubular secretion and/or reabsorption. Pregnancy induces substantial changes in the renal handling of the endogenous substrates, uric acid and glucose. However, the relative importance of changes in tubular secretion and/or reabsorption has not been determined.[128] As drugs can share many of the same renal drug transporters as endogenous substrates, this suggests that transport of drugs may also be altered during pregnancy.[131] There are several studies of drugs that are excreted predominantly unchanged by the kidneys (table V). With the exception of cefazolin, all of the drugs studied had fairly low protein binding and the effect of pregnancy-induced changes in protein binding on unbound concentrations should be minimal.

As reviewed by Loebstein et al.[9] and Little,[10] the clearance of several β-lactam antibacterials

(ampicillin,[17,46,47] cefuroxime,[48] ceftazidime,[49] cephradine,[18] cefazolin[18] and piperacillin[50]) is increased during the second and/or third trimester of pregnancy compared with postpartum and/or other values obtained in nonpregnant women (table V). There was no effect of pregnancy on the clearance of mecillinam and its oral prodrug form, pivmecillinam.[51] The renal clearance of the β-lactam antibacterials exceeds GFR, which is indicative of active tubular secretion although it does not rule out tubular reabsorption processes. Based on the studies where women were studied during pregnancy and postpartum, the effect on clearance is highly variable and for most drugs ranged between 20% and 65%. As GFR increases approximately 50% during pregnancy, this suggests an effect of pregnancy on transporters that are drug specific.

For atenolol, there was no effect of pregnancy on apparent oral clearance[52-54] despite an increase in renal clearance,[54] suggesting that the highly variable oral bioavailability of atenolol may also be affected by pregnancy. The increased clearance of lithium[56] and sotalol[16] during the third trimester has been shown to result in increased dosage requirements in pregnant patients.

Digoxin is excreted unchanged by the kidneys, with both absorption and renal excretion dependent on the P-gp. Increased renal clearance did not result in decreased serum digoxin in early studies in pregnant women.[55] The effect of pregnancy on serum concentrations of digoxin is not easily interpretable from early studies[12] as the serum digoxin assays cross-reacted with endogenous digoxin-like substance that is elevated in pregnancy.[132] For the low-molecular weight heparins, dalteparin sodium[57,58] and enoxaparin sodium,[59] the increase in clearance resulted in recommendations for increased dosages to prevent reoccurrence of thrombosis during pregnancy.

If a drug were only excreted via glomerular filtration, a 50% increase in clearance would be expected. The intensive studies of creatinine clearance during the third trimester suggest that GFR is decreased immediately prior to delivery. In studies of the β-lactam antibacterials ampicillin,[46] cefuroxime,[48] and piperacillin,[50] pharmacokinetic data were obtained immediately prior to caesarean sections. Clearance was still increased at delivery compared with postpartum. There was no difference during pregnancy compared with immediately before delivery for cefuroxime. For ampicillin, the percentage increase in clearance was considerably less than found in other studies of women during the second and third trimesters, suggesting that the decrease in GFR late in pregnancy may be a contributing factor.

The effect of pregnancy on drug transport processes is unknown and may be responsible for the intersubject variability in the effect of pregnancy. Based on the data available, drugs that are predominantly renally excreted unchanged appear to require a 20–65% dosage adjustment throughout pregnancy in order to maintain pre-pregnancy concentrations.

5. Conclusion

Drugs are routinely used in pregnant women, both for the treatment of chronic conditions as well for acute conditions that occur during pregnancy. Substantial research efforts are still needed to improve the knowledge needed to adequately treat women during pregnancy.

By evaluating the pharmacokinetic data of a variety of drugs during pregnancy and using a mechanistic-based approach, we can start to predict the effect of pregnancy for a large number of clinically used drugs (see table VI). For drug interactions, we can predict that an interaction will occur, but it is difficult to determine the overall extent of the interaction. The same will be true for pregnancy-induced effects on drug pharmacokinetics. A large number of patient factors will influence the extent of the effect. Intersubject variability in the expression of

Table VI. Summary of pregnancy-induced effects on pharmacokinetics of clinically used drugs

Metabolic pathway	Drugs/probes	Effect on clearance			References
		first trimester	second trimester	third trimester	
CYP1A2	Caffeine	↓ 33%	↓ 50%	↓ 65%	19,22
CYP2A6	Nicotine Cotinine	ND	↑ 54%[a]	↑ 54%[a]	78
CYP2C9	Phenytoin	↔	↔	↑ 20%	31,33
CYP2C19	Proguanil	ND	↓ 50%	↓ 50%	89,91
CYP2D6	Dextromethorphan Metoprolol Fluoxetine Nortriptyline	ND	ND	↑ 50%	23-27
CYP3A4	Cortisol Nifedipine Saquinavir Ritonavir Lopinavir	ND	ND	↑ Variable[b]	28-30,34,35,37
UGT1A4	Lamotrigine				
	monotherapy	↑ 200%	↑ 200%	↑ 300%	38-40
	polytherapy	↑ 65%	↑ 65%	↑ 90%	
UGT2B7	Morphine Zidovudine Oxazepam	ND	ND	↑ Variable[b]	42,43,45,96-99
Renal	Ampicillin Cefuroxime Ceftazidime Cefazolin Piperacillin Atenolol Sotalol Digoxin Lithium Dalteparin sodium Enoxaparin sodium	↑ 20–65%	↑ 20–65%	↑ 20–65%	9,10,12,16-18,46-52 54-57,59,133

a Based on combined second and third trimester data. ND available on separate trimesters.

b Extent variable depending on drug studied.

CYP = cytochrome P450; **ND** = no data; **UGT** = uridine diphosphate glucuronosyltransferase; ↓ indicates decrease; ↑ indicates increase; ↔ indicates no effect.

the CYP and UGT isoenzymes will influence the fraction of the dose associated with each metabolic pathway. The activity of the enzymes is dependent on both genetic and environmental influences, including concurrent diseases and the presence of other drugs. The influence of CYP or NAT2 polymorphisms may alter the response to pregnancy-induced changes in drug clearance.

Depending on whether a drug is excreted unchanged by the kidneys or which metabolic isoenzymes are involved in its elimination will determine whether any changes in dosages are needed for pregnant women. Drugs excreted unchanged in the urine or metabolised by CYP3A4, CYP2D6 or CYP2C9 may need to have their dosages increased during pregnancy to avoid loss of efficacy. For the UGT-metabolised drugs that have been evaluated,

UGT1A4- and UGT2B7-dependent conjugation appears to be increased during pregnancy. In contrast to the other CYP isoenzymes, CYP1A2 and CYP2C19 activity appears to be decreased with pregnancy. Drugs predominantly metabolised by these enzymes may need to have their dosages decreased during pregnancy to prevent possible concentration-dependent toxicity. The effect of pregnancy on the CYP2E1 and other UGT isoenzymes has not been evaluated.

This analysis is limited by the observational nature of the available pharmacokinetic studies. Studies had mainly focused on small numbers of women in the third trimester and postpartum, with little to no data available for the early stages of pregnancy. There are a limited number of drugs studied per isoenzyme although the available data do provide an initial estimate of dose changes. There are many drugs that are eliminated by a combination of the various pathways as well as metabolism by non-UGT or non-CYP isoenzymes. In this case, an initial estimation of the effect of pregnancy on drug metabolism may be possible. For drugs that have been on the market for a long time, information on the pathways of elimination and the specific metabolic enzymes involved is often not known. In general, for the majority of new drugs there is significantly more pharmacokinetic information available prior to marketing and these data can be useful for predicting pregnancy-induced effects on dosage administration.

Clearly, more clinical, evidence-based studies are needed to fully elucidate the effects of pregnancy on the pharmacokinetics of drugs commonly used during pregnancy. Further research should focus on:

- Well designed pharmacokinetic/pharmacodynamic studies that include analysis during all three trimesters and postpartum. This would include the time to return to baseline values. Prepregnancy data are desirable; however, it is often not feasible or practical.
- Pharmacokinetic studies that include both unbound and total concentrations for drugs with high protein binding (>90%).
- For drugs excreted unchanged by the kidneys, research evaluating the role of drug transporters in both nonpregnant and pregnant populations is needed. Grouping this class of drugs together may be similar to the historical grouping of CYP substrate drugs without consideration of the CYP isoenzymes involved.

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