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Altered drug metabolism during pregnancy: Hormonal regulation of drug-metabolizing enzymes

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Abstract

Importance of the field—Medication use during pregnancy is prevalent, but pharmacokinetic information of most drugs used during pregnancy is lacking in spite of known effects of pregnancy on drug disposition. Accurate pharmacokinetic information is essential for optimal drug therapy in mother and fetus. Thus, understanding how pregnancy influences drug disposition is important for better prediction of pharmacokinetic changes of drugs in pregnant women.

Areas covered in this review—Pregnancy is known to affect hepatic drug metabolism, but the underlying mechanisms remain unknown. Physiological changes accompanying pregnancy are likely responsible for the reported alteration in drug metabolism during pregnancy. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin. This review covers how these hormones influence expression of drug-metabolizing enzymes, thus potentially responsible for altered drug metabolism during pregnancy.

What the reader will gain—The reader will gain a greater understanding of the altered drug metabolism in pregnant women and the regulatory effects of pregnancy hormones on expression of drug-metabolizing enzymes.

Take home message—In-depth studies in hormonal regulatory mechanisms as well as confirmatory studies in pregnant women are warranted for systematic understanding and prediction of the changes in hepatic drug metabolism during pregnancy.

Keywords

hormones; CYP; pregnancy; drug metabolism

1. Introduction

Medication use in pregnancy is prevalent

According to various surveys conducted in the US, over 50% of pregnant women take at least one medication, and the average number of prescriptions per patient during pregnancy ranges from 3 to 5 (excluding prenatal vitamins, iron preparations, and medications at the time of delivery) [1, 2]. Examples of drugs used in pregnancy are listed in Table 1.

Drug therapy in pregnancy plays an essential role in maternal and fetal health. For example, poorly controlled epilepsy or diabetes during pregnancy increases the risk of perinatal death

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and prematurity, as well as complications in the mother [3]. To prevent adverse outcomes, current obstetric guidelines strongly support control of symptoms by using appropriate doses of drugs that ensure drug efficacy in mothers yet minimize fetal exposure to drugs [4, 5]. However, determining the "appropriate" doses has been difficult in part due to a lack of understanding on how and why drug disposition is altered in pregnant women. Drug safety recommendations are also inadequate as information on proper dosing is lacking. Not surprisingly, for ~40% of drugs used in pregnancy, there is no evidence of safety in pregnant women (i.e., FDA pregnancy category C) [1]. Thus, there is an enormous need to better understand how pregnancy influences drug disposition. This effort would in turn advance our ability to predict pharmacokinetic changes of drugs used during pregnancy and enable optimal drug therapy in pregnant women.

2. Pharmacokinetic changes during pregnancy

Pharmacokinetic profiles of drugs are different in pregnant women as compared to non-pregnant women mostly due to altered physiology during pregnancy (reviewed in [6-9]). Down-regulation of gastrointestinal motility by progesterone leads to delayed oral absorption of high permeability drugs [10]. Major hemodynamic changes accompanying expansion of plasma volume and increases in cardiac output (up to 50%) create dilution of plasma proteins [11]. As a result, concentrations of albumin and α1-acid glycoprotein decrease up to 20-40% at term [11, 12]. This leads to decreased drug binding to plasma proteins and increased concentrations of unbound drugs. The expansion in plasma volume also increases glomerular filtration rate (GFR) and enhances renal excretion of drugs [13]. Accordingly, clearances of many renally excreted drugs have been reported to increase during pregnancy [14, 15]. For example, renal clearance of atenolol increases by 36% during pregnancy as compared to that at 3 months post-partum [16].

Pregnancy also influences factors that may determine hepatic clearance, namely protein binding of drugs, hepatic blood flow, and hepatic enzyme activity (i.e., intrinsic clearance, CL_{int}). Changes in protein binding or hepatic enzyme activity affect hepatic clearances of low hepatic extraction ratio (E_H) drugs whereas hepatic clearances of high E_H drugs are largely influenced by changes in hepatic blood flow [17]. During pregnancy, hepatic blood flow increases by 60% [18], potentially affecting hepatic clearances of high E_H drugs. Indeed, clearances of intravenously administered morphine and nicotine (high E_H drugs) are greater (by 60-70%) during pregnancy as compared to post-partum period [19, 20]. Pregnancy also increases free fraction of drugs, which may lead to increased hepatic clearances of low E_H drugs that are highly bound to plasma proteins. The higher oral clearances of valproic acid in pregnant women could be in part due to the increased free fraction of the drug during pregnancy [21]. Apparently, pregnancy also affects hepatic CL_{int} of drugs, the effects differing by enzymatic pathways. Results from clinical pharmacokinetic studies indicate clearances of drugs metabolized by selected drug metabolizing enzymes (e.g., CYP2D6 and CYP3A4) increased, whereas those of drugs metabolized by other enzymes (e.g., CYP1A2) decreased during pregnancy as compared to non-pregnant women [7, 9, 22]. The underlying mechanisms remain mostly unknown.

3. Hepatic drug metabolism

Various drug-metabolizing enzymes (DMEs) mediate hepatic drug metabolism, and expression and activity levels of these enzymes determine CL_{int} of drugs. To date, among 18 CYP families that have been identified in humans, enzymes in three CYP families (CYP1, CYP2, and CYP3) are responsible for most phase I reactions. CYP3A (CYP3A4 and CYP3A5) and CYP2C (CYP2C8, CYP2C9, CYP2C18, and CYP2C19) are the most abundant subfamilies in the liver, accounting for 30% and 20%, respectively, of the total

amount of hepatic CYP [23]. Other isoforms are minor contributors to hepatic CYP expression: CYP1A2 (13%), CYP2E1 (7%), CYP2A6 (4%), CYP2D6 (2%), and CYP2B6 (0.4%) [23]. On the other hand, glucuronidation mediated by UDP-glucuronosyltransferases (UGTs) is the major pathway of phase II reactions [24]. UGT1A and UGT2B subfamilies are mainly responsible for hepatic glucuronidation of drugs. UGT isoforms expressed in the liver include UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, and UGT2B15.

Various factors (exogenously administered drugs or endogenous small molecules) that affect expression and/or activity levels of DMEs may alter CL_{int} of drugs. Hepatic drug metabolism can be impaired by direct inhibition of enzyme activity, either by reversible or irreversible binding of inhibitors to the enzymes [25]. On the other hand, expression of DME genes can be enhanced by a variety of transcriptional regulatory mechanisms, consequently leading to increased protein expression of the enzymes and enhanced drug metabolism [26, 27]. As shown in Fig. 1, the known regulatory pathways involve a basic helix-loop-helix transcription factor (aryl hydrocarbon receptor; AhR) or transcriptional regulators belonging to nuclear receptor family (constitutive androstane receptor, CAR; pregnane X receptor, PXR; estrogen receptor, ER). These transcriptional regulators act in a similar fashion: binding of cognate ligand (inducer) activates the transcriptional regulators, triggering homo- or hetero-dimerization and nuclear translocation of the transcriptional complex. Each complex binds to their specific DNA-binding sequences in the upstream regulatory region of target genes and promotes transcription [28]. Shown in Table 2 are CYP genes whose expression is regulated by above-mentioned transcription factors. In reality, actions of these transcription factors show significant functional redundancy. Many DME genes whose expression is induced by PXR activation (e.g., CYP2B6, CYP2C9 and CYP3A4) are also up-regulated by CAR activation although the magnitude of induction varies [29, 30]. This suggests that the overall expression level of individual CYP genes is determined by net effects of multiple regulatory factors.

4. Altered drug metabolism during pregnancy

Results from clinical pharmacokinetic studies suggest that pregnancy influences drug metabolism in a metabolic enzyme-specific manner. Elimination rates of drugs metabolized by UGT1A4, UGT2B7, CYP2A6, CYP2C9, CYP2D6 and CYP3A4 are increased, whereas those of CYP1A2 and CYP2C19 substrate drugs are decreased (Table 3) [7, 9, 22].

Underlying mechanisms for the changes in drug metabolism during pregnancy remain largely unknown. Most likely, however, physiological changes accompanying pregnancy are responsible for the altered drug metabolism, examples being rising concentrations of various hormones in maternal blood (Table 4). Effects of these hormones on hepatic drug metabolism, especially at concentrations attained during human pregnancy, are mostly unknown. Yet, accumulating evidence from various *in vitro* studies suggests that these hormones are capable of modulating expression and/or activity of certain drug-metabolizing enzymes.

4.1. Female hormones

Plasma concentrations of female hormones, consisting of different estrogens (Fig. 2) and progesterone, rise steadily until they peak at term in pregnant women. Estradiol and progesterone levels reach 0.1 and 1 μM at term (100-fold higher as compared to pre-pregnancy levels), respectively [31], while concentrations of estrone and estriol reach ~30 nM at term (as compared to 0.1-1 nM in nonpregnant women). Also, concentration of estetrol, an endogenous estrogen that is exclusively produced by the fetal liver [32], rises in maternal blood.

Female hormones at high concentrations influence hepatic DME expression by activating nuclear receptors [33, 34]. Estradiol up-regulates UGT1A4 expression by ERα activation and progesterone up-regulates UGT1A1 expression by PXR activation [33, 34]; these results provide a mechanistic basis for the elevated oral clearances of lamotrigine and labetalol, respectively, in pregnancy. In addition, estradiol up-regulates expression of CYP2A6, CYP2B6, and CYP3A4 and down-regulates CYP1A2 expression in human hepatocytes [35]. These *in vitro* observations are in part similar to the reported clinical changes in pregnancy (Table 3), suggesting that for certain CYP enzymes female hormones are potentially responsible for the altered drug metabolism during pregnancy. The up-regulation of CYP2A6 and CYP2B6 expression by estradiol is likely mediated by activation of ERα and CAR, respectively. Estrogen response elements where ERα binds have been identified in upstream regulatory region of CYP2A6 gene [36], and estrogens have been reported to activate CAR in mouse and human hepatocytes [37, 38]. Considering that nuclear receptors such as PXR and CAR are involved in up-regulation of expression of many DME genes, activation of these receptors by female hormones may play an important role in altered drug metabolism during pregnancy.

4.1.1. Other estrogens—Estriol, estrone, and estetrol were considered as “estradiol with lower potency” due to their lower binding affinity to ERα compared to estradiol [39, 40]. However, several studies show that these estrogens are as potent as estradiol in mediating certain biological functions. Estetrol induces endometrial proliferation to a comparable extent as estradiol valerate in women administered with same doses [41]. Estrone is as potent as estradiol in activating extracellular-regulated kinase (ERK) in rat pituitary tumor cells [42] and also in activating CAR in mouse hepatocytes [37]. Concentrations of these other estrogens all increase during pregnancy, and this may potentially exert additive effects on CYP expression, exhibiting greater changes in drug metabolism than expected from estradiol only.

4.1.2. Concentration-dependent hormonal effects—Biological functions of estrogen and progesterone show concentration-dependency. Interestingly, the concentration profiles of hormonal effects vary depending on the function (or target tissue). Typical EC_{50} (hormone concentration resulting in 50% of the maximal effect) values for ERα-mediated up-regulation of estradiol target gene expression are within 0.01-0.1 nM [43]; however, EC_{50} values as high as 100 nM have been reported for certain biological functions of estradiol, such as increased permeability of human cervical epithelia or modulation of NF-κB signaling in human T cells [44, 45]. Similarly, EC_{50} values of progesterone actions may vary from 1 nM to 1 μM [33, 46].

How CYP expression is influenced by different concentrations of estradiol and progesterone remains to be determined. This information would be clinically relevant because circulating hormonal concentration is influenced by various factors, such as gestational age, parity, or ethnicity [31, 47-49]. Progesterone levels are notably higher in African-American compared with Caucasian or Hispanic women [48]. Also, women during their first pregnancy have substantially higher levels of estradiol compared to women who previously had at least one full-term pregnancy [49]. Clear defining of the hormonal effects on drug metabolism should help us identify sources of pharmacokinetic variability (such as age, parity, and race) during pregnancy.

4.1.3. Combined effects of female hormones—During pregnancy, the concentrations of both estrogen and progesterone rise, which can potentially lead to additive, synergistic or antagonistic effects of these hormones on CYP expression. The combined effects of estrogen and progesterone on normal physiological functions have been previously reported, which vary depending on target tissues. In the brain, estrogen and progesterone work

synergistically for neuroprotection [50]. In endometrium, progesterone antagonizes estrogen action by repressing endometrial hyperplasia caused by estrogen [51]. In HepG2 cells, progesterone represses estrogen-mediated CAR transactivation [37]. Combined effects (synergistic, antagonistic, or additive) of female hormones on expression of DME genes remain to be determined.

4.1.4. Supporting clinical evidence—Accumulating data suggest that female hormones (estrogen and progesterone) modulate expression of major DME, potentially responsible for the altered drug metabolism during pregnancy. Several lines of clinical evidence further support this notion. For example, the directional changes in drug metabolism are same between pregnant women and estrogen-based oral contraceptive users for UGT1A4, CYP1A2, CYP2A6, and CYP2C19 substrate drugs [9, 52]. Also, changes in hepatic drug metabolism are comparable between pregnant women and postmenopausal women on hormone replacement therapy for CYP1A2 substrates [53]. Lastly, elimination rates of CYP2A6, CYP2B6, and CYP3A4 substrate drugs are faster in females than in males whereas those of CYP1A2 substrate drugs are slower in females [22, 54, 55]. Taken together, the roles of female hormones in altered drug metabolism during pregnancy appear significant although further studies are needed to dissect the differential (or combined) effects of various female hormones on CYP expression and confirm these findings in *in vivo* systems.

4.2. Human placental lactogen (hPL) and placental growth hormone (PGH)

These hormones belong to growth hormone (GH) family which also includes native GH secreted from pituitary [56]. During pregnancy, levels of native GH decrease but those of other GH-like hormones, i.e., human placental lactogen (hPL) and placental growth hormone (PGH), rise dramatically (30 and 100-folds respectively for hPL and PGH) [31]. hPL and PGH are involved in provision of fetal nutrition by regulating maternal metabolism, e.g., promotion of lipolysis in adipose tissues [31, 56]. The effects of PL and PGH on hepatic drug metabolism are largely unknown. Yet, they likely resemble the effects of native GH on CYP expression, based on their 93 to 99% amino acid sequence homology to native GH [56].

GH is known to influence expression of hepatic DME. Different temporal patterns of plasma GH contribute to sexually dimorphic expression of CYP and other hepatic genes in rats and mice [57, 58]. This is attributed to the effects of differential GH-release patterns on activities of signal transducer and activator of transcription (STAT) 5b and hepatic nuclear factor (HNF) 4α. For example, a pulsatile release of GH and subsequent activation of STAT5b are responsible for male-specific expression of CYP2C11 in rats [59], and liver-specific loss of HNF4α expression in mice leads to down-regulation of male-specific Cyp genes [60]. In humans, gender differences in expression of major CYP enzymes are not as dramatic as in rats [61], rendering the effects of GH on human CYP expression questionable. Yet, in human hepatocytes, native GH was shown to increase CYP3A4 mRNA expression by 9-fold while not affecting mRNA levels of CYP1A2, CYP2C9, and CYP2E1 [62]. Results from clinical studies also indicate that GH replacement increases CYP3A4 activity in GH-deficient boys [63] and adults [64]; the continuous release pattern GH of females was found to be responsible for the increased CYP3A4 activity in GH-deficient adults [65]. Conflicting data have also been reported; in a study conducted in healthy elderly men, GH exerted no effects on CYP3A4 activity while inducing CYP1A2 and inhibiting CYP2C9 activity [66]. This discrepancy is in part due to the differences in GH dosages used in different studies (physiologic replacement vs. pharmacologic doses) and potential effects of GH deficiency on baseline CYP expression [63]. Taken together, the effects of GH on CYP expression in humans vary and appear rather complex, but existing data strongly suggest that rising

concentration of GH may affect hepatic drug metabolism. It remains to be determined whether and how hPL and PGH, the GH-like hormones, influence CYP expression and hepatic drug metabolism in pregnant women.

4.3. Prolactin

Prolactin is secreted mainly from pituitary gland as native GH is. Prolactin shares similar tertiary protein structure with GH, which is believed to have evolved from a same protein family over millions of years [67]. During pregnancy, the maternal plasma concentrations of prolactin increase gradually until they peak at term (10-fold increase as compared to pre-pregnancy levels) [68]. The higher prolactin level during pregnancy stimulates the mammary glands to produce milk. In addition, prolactin exerts biological functions in various organs and is involved in osmoregulation, growth, reproduction, immunoregulation, and behavior [67]. After delivery, the prolactin concentrations remain elevated and fall gradually toward the pre-pregnancy levels during a 3- to 4-week interval in non-lactating mothers [68]. In lactating mothers, however, prolactin levels remain elevated and increase with each nursing episode [68].

Prolactin has shown to regulate expression of various hepatic DME. In rats, lactation was shown to increase glutathione conjugation [69] and glucuronidation of *p*-nitrophenol [70], which was attributed to the increased prolactin levels during lactation. Indeed, administration of ovine prolactin in ovariectomized rats led to increased glucuronidation of *p*-nitrophenol [71], potentially by up-regulating expression of UGT1A6 and glutathione S-transferase (m-class subunits) [69, 72]. Ovine prolactin also up-regulates hepatic Na-taurocholate cotransporting polypeptide (Ntcp) by facilitating Stat5 binding to Ntcp promoter region [73, 74]. This leads to increased bile secretary function in post partum lactating rats [75]. These results indicate diverse regulatory roles of prolactin in determining expression of hepatic genes including DME. Direct extrapolation of the animal data to humans, however, would require a caution because prolactin shows considerable species variation in amino acid sequence and protein structure [67], which may in turn lead to different biological functions. Thus, how human prolactin affects expression of major DME needs to be examined to determine its role in altering drug metabolism during pregnancy.

4.4. Cortisol

Cortisol in plasma is mostly bound to corticosteroid-binding globulin (CBG) (75%) and to a lesser extent to albumin (15%) [76]. In pregnancy, plasma levels of CBG rise about 2-fold as compared to nonpregnant women [77], which increases concentrations of total cortisol. Concentrations of biologically active, free cortisol are also elevated to 20-30 μg/dL (0.5-0.8 μM), partly due to marked increase in corticotropin-releasing hormone (CRH) during pregnancy [76-78]. This free cortisol concentration is about 3-fold higher than that in non-pregnant women.

The effects of corticosteroids on CYP expression and hepatic drug metabolism have been extensively studied. Corticosteroids (e.g., dexamethasone) induce CYP expression in a concentration-dependent manner by activating glucocorticoid receptor (GR, at nM concentration range) or PXR (at > 10 μM concentration) [79-81]. At physiological nanomolar concentrations, GR activated by corticosteroids induces CYP expression indirectly, by potentiating the inducing effects of xenobiotics. Corticosteroids increase the expression levels of nuclear receptors including CAR and PXR [82, 83] so that CYP induction by xenobiotics can be enhanced. Corticosteroids also increase trans-activation of CAR and PXR with coactivators such as glucocorticoid receptor interacting protein 1 (GRIP1) [84]. This again leads to potentiation of nuclear receptor activation.

In pregnant women, the higher concentrations of cortisol likely enhance activation of GR, leading to up-regulation of CAR and PXR expression. This may in turn potentiate the induction of CYP expression by other endogenous hormones such as GH-like hormones or female hormones (estrogen and progesterone). For example, CAR-mediated activation of CYP2B6 by estrogens may be further enhanced by increased expression of CAR by the higher cortisol levels during pregnancy. Although further confirmatory studies are needed, this appears to provide additional potential mechanism underlying the increased elimination of substrates for PXR or CAR target genes, e.g., CYP2C9 and CYP3A4, in pregnant women [9].

5. Effects of pregnancy on drug metabolism in animals

The effects of pregnancy on hepatic drug metabolism have been extensively examined in rodents (Table 5) [55, 72, 85-90]. The studies in mice are limited to enzymes in Cyp3a subfamily, and the results show that pregnancy has Cyp3a isoform-specific effect on Cyp expression. In rats, pregnancy generally decreases CYP contents and activities, as well as mRNA or protein expression of many DME, per gram rat liver. For example, protein expression levels of UGT and mRNA expression of many CYP genes are down-regulated during pregnancy [72, 89], consistent with the decreased DME activities in rats. Interestingly however, the decreased enzyme activity is often compensated by enlarged liver during pregnancy (50-60% increased as compared to the size at pre-conception) [91]. As a result, the extent of hepatic drug metabolism may stay unchanged in pregnant rats. For example, biphenyl-4-hydroxylase activity per gram liver was 30% lower in pregnant rats as compared to non-pregnant controls, but after adjustment for liver size, the drug-metabolizing enzyme activities (i.e., the enzyme activity per liver) were similar between the pregnant and non-pregnant rats [87]. The mechanisms underlying the liver enlargement in rat pregnancy remain unknown. In humans, such dramatic increases in liver size do not occur during pregnancy [92], suggesting that the results in rats may not be extrapolated to humans. In addition, for most CYP pathways the directional changes shown during rat pregnancy do not correspond to those reported in pregnant women. For instance, CYP1A activity (or expression) was reported to decrease in human pregnancy while the marker activity (ethoxyresorufin-O-deethylation) increased in pregnant rats [85]. In addition to the effects of pregnancy on liver size, other inter-species differences in pregnancy-related physiology may contribute to the discrepancy. For example, the rise in estrogen or progesterone concentrations in blood is less than 5-fold in rat pregnancy [93, 94] compared to the ~100-fold increase in humans. Moreover, inter-species differences in regulation of CYP expression and activities are well-known to be significant between rodents and humans [95]. Information regarding how pregnancy influences hepatic drug metabolism in other animals is uncommon.

6. Conclusion

Pregnancy affects the extent of hepatic drug metabolism in humans. The underlying mechanisms remain unknown, but physiological changes accompanying pregnancy are likely responsible for the reported alteration in drug metabolism during pregnancy. These changes include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin. The hormones are known to exert regulatory effects on expression of DME, suggesting that rising hormonal concentrations during pregnancy are potentially responsible for the altered drug metabolism. Better understanding of the regulatory mechanisms underlying the hormonal effects on expression and/or activity of DME is warranted, which would help advance our abilities to predict pharmacokinetic changes of drugs in pregnant women.

7. Expert opinion

Medical conditions in the mother, such as diabetes or epilepsy, can adversely affect the health of both the mother and fetus. These conditions need to be treated with the lowest effective doses of drugs. However, defining treatment regimens has been difficult due to a lack of pharmacokinetic information on drugs used in pregnancy. This uncertainty may lead to delayed drug treatment in pregnant women and detrimental clinical outcomes. Clear understanding of altered drug disposition during pregnancy is thus necessary for development of optimal dosing strategies in pregnant women.

Mechanistic understanding of drug disposition has advanced our ability to predict and prevent adverse events, such as drug-drug interactions. For example, elucidation of the PXR-mediated regulatory mechanisms for CYP expression established PXR ligands as potential perpetrators of drug interactions and assisted in predicting pharmacokinetic changes of drugs co-administered with PXR ligands. Similarly, for prediction of pharmacokinetic changes for individual drugs used during pregnancy, it would be necessary to identify and investigate the responsible factors affecting hepatic drug disposition.

Rising hormonal concentrations in maternal blood are potentially responsible for the altered hepatic drug metabolism during pregnancy. Accumulating *in vitro* evidence suggests that certain pregnancy hormones (such as female hormones, GH-like hormones, and cortisol) are capable of modulating CYP expression; however, confirmatory studies or in-depth mechanisms studies are still lacking. Also, there is a lack of knowledge on whether and how other pregnancy hormones (such as aldosterone) can influence drug disposition, potentially leading to altered pharmacokinetics of drugs in pregnancy. Thus, more studies are needed to determine and characterize the effects of pregnancy hormones on hepatic drug metabolism.

Pregnancy is a complex physiological system. Extensive mechanistic studies and correlative analysis of *in vitro* and *in vivo* data are required for accurate prediction of pharmacokinetic changes in pregnancy. Results obtained from the above studies can serve as groundwork for development of a predictive model, which may ultimately incorporate effects of multiple physiological changes in pregnancy on hepatic drug metabolism. Collectively, these efforts will improve our ability to optimize drug treatment in pregnant women and enhance women's health.

Abbreviations

CYP	cytochrome P450
UGT	UDP-glucuronosyltransferase
AhR	Aryl hydrocarbon receptor
CAR	constitutive androstane receptor
PXR	prengane X receptor
ER	estrogen receptor

Bibliography

1. Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. Am J Obstet Gynecol. 2004; 191(2):398–407. [PubMed: 15343213]
2. Glover DD, Amonkar M, Rybeck BF, et al. Prescription, over-the-counter, and herbal medicine use in a rural, obstetric population. Am J Obstet Gynecol. 2003; 188(4):1039–45. [PubMed: 12712107]

3. Tatum, WOt; Liporace, J.; Benbadis, SR., et al. Updates on the treatment of epilepsy in women. Arch Intern Med. 2004; 164(2):137–45. [PubMed: 14744836]
4. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. Obstet Gynecol. 2006; 107(5):1120–38. [PubMed: 16648419]
5. Dombrowski MP, Schatz M. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists number 90, February 2008: asthma in pregnancy. Obstet Gynecol. 2008; 111(2 Pt 1):457–64. [PubMed: 18238988]
6. Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. Jama. 2005; 294(21): 2751–7. [PubMed: 16333011]
7. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. Clin Pharmacokinet. 2005; 44(10):989–1008. [PubMed: 16176115] • Review of altered drug disposition during pregnancy
8. Dawes M, Chowienczyk PJ. Drugs in pregnancy. Pharmacokinetics in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2001; 15(6):819–26. [PubMed: 11800526]
9. Hodge LS, Tracy TS. Alterations in drug disposition during pregnancy: implications for drug therapy. Expert Opin Drug Metab Toxicol. 2007; 3(4):557–71. [PubMed: 17696806] • Review of altered drug disposition during pregnancy
10. Best BM, Mirochnick M, Capparelli EV, et al. Impact of pregnancy on abacavir pharmacokinetics. AIDS. 2006; 20(4):553–60. [PubMed: 16470119]
11. Notarianni LJ. Plasma protein binding of drugs in pregnancy and in neonates. Clin Pharmacokinet. 1990; 18(1):20–36. [PubMed: 2178848]
12. Israili ZH, Dayton PG. Human alpha-1-glycoprotein and its interactions with drugs. Drug Metab Rev. 2001; 33(2):161–235. [PubMed: 11495502]
13. Baylis C. Glomerular ultrafiltration in the pseudopregnant rat. Am J Physiol. 1982; 243(3):F300–5. [PubMed: 7114260]
14. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. Clin Pharmacokinet. 1997; 33(5):328–43. [PubMed: 9391746]
15. Little BB. Pharmacokinetics during pregnancy: evidence-based maternal dose formulation. Obstet Gynecol. 1999; 93(5 Pt 2):858–68. [PubMed: 10912434]
16. Hebert MF, Carr DB, Anderson GD, et al. Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum. J Clin Pharmacol. 2005; 45(1):25–33. [PubMed: 15601802]
17. Rowland, M.; Tozer, TN. Clinical pharmacokinetics: concepts and applications. 2 nd ed.. Lea & Febiger; hiladelphia: 1989.
18. Nakai A, Sekiya I, Oya A, et al. Assessment of the hepatic arterial and portal venous blood flows during pregnancy with Doppler ultrasonography. Arch Gynecol Obstet. 2002; 266(1):25–9. [PubMed: 11998960]
19. Dempsey D, Jacob P 3rd, Benowitz NL. Accelerated metabolism of nicotine and cotinine in pregnant smokers. J Pharmacol Exp Ther. 2002; 301(2):594–8. [PubMed: 11961061]
20. Gerdin E, Salmonson T, Lindberg B, et al. Maternal kinetics of morphine during labour. J Perinat Med. 1990; 18(6):479–87. [PubMed: 2097341]
21. Pennell PB. Antiepileptic drug pharmacokinetics during pregnancy and lactation. Neurology. 2003; 61(6 Suppl 2):S35–42. [PubMed: 14504308]
22. Anderson GD. Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. J Womens Health (Larchmt). 2005; 14(1):19–29. [PubMed: 15692274]
23. Shimada T, Yamazaki H, Mimura M, et al. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. J Pharmacol Exp Ther. 1994; 270(1):414–23. [PubMed: 8035341]
24. Tukey RH, Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. Annu Rev Pharmacol Toxicol. 2000; 40:581–616. [PubMed: 10836148]

25. Hollenberg PF. Characteristics and common properties of inhibitors, inducers, and activators of CYP enzymes. Drug Metab Rev. 2002; 34(1-2):17–35. [PubMed: 11996009]
26. Honkakoski P, Negishi M. Regulation of cytochrome P450 (CYP) genes by nuclear receptors. Biochem J. 2000; 347(Pt 2):321–37. [PubMed: 10749660]
27. Urquhart BL, Tirona RG, Kim RB. Nuclear receptors and the regulation of drug-metabolizing enzymes and drug transporters: implications for interindividual variability in response to drugs. J Clin Pharmacol. 2007; 47(5):566–78. [PubMed: 17442683]
28. Honkakoski P, Zelko I, Sueyoshi T, et al. The nuclear orphan receptor CAR-retinoid X receptor heterodimer activates the phenobarbital-responsive enhancer module of the CYP2B gene. Mol Cell Biol. 1998; 18(10):5652–8. [PubMed: 9742082]
29. di Masi A, Marinis ED, Ascenzi P, et al. Nuclear receptors CAR and PXR: Molecular, functional, and biomedical aspects. Mol Aspects Med. 2009
30. Dixit SG, Tirona RG, Kim RB. Beyond CAR and PXR. Curr Drug Metab. 2005; 6(4):385–97. [PubMed: 16101576]
31. Cunningham, FG. Williams obstetrics. 21st ed.. McGraw-Hill Medical Publishing Division; New York: 2001.
32. Holinka CF, Diczfalusy E, Coelingh Bennink HJ. Estetrol: a unique steroid in human pregnancy. J Steroid Biochem Mol Biol. 2008; 110(1-2):138–43. [PubMed: 18462934]
33. Jeong H, Choi S, Song JW, et al. Regulation of UDP-glucuronosyltransferase (UGT) 1A1 by progesterone and its impact on labetalol elimination. Xenobiotica. 2008; 38(1):62–75. [PubMed: 18098064]
34. Chen H, Yang K, Choi S, et al. Upregulation of UDP-glucuronosyltransferase (UGT) 1A4 by 17{beta}-Estradiol: a Potential Mechanism of Increased Lamotrigine Elimination in Pregnancy. Drug Metab Dispos. 2009
35. Koh K, Jeong H. Effects of 17β-estradiol (E2) on expression of CYP enzymes in human hepatocytes. Drug Metabolism Reviews. 2009; 41(Suppl. 3):49.
36. Higashi E, Fukami T, Itoh M, et al. Human CYP2A6 is induced by estrogen via estrogen receptor. Drug Metab Dispos. 2007; 35(10):1935–41. [PubMed: 17646279]
37. Kawamoto T, Kakizaki S, Yoshinari K, et al. Estrogen activation of the nuclear orphan receptor CAR (constitutive active receptor) in induction of the mouse Cyp2b10 gene. Mol Endocrinol. 2000; 14(11):1897–905. [PubMed: 11075820]
38. Yang K, Koh K, Choi S, et al. CAR (constitutive androstane/active receptor)-mediated up-regulation of CYP2B6 expression by 17 b-estradiol. Drug Metab Rev. 2009; 41(Suppl. 3):89. [PubMed: 19514967]
39. Korenman SG. Comparative binding affinity of estrogens and its relation to estrogenic potency. Steroids. 1969; 13(2):163–77. [PubMed: 5773887]
40. Martucci C, Fishman J. Uterine estrogen receptor binding of catecholestrogens and of estetrol (1,3,5(10)-estratriene-3,15alpha,16alpha,17beta-tetrol). Steroids. 1976; 27(3):325–33. [PubMed: 178074]
41. Visser M, Coelingh Bennink HJ. Clinical applications for estetrol. J Steroid Biochem Mol Biol. 2009; 114(1-2):85–9. [PubMed: 19167495]
42. Watson CS, Jeng YJ, Kochukov MY. Nongenomic actions of estradiol compared with estrone and estriol in pituitary tumor cell signaling and proliferation. FASEB J. 2008; 22(9):3328–36. [PubMed: 18541692]
43. Ekena K, Katzenellenbogen JA, Katzenellenbogen BS. Determinants of ligand specificity of estrogen receptor-alpha: estrogen versus androgen discrimination. J Biol Chem. 1998; 273(2):693–9. [PubMed: 9422719]
44. Gorodeski GI, Pal D. Involvement of estrogen receptors alpha and beta in the regulation of cervical permeability. Am J Physiol Cell Physiol. 2000; 278(4):C689–96. [PubMed: 10751318]
45. Hirano S, Furutama D, Hanafusa T. Physiologically high concentrations of 17 beta-estradiol enhance NF-kappaB activity in human T cells. Am J Physiol Regul Integr Comp Physiol. 2007; 292(4):R1465–71. [PubMed: 17194723]
46. Attardi BJ, Zeleznik A, Simhan H, et al. Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alpha hydroxyprogesterone

caproate, and related progestins. Am J Obstet Gynecol. 2007; 197(6):599 e1–7. [PubMed: 18060946]

47. Thomas HV, Murphy MF, Key TJ, et al. Pregnancy and menstrual hormone levels in mothers of twins compared to mothers of singletons. Ann Hum Biol. 1998; 25(1):69–75. [PubMed: 9483208]
48. Potischman N, Troisi R, Thadhani R, et al. Pregnancy hormone concentrations across ethnic groups: implications for later cancer risk. Cancer Epidemiol Biomarkers Prev. 2005; 14(6):1514–20. [PubMed: 15941965]
49. Arslan AA, Zeleniuch-Jacquotte A, Lukanova A, et al. Effects of parity on pregnancy hormonal profiles across ethnic groups with a diverse incidence of breast cancer. Cancer Epidemiol Biomarkers Prev. 2006; 15(11):2123–30. [PubMed: 17119037]
50. Nilsen J, Brinton RD. Impact of progestins on estrogen-induced neuroprotection: synergy by progesterone and 19-norprogesterone and antagonism by medroxyprogesterone acetate. Endocrinology. 2002; 143(1):205–12. [PubMed: 11751611]
51. Moyer DL, Felix JC. The effects of progesterone and progestins on endometrial proliferation. Contraception. 1998; 57(6):399–403. [PubMed: 9693400]
52. Anderson GD. Gender differences in pharmacological response. Int Rev Neurobiol. 2008; 83:1–10. [PubMed: 18929073]
53. O'Connell MB, Frye RF, Matzke GR, et al. Effect of conjugated equine estrogens on oxidative metabolism in middle-aged and elderly postmenopausal women. J Clin Pharmacol. 2006; 46(11): 1299–307. [PubMed: 17050794]
54. Lamba V, Lamba J, Yasuda K, et al. Hepatic CYP2B6 expression: gender and ethnic differences and relationship to CYP2B6 genotype and CAR (constitutive androstane receptor) expression. J Pharmacol Exp Ther. 2003; 307(3):906–22. [PubMed: 14551287]
55. Zhang H, Wu X, Wang H, et al. Effect of pregnancy on cytochrome P450 3a and P-glycoprotein expression and activity in the mouse: mechanisms, tissue specificity, and time course. Mol Pharmacol. 2008; 74(3):714–23. [PubMed: 18509067] • Review of sex differences in DME expression
56. Fuglsang J, Ovesen P. Aspects of placental growth hormone physiology. Growth Horm IGF Res. 2006; 16(2):67–85. [PubMed: 16632396]
57. Waxman DJ, Connor C. Growth hormone regulation of sex-dependent liver gene expression. Mol Endocrinol. 2006; 20(11):2613–29. [PubMed: 16543404]
58. Waxman DJ, Holloway MG. Centennial Perspective: Sex Differences in the Expression of Hepatic Drug Metabolizing Enzymes. Mol Pharmacol. 2009
59. Thangavel C, Garcia MC, Shapiro BH. Intrinsic sex differences determine expression of growth hormone-regulated female cytochrome P450s. Mol Cell Endocrinol. 2004; 220(1-2):31–9. [PubMed: 15196697]
60. Holloway MG, Miles GD, Dombkowski AA, et al. Liver-specific hepatocyte nuclear factor-4alpha deficiency: greater impact on gene expression in male than in female mouse liver. Mol Endocrinol. 2008; 22(5):1274–86. [PubMed: 18276827]
61. Dhir RN, Dworakowski W, Thangavel C, et al. Sexually dimorphic regulation of hepatic isoforms of human cytochrome p450 by growth hormone. J Pharmacol Exp Ther. 2006; 316(1):87–94. [PubMed: 16160083]
62. Liddle C, Goodwin BJ, George J, et al. Separate and interactive regulation of cytochrome P450 3A4 by triiodothyronine, dexamethasone, and growth hormone in cultured hepatocytes. J Clin Endocrinol Metab. 1998; 83(7):2411–6. [PubMed: 9661620]
63. Sinues B, Mayayo E, Fanlo A, et al. Effects of growth hormone deficiency and rhGH replacement therapy on the 6beta-hydroxycortisol/free cortisol ratio, a marker of CYP3A activity, in growth hormone-deficient children. Eur J Clin Pharmacol. 2004; 60(8):559–64. [PubMed: 15365655]
64. Cheung NW, Liddle C, Coverdale S, et al. Growth hormone treatment increases cytochrome P450-mediated antipyrine clearance in man. J Clin Endocrinol Metab. 1996; 81(5):1999–2001. [PubMed: 8626872]
65. Jaffe CA, Turgeon DK, Lown K, et al. Growth hormone secretion pattern is an independent regulator of growth hormone actions in humans. Am J Physiol Endocrinol Metab. 2002;

283(5):E1008–15. [PubMed: 12376329] • Clinical examiniation of the effects of GH pulsatility on CYP expression

66. Jurgens G, Lange KH, Reuther LO, et al. Effect of growth hormone on hepatic cytochrome P450 activity in healthy elderly men. Clin Pharmacol Ther. 2002; 71(3):162–8. [PubMed: 11907490]
67. Forsyth IA, Wallis M. Growth hormone and prolactin--molecular and functional evolution. J Mammary Gland Biol Neoplasia. 2002; 7(3):291–312. [PubMed: 12751893]
68. Creasy, RK.; Resnik, R.; Iams, JD. Maternal-fetal medicine: principles and practice. 5th ed.. Saunders; Philadelphia, Pa.: 2004.
69. Luquita MG, Catania VA, Sanchez-Pozzi EJ, et al. Prolactin increases the hepatic content of mu-class subunits of glutathione S-transferase in the rat. Drug Metab Dispos. 1999; 27(1):122–4. [PubMed: 9884320]
70. Luquita MG, Sanchez Pozzi EJ, Catania VA, et al. Analysis of p-nitrophenol glucuronidation in hepatic microsomes from lactating rats. Biochem Pharmacol. 1994; 47(7):1179–85. [PubMed: 8161347]
71. Luquita MG, Catania VA, Sanchez-Pozzi EJ, et al. Ovine prolactin increases hepatic UDP-glucuronosyltransferase activity in ovariectomized rats. J Pharmacol Exp Ther. 1996; 278(2):921–5. [PubMed: 8768748]
72. Luquita MG, Catania VA, Pozzi EJ, et al. Molecular basis of perinatal changes in UDP-glucuronosyltransferase activity in maternal rat liver. J Pharmacol Exp Ther. 2001; 298(1):49–56. [PubMed: 11408524]
73. Ganguly TC, O'Brien ML, Karpen SJ, et al. Regulation of the rat liver sodium-dependent bile acid cotransporter gene by prolactin. Mediation of transcriptional activation by Stat5. J Clin Invest. 1997; 99(12):2906–14. [PubMed: 9185514]
74. Cao J, Gowri PM, Ganguly TC, et al. PRL, placental lactogen, and GH induce NA(+)/taurocholate-cotransporting polypeptide gene expression by activating signal transducer and activator of transcription-5 in liver cells. Endocrinology. 2001; 142(10):4212–22. [PubMed: 11564677]
75. Liu Y, Hyde JF, Vore M. Prolactin regulates maternal bile secretory function post partum. J Pharmacol Exp Ther. 1992; 261(2):560–6. [PubMed: 1578373]
76. Greenspan, FS.; Gardner, DG. Basic & clinical endocrinology. 7th ed.. Lange Medical Books/McGraw-Hill; New York: 2004.
77. Gabbe, SG.; Niebyl, JR.; Simpson, JL. Obstetrics: normal and problem pregnancies. 5th ed.. Churchill Livingstone/Elsevier; Philadelphia, PA: 2007.
78. Soldin OP, Guo T, Weiderpass E, et al. Steroid hormone levels in pregnancy and 1 year postpartum using isotope dilution tandem mass spectrometry. Fertil Steril. 2005; 84(3):701–10. [PubMed: 16169406]
79. Pascussi JM, Gerbal-Chaloin S, Drocourt L, et al. The expression of CYP2B6, CYP2C9 and CYP3A4 genes: a tangle of networks of nuclear and steroid receptors. Biochim Biophys Acta. 2003; 1619(3):243–53. [PubMed: 12573484]
80. LeCluyse E, Madan A, Hamilton G, et al. Expression and regulation of cytochrome P450 enzymes in primary cultures of human hepatocytes. J Biochem Mol Toxicol. 2000; 14(4):177–88. [PubMed: 10789495]
81. Pascussi JM, Drocourt L, Gerbal-Chaloin S, et al. Dual effect of dexamethasone on CYP3A4 gene expression in human hepatocytes. Sequential role of glucocorticoid receptor and pregnane X receptor. Eur J Biochem. 2001; 268(24):6346–58. [PubMed: 11737189]
82. Pascussi JM, Gerbal-Chaloin S, Fabre JM, et al. Dexamethasone enhances constitutive androstane receptor expression in human hepatocytes: consequences on cytochrome P450 gene regulation. Mol Pharmacol. 2000; 58(6):1441–50. [PubMed: 11093784]
83. Pascussi JM, Drocourt L, Fabre JM, et al. Dexamethasone induces pregnane X receptor and retinoid X receptor-alpha expression in human hepatocytes: synergistic increase of CYP3A4 induction by pregnane X receptor activators. Mol Pharmacol. 2000; 58(2):361–72. [PubMed: 10908304]
84. Sugatani J, Nishitani S, Yamakawa K, et al. Transcriptional regulation of human UGT1A1 gene expression: activated glucocorticoid receptor enhances constitutive androstane receptor/pregnane

X receptor-mediated UDP-glucuronosyltransferase 1A1 regulation with glucocorticoid receptor-interacting protein 1. Mol Pharmacol. 2005; 67(3):845–55. [PubMed: 15557560]

85. Borlakoglu JT, Scott A, Henderson CJ, et al. Alterations in rat hepatic drug metabolism during pregnancy and lactation. Biochem Pharmacol. 1993; 46(1):29–36. [PubMed: 8347134]
86. Turcan RG, Tamburini PP, Gibson GG, et al. Drug metabolism, cytochrome P450 spin state, and phospholipid changes during pregnancy in the rat. Biochem Pharmacol. 1981; 30(11):1223–5. [PubMed: 7271821]
87. Neale MG, Parke DV. Effects of pregnancy on the metabolism of drugs in the rat and rabbit. Biochem Pharmacol. 1973; 22(12):1451–61. [PubMed: 4738892]
88. Vore M, Soliven E. Hepatic estrone and estradiol glucuronyltransferase activity in pregnancy. Induction by pretreatment with 3-methylcholanthrene and phenobarbital. Drug Metab Dispos. 1979; 7(5):247–51.
89. He XJ, Yamauchi H, Suzuki K, et al. Gene expression profiles of drug-metabolizing enzymes (DMEs) in rat liver during pregnancy and lactation. Exp Mol Pathol. 2007; 83(3):428–34. [PubMed: 16824515]
90. Masuyama H, Hiramatsu Y, Mizutani Y, et al. The expression of pregnane X receptor and its target gene, cytochrome P450 3A1, in perinatal mouse. Mol Cell Endocrinol. 2001; 172(1-2):47–56. [PubMed: 11165039]
91. Ochs H, Dusterberg B, Gunzel P, et al. Effect of tumor promoting contraceptive steroids on growth and drug metabolizing enzymes in rat liver. Cancer Res. 1986; 46(3):1224–32. [PubMed: 3943094]
92. First Principles of Gastroenterology: The Basis of Disease and an Approach to Management. 2 nd ed.. Canadian Public Health Association; Ottawa, Ontario, Canada: 1992.
93. Shaikh AA. Estrone and estradiol levels in the ovarian venous blood from rats during the estrous cycle and pregnancy. Biol Reprod. 1971; 5(3):297–307. [PubMed: 5163522]
94. Dean ME, Stock BH. Hepatic microsomal metabolism of drugs during pregnancy in the rat. Drug Metab Dispos. 1975; 3(5):325–31. [PubMed: 241612]
95. Graham MJ, Lake BG. Induction of drug metabolism: species differences and toxicological relevance. Toxicology. 2008; 254(3):184–91. [PubMed: 18824059]
96. Cunningham, F.; Levono, K.; Bloom, S., et al. Williams Obstetrics. 22 nd ed. McGRAW-HILL; 2005.
97. Yallampalli C, Chauhan M, Thota CS, et al. Calcitonin gene-related peptide in pregnancy and its emerging receptor heterogeneity. Trends Endocrinol Metab. 2002; 13(6):263–9. [PubMed: 12128288]
98. Lambert GH, Lietz HW, Kotake AN. Effects of pregnancy on the cytochrome P-450 system in mice. Biochem Pharmacol. 1987; 36(12):1965–71. [PubMed: 3593403]

Article highlight box

- Pregnancy influences hepatic metabolism of drugs in a CYP-dependent manner.
- Hormones the plasma levels of which rise during pregnancy are capable of regulating expression of hepatic drug metabolism enzymes. These hormones include estrogens, progesterone, cortisol, and prolactin.
- Appropriate animal models to study altered drug metabolism during pregnancy are lacking.
- Further studies are needed to examine the role of pregnancy hormones in altered drug metabolism during pregnancy.

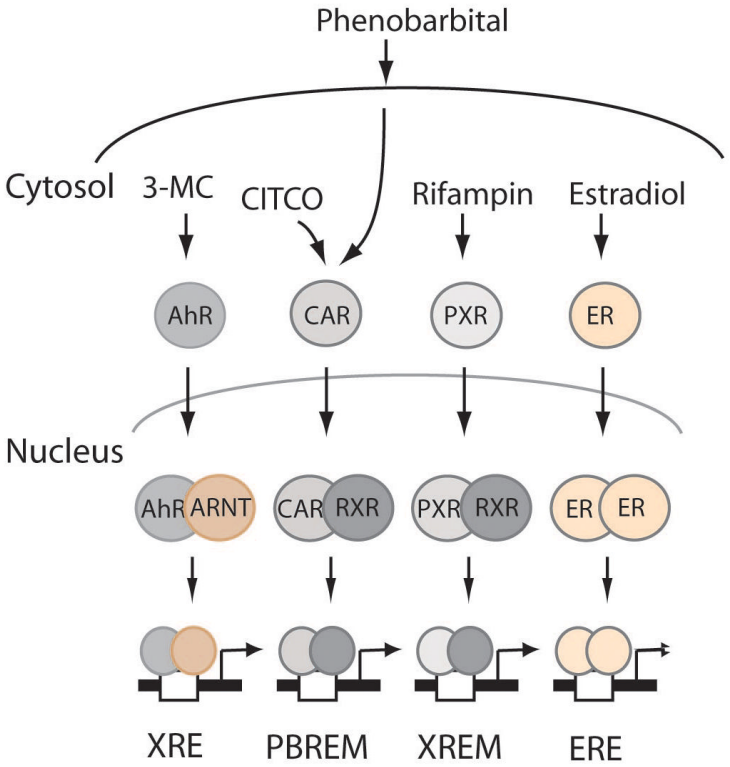

Fig. 1.

Signaling pathways for regulation of CYP expression. 3-MC, 3-methylcholanthrene; CITCO, 6-(4-chlorophenyl)imidazo [2,1-b][1.3]thiazole-5-carbaldehyde O-(3,4-dichlorobenzyl) oxime; PBREM, phenobarbital responsive enhancer module; XREM, xenobiotic responsive enhancer module; ARNT, aryl hydrocarbon receptor nuclear translocator; RXR, retinoid X receptor; ERE, estrogen response element; XRE, xenobiotic-responsive element

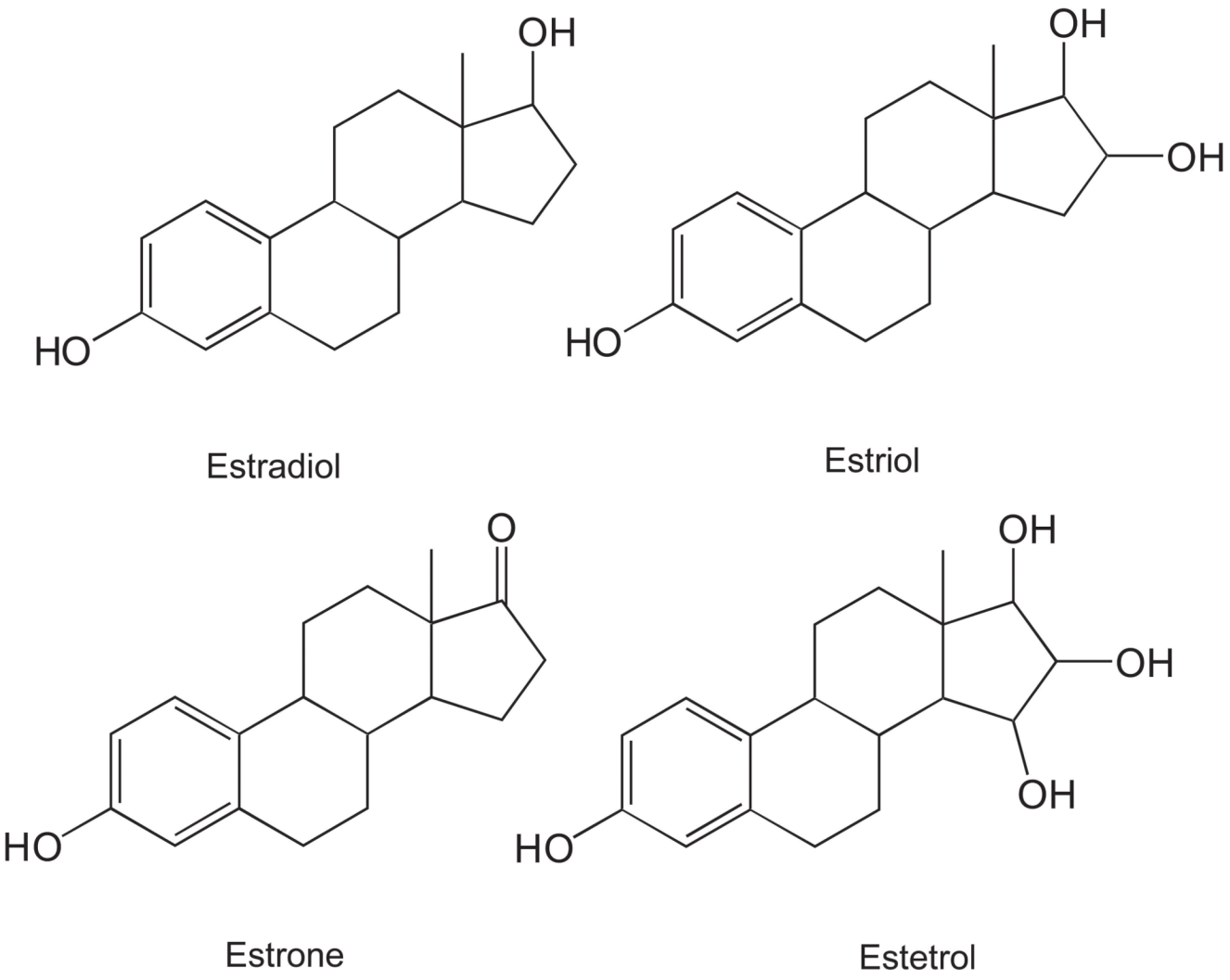

Fig. 2.
Various endogenous estrogens

Table 1

Drugs used in pregnancy

Drug class	Drugs
Antihypertensive	Labetalol, methyldopa, hydralazine
Antidiabetic	Insulin, glyburide, metformin
Antidepressants	Fluoxetine, sertraline, citalopram
Antidyspepsia	Omeprazole
Antibiotics	Cefoxitin, cephazolin, nitrofurantoin
Antiretroviral	Ritonavir, atazanavir, nelfinavir
Antipsychotic	Haloperidol, risperidone

Table 2

Hepatic transcription factors involved in up-regulation of CYP expression [27, 36]

Transcriptional regulator	Ligand/activator	Target CYP genes
ER	Estradiol	CYP2A6
AhR	3-methylcholanthrene	CYP1A2
CAR	Phenobarbital, CITCO	CYP2B6, CYP2C9, CYP2C19, CYP3A4
PXR	Rifampin	CYP2A6, CYP2B6, CYP2C9, CYP3A4

Table 3

Changes in drug metabolism in pregnancy [7, 9, 19]

CYP	Direction of activity change	Clinical evidence
CYP1A2	Decrease	Decreased apparent clearances or increased metabolic ratios* of caffeine, theophylline, olazapine, and clozapine
CYP2A6	Increase	Increased clearance of nicotine
CYP2D6	Increase	Increased apparent clearances or decreased metabolic ratio of fluoxetine, citalopram, metoprolol, and dextromethorphan
CYP2C9	Increase	Increased apparent clearances of phenytoin and glyburide
CYP2C19	Decrease	Increased metabolic ratio of proguanil
CYP3A4	Increase	Increased apparent clearances of midazolam, nifenidine, and indinavir
UGT1A4	Increase	Increased apparent clearances of lamotrigine

* metabolic ratio: the ratio of concentrations of parent drug to metabolite

Table 4

Endogenous entities the plasma concentrations of which increase during pregnancy [78, 96, 97]

Small molecules	Peptides/Proteins
• Estrogen	• Neuropeptide Y
• Pregesterone	• Calcitonin gene related peptide
• 17α-hydroxyprogesterone	• Prolactin
• Aldosterone	• Human placental lactogen
• Cortisol	• Leptin
• 11-Deoxycortisol	• Growth hormone variant (placental growth hormone)
• Androstenedione	• Inhibin
	• Human chorionic gonadotropin

Table 5

Altered drug metabolism during pregnancy in rodents

Rats

Decreased specific activities* of

- Ethymorphine N-demethylase [86]
- Aniline hydroxylase [86]
- *p*-Nitroebnzoic acid reductase [86]
- Biphenyl-4-hydroxylase [87]
- Aminopyrine N-demethylation [85]
- Aldrin epoxidation [85]
- Estrone and estradiol glucuronosyltransferase [88]
- 4-methylumbelliferone glucuronosyl transferase [87]

Decreased protein expression of

- UGT1A (UGT1A1, 1A5, 1A6) and UGT2B1 [72]

Decreased mRNA expression of

- CYP2C11, CYP2E1, CYP2D2, CYP2D23, and CYP2A1 [89]

Increased specific activities of

- Ethoxyresorufin-O-deethylase [85]
- 4-Nitroanisole-O-demethylase [85]

Increased mRNA expression of

- CYP2C37 [89]
- CYP1A2 [85]

Mice

Decreased mRNA expression of

- Cyp3a11 and Cyp3a25 [55]

Increased mRNA expression of

- Cyp3a1 [90]
- Cyp3a16, Cyp3a41, and Cyp3a44 [55]

Increased specific activities of

- Aminopyrine-N-demethylase [98]

*drug metabolism per gram liver or per mg microsomal protein