24 Influence of Changes in Physiology, Transporters, and Enzyme Expression on Disposition and Metabolism of Drugs during Pregnancy and Clinical Implications

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24.1 INTRODUCTION

During pregnancy, progesterone, a steroidal sex hormone, plays an important role in the discontinuation of female menstrual cycle and in the embryogenesis. The increase in progesterone levels starts during ovulation, continues to increase during pregnancy, and

Encyclopedia of Drug Metabolism and Interactions, 6-Volume Set, First Edition.
Edited by Alexander V. Lyubimov.
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helps in the development of the uterine lining for implantation of the fertilized egg. In reverse, decreased progesterone levels are associated with the risk of miscarriage. The levels of progesterone during menstrual cycle and in the first trimester of pregnancy are controlled by ovaries, but as the placenta grows (ninth–tenth week), it takes over this role of the ovary and maintains progesterone during pregnancy.

The changes in levels of progesterone and other associated hormones are linked to changes in physiological conditions of the pregnant mother, such as increase in blood plasma volume, extracellular fluids, cardiac output, renal flow, white blood cells, platelet and decreases in albumin, hemoglobin, urea, creatinine, and so on. These physiological adaptations are to favor the development of the fetus, but this also results in alterations to drug-metabolizing enzymes (DMEs) and xenobiotic transporters, thereby affecting pharmacokinetics of drugs in the body and leading to increased potential for side effects.

During pregnancy, human placenta functions as both a barrier and a transport organ, helping in exchange of nutrients and oxygen as well as waste products between the mother and the fetus. These functions are assisted by transporter proteins expressed on the placental syncytiotrophoblasts, which have differential localization in the maternal-facing brush border membrane and fetal-facing basal membrane. The transporters expressed on maternal-facing brush border membrane facilitate the entry of xenobiotics from mother to fetus. The passage of nutrients and xenobiotics across the placental barrier is chemically regulated by enzymes such as hydrases, transferases, oxidoreductases, lyases, and isomerases. These enzymes have been implicated in xenobiotic metabolism, the generation of reactive metabolites, and in rare cases, birth defects and teratogenicity.

The purpose of this chapter is to review the aspects of transport, metabolism, and clinical implications of administered drugs during pregnancy. It covers the nature of physiological changes occurring during pregnancy, types of transporters expressed, differential enzymes present, and clinical implications of these factors on drug therapy for the pregnant mother and fetus.

24.2 PHYSIOLOGICAL CHANGES OCCURRING IN PREGNANT MOTHERS AND THEIR INFLUENCE ON DRUG DISPOSITION

The physiology of a pregnant woman is significantly different from that of a non-pregnant woman. Practically, physiological changes begin in early gestation and are most pronounced in the third trimester of pregnancy. Some of these are normalized within 24 h of delivery, while others return to normal in 12 weeks after delivery [1]. Table 24.1 lists the nature of physiological changes in the body through the pregnancy period and postpartum. Major changes occur within the gastrointestinal tract (GIT), cardiovascular, renal, and hepatic systems. These changes have the potential to influence absorption, distribution, metabolism, and excretion (ADME) of drugs. A few examples are included in Table 24.2.

24.2.1 Physiological Changes in the Cardiovascular System

Cardiovascular changes occurring during pregnancy include alterations in cardiac output, blood volume, blood pressure, extracellular fluid space, plasma albumin, and

TABLE 24.1 Physiological Changes during Pregnancy

Physiological Parameter	Nonpregnant Women	Pregnant Women	References
BP	SBP = 120 ± 9.8 mm Hg DBP = 80.0 ± 7.2 mm Hg	SBP = 119.6 ± 9.8 mm Hg DBP = 65.0 ± 7.2 mm Hg	2
Cardiac output	2.90 ± 0.17 L/min	6.7 L/min at 8–11 wk and 8.7 L/min at 36–39 wk	3
Blood plasma volume	4–5 L	Increase by 40–50%	3
RBC count	4.2–5.4 million cells/mL	Increased by 20–30%	3
Hb	10.5–13.5 g/dL	Decrease in Hb due to relatively less increase in RBC count in comparison to blood plasma volume	4,5
Alkaline phosphatase, plasma	26–110 IU/L	Increased during pregnancy	6
Platelets count	200–600 × 10^9 cells/L	Unchanged/slightly increased	3
Urine creatinine	37–250 mg/dL	Decreased in pregnancy	3
Albumin	24–31 g/L	Decreased in pregnancy	6
Fasting glucose	3.0–5.0 mmol/L	Unchanged in pregnancy	3
Alanine	407 ± 66 μmol/L	10–20 wk = 321 ± 58 μmol/L, 30–40 wk = 321 ± 58 μmol/L	7
Citrulline	43 ± 11 μmol/L	10–20 wk = 24 ± 6 μmol/L, 30–40 wk = 29 ± 9 μmol/L	7
Arginine	79 ± 10 μmol/L	10–20 wk = 51 ± 10 μmol/L, 30–40 wk = 39 ± 8 μmol/L	7
Ornithine	50 ± 4 μmol/L	10–20 wk = 23 ± 5 μmol/L, 30–40 wk = 21 ± 4 μmol/L	7
Total bilirubin	0.0–1.0 mg/dL	Decreased during pregnancy	6

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; RBC, red blood cells; SBP, systolic blood pressure; wk, weeks.

RBC count. Cardiac output rises by 30–50% by the end of the second trimester and remains the same until delivery. Likewise, blood volume increases progressively from six to eight weeks to reach a maximum at 32–34 weeks with little change thereafter, with overall increase being 40–50% during normal pregnancy [23–26]. The increase in blood and total body water volumes alter the volume of distribution of various drugs. These changes affect drug disposition and elimination, as well as the terminal elimination half-life [27]. Albumin content has been shown to decrease, while there is increase in α 1-acid glycoprotein during pregnancy. These changes lead to alterations in protein binding of drugs and result in increase in their plasma concentration beyond the therapeutic window. For example, diazepam, phenytoin, and sodium valproate have significantly elevated free fractions in the last trimester because of the decrease in the

TABLE 24.2 Select List of Drugs Showing Alterations in Pharmacokinetics and Metabolism during Pregnancy

Drug	Gestational Age	ADME	Enzyme/ Transporter	Significance	References
Methadone	27–30 wk	Increased metabolism and decreased absorption	NS	Higher elimination rate constant and lower half-life compared to nonpregnant controls	8
Caffeine	Second and third trimesters	Decreased metabolism	CYP1A2	Decrease in clearance	9
Nelfinavir	31–36 wk	Increased metabolism	Induction of hepatic CYP3A4 or inhibition of CYP2C19	Safety and efficacy (therapeutic drug monitoring)	10
Indinavir	Correlation between during pregnancy and postpartum	Increased metabolism	NS	Warrant dosage adjustment during pregnancy	11
Cotinine	NS	Increased metabolism	CYP2A6	Clearance increased by 140% and half-life by 50%	12
Lamotrigine	Second and third trimesters	Drug distributed in fetus	NS	Leads folate deficiency that finally results in teratogenic effects	13
Labetalol	NS	Increased metabolism	UGT1A1, UGT2B7	Clearance increased	14
Metoprolol	Third trimester	Increased metabolism	CYP3A4	Clearance increased	15,16
Nifedipine	Third trimester	Increased metabolism	CYP3A4	Clearance increased	17
Phenytoin	NS	Altered absorption or metabolism	NS	Seizures appear	18,19
Citalopram	20, 30, and 36 wk	Increased metabolism	NS	Dose adjustment required	20
Escitalopram	20, 30, and 36 wk	Increased metabolism	NS	Dose adjustment required	20
Sertraline	20, 30, and 36 wk	Increased metabolism	NS	Dose adjustment required	20
Proguanil	Third trimester	Decreased metabolism	CYP2C19	Active metabolite formation decreased, so dose required to be increased by 50%	21,22

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; CYP, cytochrome; NS, not specified; UGT, UDP glucuronosyltransferase.

albumin content. The increase in body weight during pregnancy further results in a decrease in dose/kg of administered drugs and leads to a significant lowering of a drug's steady-state concentration with resultant suboptimal treatment.

24.2.2 Physiological Changes in the Gastrointestinal System

Motility disturbances of the GIT are common during pregnancy. These disturbances are largely due to alterations in sex hormone levels, including heartburn, nausea and vomiting, abdominal bloating, and constipation [28]. Among these symptoms, nausea and vomiting have greater influence on absorption and bioavailability of drugs, especially during the first trimester [29]. Also, increase in plasma progesterone concentration during pregnancy corresponds to decrease in gastrointestinal motility, with associated prolonged gastric emptying and intestinal transit times. This may lead to delayed drug absorption and reduced peak concentration [30]. In addition, gastric pH is slightly increased during pregnancy due to the reduced gastric acid secretion, which may affect ionization and absorption of weak acidic and basic drugs [31].

24.2.3 Physiological Changes in the Renal System

Renal physiological changes are characterized by marked vasodilatation that leads to an increase in the glomerular filtration rate (GFR) and renal plasma flow (RPF). These changes are initiated during the first trimester, by the end of which GFR and RPF increase by 50% and 60–80%, respectively. Apparently, there is higher increase in RPF in comparison to GFR, resulting in a significant decrease in filtration fraction (GFR/RPF). In addition, creatinine clearance is increased during pregnancy, while its production remained unchanged. This results in lowering of serum creatinine. As a fallout of the above conditions, there is increased clearance of polar drugs via kidney during pregnancy, with the likelihood of failure of the treatment [32–34].

24.2.4 Physiological Changes in the Hepatic System

During pregnancy, the mass of the liver is increased up to 50%, which results in a decrease in the per milligram expression of DMEs. In addition, alterations in sex hormone levels also affect expression of different phase I and phase II DMEs. Davis *et al*. [35] found that hepatic microsomal enzymes started rising progressively from the twelfth week of pregnancy and continued till delivery, with a gradual fall to normal levels by the sixth week postpartum. Sulfate conjugation was decreased during pregnancy, and this was attributed to the inhibitory effect of the high levels of estrogen during pregnancy. In a similar manner, inhibitory effects of progestogens on the glucuronide conjugation of drugs were also established [7]. Additional pregnancy-induced changes included decrease in bilirubin and γ-glutamyltransferase and increase in aminotransferases, alkaline phosphate (used in the diagnosis of hepatotoxicty), and $5'$-nucleotidase (used in the diagnosis of cholestasis) [6]. Some changes during pregnancy were similar to those observed in hepatotoxicity, for example, increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity during the third trimester, although this typically remained below the upper margin of normal limit. However, other reports indicate that there were no changes in ALT and AST activity during pregnancy [36–40]. However, their activity increased during labor due to the contractions of the uterine muscles [41,42].

24.3 CHANGES IN TRANSPORTERS DURING PREGNANCY

The efflux [ATP-binding cassette (ABC)] and uptake [solute carrier (SLC)] transporters are altered during pregnancy and ontogeny. The changes occurring at placental and fetal levels are primarily meant to provide nutrition to the fetus and provide protection from undesired xenobiotics and endogenous waste products. This barrier is not absolute, and some of the xenobiotics and drugs do cross and influence the fetus.

24.3.1 Transporters in Human Placenta

Drugs used during pregnancy are for the treatment of either the mother or, to a lesser extent, the fetus. During pregnancy, drug selection is mainly dependent on the ability of the drug to cross the physical barrier between the maternal and fetal compartments. If therapy is needed only for the mother then transfer of drugs through the placenta can lead to toxic effects in the fetus. On the other hand, if the fetus requires therapy, transfer of the drugs from the mother to the fetus becomes an important determinant.

Major functions of the placenta are to transfer nutrients from the mother to the fetus and to eliminate metabolic waste products from the fetus through the mother, which is performed by transporters that are expressed in the maternal-facing brush border membrane and the fetal-facing basal membrane of the syncytiotrophoblasts. These transporters are involved not only in maintenance of the flow of nutrients and macromolecules that are needed for placental function and fetal development but also in the transportation of xenobiotics, including therapeutic agents, environmental pollutants and toxins, and even drugs of abuse. The ABC efflux transporters expressed in placenta are P-glycoprotein (PgP/MDR1/ABCB1), breast cancer resistance protein (BCRP/ABCG2) and multidrug resistance proteins 1–3 and 5 (MRP1–3 and 5/ABCC1–3 and 5). The SLC influx transporters are organic anion transporting polypeptides (OATPs), organic anion transporters (OATs), organic cation transporters (OCTs), monocarboxylate transporters and nucleoside transporters [43–46]. Table 24.3 lists placental transporters along with their drug substrates and their clinical impact on the fetus. The human placental barrier at term, the microstructure of placental barrier, and the main transporter proteins expressed in human placental barrier and their localization are illustrated in Fig. 24.1 [46].

24.3.1.1 ABC Transporters. ABC efflux transporters are located on the maternal-facing and the fetal-facing sides of syncytiotrophoblasts and/or the endothelium of fetal capillaries. These are involved in transport of exogenous and endogenous compounds and metabolites across the placenta, so as to limit the fetal exposure to potential toxins from maternal circulation, thereby protecting it. Drug substrates for this category of transporters include cardiovascular, anticancer, and anticonvulsant drugs; anti-HIV protease inhibitors; and so on. The ABC efflux transporters expressed in placenta are PgP/MDR1/ABCB1, BCRP/ABCG2, MRP1–3 and 5/ABCC1–3 and 5.

24.3.1.1.1 PgP/MDR1/ABCB1. This transporter is a product of the multiple drug resistance (MDR) ABCB1 gene and is expressed in the placental trophoblast layer located in the brush border membrane. PgP is involved in active efflux of lipophilic

TABLE 24.3 Transporters Involved in Drug Transfer Across the Placenta

Transporter	Substrate	Clinical Impact	References
OATP	Streptomycin	Hearing loss in infants	47
Na^+-dependent organic cation transporter	Tetracycline	Deformations in bone and formation of teeth, enamel in infants	48,49
Active transport	Warfarin	Bleeding in fetal brain	50,51
Mrp2	ACE inhibitor	Damage to fetal kidney	52,53
PgP	Glyburide	Active efflux reduces toxicity in fetus	54
mdr1a-/-/1*b*-/-	Saqunavir, paclitaxel	16 times more drug required	55
PgP	Avermecitin	Protects from cleft palate in fetus	56
PgP	Indinavir	Lower fetomaternal clearance, bidirectional transfer	57
PgP	Vinblastine	Increased maternofetal clearance	56
PgP	Methadone	Active efflux reduces toxicity in fetus	58
PgP	Anthracyclines, taxanes	Decreased exposure to fetus and reduced toxicity	43
PgP	HIV protease inhibitor	Reduced mother to child HIV transmission	59
Passive transport	Ganciclovir	Teratogenic and embryotoxic effects	60
ABC transporters	Antiepileptic drugs	Congenital malformations, minor anomalies, congenital syndrome, and developmental disorders	61
Passive transport	Lidocaine, bupivacaine	Epileptiform discharges, immaturity of the autonomic nervous supply to the cardiovascular system, fetal methamoglobenemia	62,63
Carrier-mediated transport	Metformin	Polycystic ovary syndrome	64,65

Abbreviations: ABC, ATP-binding cassette transporter; ACE, angiotensin converting enzyme; HIV, human immunodeficiency virus; OATP, organic anion transporter polypeptides; PgP, P-glycoprotein; MRP, multiple drugs resistance protein.

substances from the cell. Transport by PgP is unidirectional, and the substrate is effluxed out from the cell due to its asymmetrical membrane topology. Thus, by moving out toxic substances/xenobiotics, PgP protects the fetus from potential toxins that can cross the placenta [66].

The placental expression of PgP is significantly high in preterm as compared to term placenta and gradually decreases with gestational age [67]. Cyclosporine was used to directly evaluate the influence of PgP on transplacental

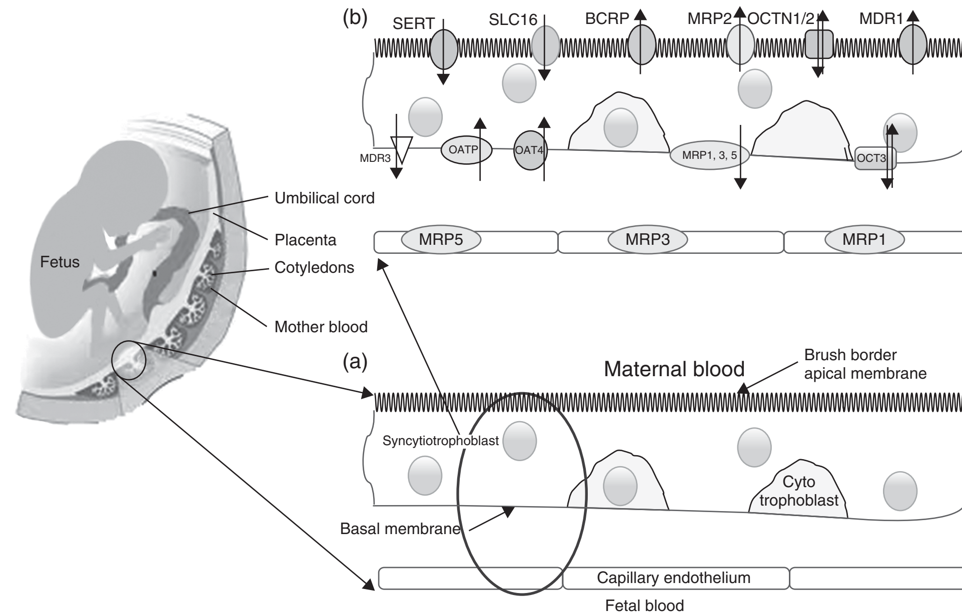

Figure 24.1 Pictorial representation of term placenta along with the developed fetus, indicating the expression of transporter proteins (BCRP, breast cancer resistance protein; MDR, multidrug resistance protein; MRP, multidrug-resistance-associated protein; NET, noradrenalin transporter; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCTN, novel organic cation transporter; SER, serotonin transporter). (a) Zoomed section of placenta. (b) Enlarged view of placental cellular structure. (See color insert.)

transfer with a dually perfused human placenta model. The clearance of cyclosporine was increased significantly when it was coadministered with quinidine (a potent PgP inhibitor) [68]. PgP decreased the uptake of rhodamine123 from the maternal to the fetal side, while accelerating elimination of PgP substrates from the fetal side [69]. This perfused placenta model has also been used to demonstrate efflux of the PgP substrate drugs, saquinavir [70], methadone [38], indinavir [58], and prazosin [71]. Interestingly, a reverse pattern was found in the rat, where an increase in Mdr1a and Mdr1b expression was observed with advancing gestation [72].

24.3.1.1.2 BCRP. BCRP expression is very high in the human placenta, suggesting a role similar to PgP in limiting fetal exposure to xenobiotics and facilitating elimination of xenobiotics from the fetal compartment. In membrane vesicles prepared from human term placenta, BCRP transported mitoxantrone [73] and glyburide [74], and the perfused human placenta model revealed BCRP-mediated efflux of glyburide [75] and cimetidine [76]. A role has been suggested for BCRP (and OATP2B1) in regulating placental estrogen synthesis by mediating the concentrations of dehydroepiandrosterone sulfate and estrone 3-sulfate [77]. BCRP and its mRNA expression was twice as high in the preterm (28 ± 1 weeks) relative to the term (39 ± 2 weeks) human placenta [78]. Similar decrease with gestation was also observed in the rat [79].

24.3.1.1.3 MRPs. MRP1 is present in the apical membrane of the placental syncytiotrophoblasts [80] and the human choriocarcinoma cell line BeWo, where it transports unconjugated bilirubin [81] and mediates 2,4-dinitrophenyl-*S*-glutathione efflux [82]. MRP1 expression in BeWo cells is induced by zearalenone, a nonsteroidal estrogenic mycotoxin [83]. Similar to MRP1, MRP2 is also expressed in the apical membrane of the placental syncytiotrophoblasts [84]. The maternal-to-fetal transfer of talinolol is increased by probenecid, an MRP2 inhibitor, demonstrating functional significance in the human placenta [85]. There is increase in placental MRP2 mRNA and the protein with gestation, indicating developmental control of MRP2 in human placenta [84]. MRP3 is localized in the fetal vessel endothelial cells and at lower concentrations on the apical side of the placental syncytiotrophoblasts [80]. MRP5 is expressed at the basal membrane of syncytiotrophoblasts and endothelial cells of the fetal vessels [86]. MRP5 protein expression decreases with pregnancy, with the highest expression in early preterm placenta [86]. The excretion of potentially toxic anions such as bile acids and biliary pigments is performed by the fetus in conjunction with the placenta and the maternal liver. Bile acids and bilirubin are transferred to the maternal blood by MRP1–3 and BCRP [87]. Under physiological circumstances, fetal bile acids and bilirubin are transported across the placenta and taken up by the maternal liver, which eliminates them via MRP2 and bile salt export pump (BSEP).

24.3.1.2 SLC Transporters. These are uptake proteins present in the placenta and are involved in the transportation of nutrients and proteins toward the developing fetus and of potential toxins and endogenous waste toward the maternal side. The SLC

uptake transporters include OATPs, OATs, OCTs, monocarboxylate and nucleoside transporters.

24.3.1.2.1 OATP. These are bidirectional transporters, which work along the substrate concentration gradient. To transport organic anions, including steroid conjugates, thyroid hormones, prostanoids, digoxin, statins, methotrexate, and antibiotics. OATP1B1, OATP1B2, OATP2B1, OATP3A1, and OATP4A1 are expressed in the human placenta [88–91]. OATP2B1 is abundantly expressed in the placenta and localized in the basolateral membrane of the syncytium [88] and OATP1B3 is located on the apical surface of syncytiotrophoblasts [90].

Repaglinide, a known OATP substrate was used in the *ex vivo* placental perfusion model to evaluate the placental transfer of this drug. Using antipyrene as a reference for passive diffusion, it was observed that the rate of repaglinide transport from the mother to the fetus was low, while this was higher in the fetal-to-maternal direction. This highlighted the importance of active transport by the OATP transporters in fetal exposure to repaglinide [92]. OATPs play a role in bile acid and bilirubin efflux from fetal hepatocytes toward the fetal blood and from the trophoblast to the maternal blood, facilitating the transfer of these potential toxins from the fetus to the maternal circulation [87]. The bile acid transporter, OATP1A2, is localized to the vasculosyncytial membrane and apical surface of syncytiotrophoblasts and OATP1B3, to the vasculosyncytial membrane of the syncytiotrophoblasts. In intrahepatic cholestasis occurring during pregnancy, the expression of both transporters is significantly reduced, relative to the normal placenta [93].

24.3.1.2.2 OAT. OATs are involved in the elimination of a variety of endogenous substances, xenobiotics, and their metabolites from the body and have weak structural similarity to the OCTs. The endogenous substrates of OATs are cyclic nucleotides, prostaglandins, urate, dicarboxylates, and so on, while exogenous substrates are anionic drugs and environmental substances. Most OATs are expressed in the kidney and some are expressed in the liver, brain, and placenta. These transporters are involved in renal secretory pathways for organic anions and in the distribution of organic anions throughout the body. OATs expressed in the human placenta were OAT1/SLC22A6, OAT3/SLC22A8, and OAT4/SLC22A11. OAT1 and 3 are present in syncytial basement membrane and involved in the elimination of toxins and xenobiotics from the fetal circulation, whereas OAT4 is expressed in the cytotrophoblast layer that underlies the syncytium [52].

24.3.1.2.3 OCT. OCTs expressed in human placenta are OCT1, OCT2, OCT3 (SLC22A3), OCTN1 (SLC22A4), and OCTN2 (SLC22A5). OCT1–3 are high capacity nonneuronal monoamine transporters. Their substrates include amiloride and cimetidine. The OCT inhibitor quinidine is reported to inhibit acetylcholine release in human placental tissue [94]. OCTN1 is localized to the brush border membrane of the syncytiotrophoblasts of term placenta, and involved in transport of fluoxetine, citalopram, and verapamil [52]. OCTN2 is a high affinity L-carnitine uptake protein localized on the apical surface of syncytiotrophoblasts of the placenta. It has been reported to be involved in the transport of L-carnitine across the placenta, which is

inhibited by levamisole and progesterone in human trophoblast cells. The transporter is additionally involved in the movement of methamphetamine, quinidine, verapamil, cephaloridine, glibenclamide, and imipramine. Thus, it plays an important role, as some of these drugs have been shown to be toxic for the fetus [52,94].

24.3.1.2.4 Other SLC Transporters. Other SLC transporters expressed in placenta are monoamine transporter (SLC6A), nucleoside transporter (SLC29A), and carboxylate transporter (SLC16). SLC6A transporters that are involved in the transport of serotonin and dopamine are named *serotonin transporters* (SERT/SLC6A4) and *dopamine transporters* (NET/SLC6A2), respectively. They are involved in the transport of amphetamines and cocaine, respectively. SLC29A is located on the brush border membrane of the syncytium and transports purine and pyrimidine across the placenta. It was also found to be involved in the transport of chemotherapeutics, nucleoside analogs, and vasodilator drugs such as dipyridamole and dilazep. SLC16 is an H^+ cotransporter that is involved in the movement of carboxylates across the syncytium [52].

24.3.2 Transporters in the Fetus

There are relatively limited drug-transporter-based studies on the human fetus. PgP is the most studied transporter, and its distribution in the fetus is represented in Fig. 24.2. Highest expression is in the cardiac muscles and the kidney tubules during the gestation period. It is not expressed in the pneumocyte and bronchiole of the lungs, but the expression is higher in the bronchi during 18 to 20 weeks' gestation. In the adrenal gland, PgP is expressed only in the definitive cortex zone and no expression is reported in the fetal zone and medulla of the adrenal gland [95]. The early fetal brain has low expression of microvessel PgP, rendering the fetus more susceptible to the toxins in maternal circulation. With advancement of pregnancy, there is a significant increase in PgP expression in the fetus and is likely the reason for the observed higher responsiveness of PgP function in primary brain endothelial cells to glucocorticoids [95]. Synthetic glucocorticoids administered to pregnant women at risk of preterm delivery were found to increase the protective capacity of the developing fetal blood–brain barrier, depending on the time of exposure [96]. Immunohistochemical staining was used to visualize the expression and localization of PgP in the developing human fetus during cerebral cortex formation [97]. At 12 weeks of gestation, PgP was diffusely located in the endothelial cells lining the primary cortex microvessels. At 18 weeks, PgP was present in the cortex and subcortical vessels, and at 22 weeks, it was concentrated in the endothelial cell membranes. Radial glial cells and astrocytes did not stain for PgP in any of the samples. There was low expression of PgP in the radial glia at 18 weeks' gestation and at midgestation, where it was observed in the abluminal endothelial cell membrane. These studies demonstrate that PgP is expressed early during human cerebrocortical microvessel development and at midgestation, where its efflux activity is regulated by interactions with the caveolar endothelial cell compartment [97].

MRP1 and BCRP are also expressed in the developing human central nervous system (CNS). While MRP1 is expressed in choroid plexus and ependymal cells, BCRP is most prominently expressed in microvessel endothelial cells of the CNS. Both PgP and MRP1 are also found in large pyramidal neurons. Immunostaining during

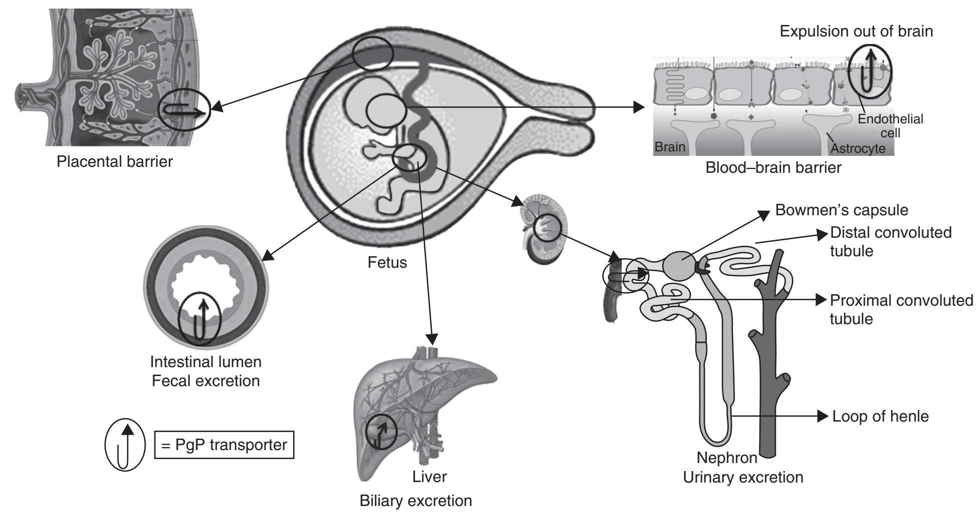

Figure 24.2 Pictorial representation showing distribution of PgP transporter in placenta and organs of the fetus. (See color insert.)

different stages of gestation showed increase in PgP expression during gestational maturation, whereas MRP1 and BCRP expression remained constant [98]. In embryonic and fetal membranes, BCRP expression helped to ensure proper function of the fetoplacental unit [99].

BSEP, MRP2, and MDR3 are the major hepatic canalicular transporters, mediating bile secretion in the fetus [100]. Human liver samples from the fetus at 14–20 weeks of gestational age and adults were tested for mRNA expression of BSEP, MDR3, MRP2, Na^+-taurocholate cotransporting polypeptide (NTCP), and farnesoid X receptor (FXR) genes. Immunohistochemical staining of BSEP, MDR3, and MRP2 was performed on the fetal and adult livers. All genes tested were expressed at midgestational age. MDR3 and NTCP showed significantly lower levels in fetal liver as compared to the adult. Immunohistochemical staining of MRP2 in the fetal liver was canalicular, BSEP was both intracellular and canalicular, and there was low expression of MDR3, which was found only occasionally along the canaliculi.

In a mouse model, Ntcp and Bsep were the key transporters for hepatic bile acid uptake and excretion. Ntcp and Bsep mRNA levels in the liver were low in the fetus and reached the highest levels at parturition. After birth, mouse Ntcp and Bsep mRNA levels decreased to less than half, before gradually increasing to adult levels by day 30 [101].

24.4 DRUG-METABOLIZING ENZYMES (DMEs)

Owing to changes in the sex hormones progesterone and estrogen in different trimesters of pregnancy, alterations occur in the expression and activity of DMEs in the mother, particularly in the placenta [14,102–106]. Some of the DMEs are typically absent in the fetus and develop either immediately or subsequently after birth.

24.4.1 DME Changes in the Pregnant Mother

The sex hormones are ligands of pregnane X receptor (PXR) and thus significantly influence the expression of CYPs. For example, levels of CYP2A6, CYP2C9, CYP2D6, and CYP3A4 were increased, while expression of CYP1A2 and CYP2C19 was lowered during pregnancy [107]. Also, expression of UGT1A4 and UGT2B7 was enhanced. Such changes in DME expression have the potential to alter the pharmacokinetics of drugs and even carry the propensity to form toxic metabolites, with the possibility to even cause birth defects. For example, a genetic defect in arene oxide detoxification increased the risk of birth defects in case of an epileptic mother who has been treated with phenytoin [108]. A study to assess potential contribution of enzymatic bioactivation of phenytoin to a teratogenic metabolite, using a murine embryo culture model, suggested that the embryo had expression of responsible DMEs [109]. Similarly, a direct relationship between pharmacogenetics and drug-induced birth defects has been proposed for folate metabolism [110]. It has been suggested that enhanced metabolic conversion of valproate to its toxic metabolites (e.g., 2-propyl-4-pentenoic acid) during pregnancy is associated with its teratogenicity at higher doses [111].

24.4.1.1 CYP450. Endogenous sex hormones, namely, progesterone and estrogen, and exogenous substances, such as rifampicin, phenobarbital, and polyaromatic hydrocarbons (PAHs), influence expression and activity of CYPs via influence on nuclear

receptors and/or immunomodulators [112]. Hepatic transcription factors such as aryl hydrocarbon receptor (AhR), PXR, and constitutive androstane receptor (CAR) play a critical role in the upregulation of the expression of hepatic CYPs [113].

Among the CYPs, CYP1A2 activity reduces gradually from early to late pregnancy [107]. The respective reduction was as much as 33%, 48%, and 65% during 14–18, 24–28, and 36–40 weeks of pregnancy relative to the postpartum period [114]. A typical example of the influence of lowering in activity of this enzyme is the decrease in clearance of caffeine that becomes half in the second and third trimesters, with no change during first trimester or after delivery [9]. Similarly, CYP2C9-mediated metabolism increased during pregnancy in humans, while CYP2C19-dependent metabolism was decreased. The clearance of phenytoin, a CYP2C9 substrate, was increased during pregnancy [115], and the dosage of the drug was required to be increased by 85% to maintain therapeutic plasma concentration [116]. In contrast, CYP2C19-mediated metabolism of proguanil to its active metabolite (cycloguanil) decreased during the pregnancy. The proguanil to cycloguanil plasma concentration ratio increased by 63% during second and third trimesters of pregnancy, as compared to postpartum [117]. In a rat study, cyp2c6 and cyp2c12 transcription and protein expression were not significantly changed during pregnancy, although intrinsic clearance of cyp2c6-mediated diclofenac 4′-hydroxylation was increased twofold on day 19 of gestation, when compared to nonpregnant controls. This was explained through the decrease in K_m for 4′-hydroxydiclofenac formation [118].

The expression of CYP2D6 is predominantly under the genetic control, and thus far, no chemical inducers of this enzyme have been reported. The enzyme’s activity fluctuated from preovulatory to luteal phases and subsequently during different terms of pregnancy. CYP2D6 activity was found to be 25% lower during luteal phase, as compared to the preovulatory phase. This was attributed to fluctuations in the progesterone levels [119,120]. This steroid has also been implicated in increased CYP2D6 activity, which goes up by 26%, 35%, and 48% at 14–18, 24–28, and 36–40 weeks of pregnancy, respectively [114]. CYP2D6 mRNA is reported in the fetal liver and term placenta, while protein expression was not found [114,121–125]. In other reports, two classical CYP2D6 probe substrate drugs, dextromethorphan and metoprolol, were used to assess the enzyme’s activity. Data showed significant increase in CYP2D6 activity [121,126]. At 26–30 weeks of gestation, metoprolol oral clearance was increased sixfold and its bioavailability decreased to half as compared to postpartum [126]. A significant decrease in the urinary dextromethorphan/dextrorphan metabolic ratio, indicative of an increase in CYP2D6 activity, was also observed during all trimesters of pregnancy [114]. In another study, 53% decrease and 63% increase in the dextromethorphan to dextrorphan plasma concentration ratio was found in extensive metabolizers and poor metabolizers of pregnant mothers, respectively [121].

The expression of CYP2E1 has been shown to be suppressed, particularly during late pregnancy [127]. Koh *et al*. [128] correlated CYP2E1 expression in mouse livers with that of peroxisome proliferator-activated receptor α (PPAR-α). The authors observed potential involvement of PPAR-α in the downregulation of CYP2E1 during pregnancy. CYP2E1 induction/suppression profile in pregnant females who consume alcohol has been correlated with congenital abnormalities including low birth weight, mandibular hyperplasia, and developmental delay [129]. In the rodents, cyp2e1 expression has been demonstrated to be controlled at three different levels: posttranslationally by

ligand-dependent enzyme stabilization, translationally by stabilization of its RNA, and transcriptionally during ontogenesis [130].

CYP3A4 and CYP3A7 are the major isoforms expressed in adult and fetal livers, respectively. Unadkat *et al*. [113,131–136] studied changes in pharmacokinetics of CYP3A4 substrates (anti-HIV drugs) during pregnancy in different species, including humans, and suggested that decrease in C_{max} of anti-HIV drugs during pregnancy was due to increase in CYP3A4 expression. On the other hand, the expression of CYP3A7 was downregulated during intrauterine development in the first trimester of pregnancy [137].

24.4.1.2 Uridine 5′-Diphosphoglucuronosyltransferase (UGT). UGT is a phase II enzyme that consists of two major families, UGT1 and UGT2. UGT expression is significantly influenced by changes in female sex hormone levels and by activation of nuclear receptors [14,102]. UGT1A is expressed in the first trimester but not in the term human placenta [138,139]. UGT1A1 is involved in the glucuronidation of bilirubin. During pregnancy, its activity is enhanced by progesterone in a concentration-dependent manner, whereas estrogens have no influence [14]. UGT2B isozyme expression is not influenced by changes in progesterone and estrogen during pregnancy [14].

24.4.1.3 Glutathione S-Transferase (GST). GSTs play a central role in xenobiotic detoxification and have been classified as GST-alpha (GSTA), GST-mu (GSTM), GST-pi (GSTP), and GST-theta (GSTT) subtypes. These enzymes neutralize electrophilic metabolites by conjugating them with glutathione. Overall hepatic GST activity was induced during pregnancy [140].

24.4.1.4 Sulfotransferase (SULT). Sulfation is an important mechanism for regulating biological activity of numerous hormones and neurotransmitters. Tissue-specific regulation of SULT expression was observed during placental development. SULT activity assays and Western blot analysis in human placental cotyledon and membranes (amnion, chorion, and decidua basalis) from 13 to 42 weeks of gestation revealed expression of phenol and catecholamine sulfotransferases at the highest levels. These were generally higher in the villous than membranous tissues [141]. Estrogen sulfotransferase existed at extremely low levels during early pregnancy and gradually increased through midgestation and late gestation in the decidual component of the placenta [141].

24.4.2 Changes in DMEs in the Placenta

The placenta undergoes changes during different stages of gestation and this contributes to a high degree of variability in enzymatic activities and biochemical components. In the human placenta, many changes occur during the course of gestation periods, with variability contributed by factors, such as diet and exposure to environmental chemicals. However, biochemical processes related to the drug metabolism are not extensively studied in placental tissues, as compared to the liver. This is likely due to the strong association between the hemoglobin/methemoglobin and the homogenized placental membranes, which contributes to difficulty in the preparation of placental DMEs [142–144].

The enzymes CYP1A1, CYP1A2, CYP2C, CYP2D6, CYP2E1, CYP2F1, CYP3A4, CYP3A5, and CYP3A7 are expressed at mRNA levels in the first-trimester placenta. CYPs reported in full-term placenta are CYP1A1, CYP2E1, CYP2F1, CYP3A3/4, CYP3A5, and CYP3A7. The expression of these enzymes in placenta was much lower than that in the liver and lungs. The methodologies used for the detection of CYPs in human placenta in the first-trimester and full-term placenta are listed in Table 24.4.

The subtype CYP1A1 was expressed during both first trimester and full term, which was reflected by ethoxyresorufin-O-deethylase (EROD) activity in the human placenta. The enzyme was involved in the metabolism of xenobiotics that are widely used in pharmacotherapy or even present in the diet. It also played a key role in the metabolic activation of procarcinogens, such as arylamines and PAHs, that form adducts with placental and fetal DNA. CYP1A1 expression was transcriptionally upregulated through ligand-activated AhR, which plays an important role in adaptive response to xenobiotics. AhR was activated in the placenta by maternal cigarette smoking, polychlorinated biphenyls and dichlorodiphenyltrichloroethane (DDT) [150–152]. The toxicological consequences of CYP1A1 induction in the placenta of women smokers, have been summarized, which include premature birth, intrauterine growth retardation (IUGR), structural abnormalities, fetal death or placental abruption, risk of low birth weight, low birth length, and low head circumference [153]. The expression of the subtype CYP1A2 is reported in the first-trimester placenta, while it was absent in full-term placenta [123]. Similarly, CYP2C and CYP2D6 showed mRNA expression in first-trimester placenta, while protein expression was not detected at any stage of pregnancy [154].

CYP2E1 was detected at mRNA level in the placenta but was not detected immunochemically and by enzyme activity assays. This could be due to lower sensitivity of the assays or there is the possibility that mRNA might not have translated into active protein as both posttranscriptional and posttranslational mechanisms regulated its expression [155]. Placental CYP2E1 was induced on heavy alcohol consumption and is held responsible for susceptibility to alcohol-related birth defects. The proposed reason is the increase in the amount of circulating placental acetaldehyde [156,157]. The expression of CYP2F1 mRNA was established in both first-trimester and full-term placenta using RT-PCR, but protein expression and function values are yet not proven [154].

CYP3A isoforms were expressed in the placental trophoblast cell lines [158]. Although the activity of CYP3A *per se* was not found in the human placenta, the expression of CYP3A4/5 was found in the full-term placenta [123]. In comparison, CYP3A7 was detected in the first- and second-trimester placentas, while it was absent in full-term placenta [159].

24.4.3 Changes in DMEs in the Fetus

A study to assess the effect of smoking and genetic polymorphisms on the fetus in 293 women in Japan revealed that birth weight and length were significantly lower in infants born to heavy smokers with the wild-type *AhR* and the *CYP1A1* variant genotypes (m1/m2 + m2/m2) or the *GSTM1* null genotype [160]. CYP1A2 has been reported to be absent in the human fetal liver, appears gradually after birth, and takes several months to years to reach the adult levels [161]. Another important subtype is CYP2D6. Its mRNA is reported in the fetal liver but no protein expression was found [114,121–125]. The concentration of CYP2D6 is shown to increase a few days after birth [125], but remains low during the first month of life (about 20% of an adult’s levels) [162]. Its level in

TABLE 24.4 **The Presence of CYPs in Human Placenta during Different Gestational Stages and Methodologies Used for their Detection**

CYP	First-Trimester Placenta	Methodology Used for Detection	Full-Term Placenta	Methodology Used for Detection	Metabolic Role
CYP1A1	+	Enzymatic activity determinations [139], immunoblot methods [124], RT−PCR [145], Western blot, slot-blot analyses [146]	+	Enzymatic activity determinations [123], mRNA in northern blot, RT-PCR [123], immunohistochemistry, immunoinhibition assays [123]	Detoxification of aromatic hydrocarbons 146,147
CYP1A2	+	RT-PCR	−	RT-PCR, diagnostic inhibitors [123]	Detoxification of aromatic amines [148]
CYP1B1	+	RT-PCR	+	RT-PCR [123]	
CYP2C	+	RT-PCR [124]	−	RT-PCR [123]	
CYP2D6	+	RT-PCR [124]	−	RT-PCR [123]	
CYP2E1	+	RT-PCR [124]	+	RT-PCR [123], western blot	Low molecular weight procarcinogens (nitrosamines), organic solvents, and drugs such as paracetamol and chlorzoxazone [149]
CYP2F1	+	RT-PCR [124]	+	RT-PCR [123]	
CYP3A4/7	+	RT-PCR, immunoblot methods [123], Western blot,	+	Northern blot, RT-PCR [123], Western blot	

Abbreviations: RT-PCR, reverse transcription polymerase chain reaction.

newborn is low even during lactation, and the same is independent of the functional genotype. Thus, fetuses and neonates have been categorized as poor metabolizers of CYP2D6 substrates (such as dextromethorphan), as the clearance of the latter is low. Therefore, individualization of dosing has been suggested in order to prevent drug accumulation or toxicity of CYP2D6 substrates [163]. The variability of CYP2D6 activities in infants older than 1–2 weeks is found to be similar to the adults, and is also influenced by the genotype [164].

On the other hand, CYP2E1 is not detected in the fetal liver but was expressed in the first few hours following birth, and the same was independent of the gestational age (between 25 and 40 weeks). The steady increase in expression continued during the first year [130]. Similarly, CYP3A4 expression level was initially very low (10 pmol/mg protein), which increased with age [137]. Against it, the expression of CYP3A7 in fetal liver microsomes falls between 311 and 158 pmol/mg protein and showed significant expression till six months of postnatal age [165].

In a report on UGTs [166], UGT1A1 was found to be absent in the prenate and its expression was triggered during birth. It reached adult levels by three to six months of postnatal age. UGT1A3 expression was observed in the fetus and neonate liver, which was one-third of the adult expression. The same conclusion is drawn in other studies where UGT1A subfamily members were found to be absent in the fetus, their expression appeared in neonates and gradually reached adult levels at 10 years of age [167,168]. UGT2B7 is the only UGT2B isoform observed in the liver of fetus aged 15–27 weeks, where its expression was 10–20% of the adults. These levels remained consistent till birth, after which there was a rapid increase in expression that reached adult levels by two to six months of age [169,170].

Expression of GSTs has been found to vary to a large extent during fetal growth. At gestational age of 10 weeks, expression of hepatic GSTA1 and GSTA2 was to the extent of 182.4–247.2 and 14.2–31.2 pmol/mg cytosolic protein, respectively. During the initial two years, the levels of GSTA1 and GSTA2 increased by 1.5- and 4-folds, respectively. Thereafter, they were detected in the liver throughout life. Like GSTA, the GSTM subtype also exhibited very low expression during early stages of life and the expression increased fivefold by adulthood. GSTP1 was detected at the level of 18.0–25.2 pmol/mg cytosol proteins during 10–22 weeks of gestational age and decreased continuously in the subsequent trimester. The expression is not reported in the adult liver. The pattern of fetal kidney expression of GSTP1 before 35 weeks' gestational age was similar to that observed for GSTA1/A2. After 35 weeks of gestation till term, the same was restricted to the collecting tubules and the distal loop of Henle [171–173]. The presence of GST isoforms in the urinary epithelia, digestive tract, and respiratory tract highlighted the importance of GST in detoxification reactions at a very early age, suggesting that an embryo has the capability to defend against toxic compounds to some extent [163].

No activity of SULT1A3 has been reported in adult human liver, although it is expressed at high levels early in the fetal development [174]. The same decreased significantly in the late fetal and early neonatal development. The fetal lung had significant SULT1A3 activity, while neonatal levels were considerably lower. The expression of SULTs in the developing fetus is more widespread than that in the adult. Studies on enzyme activity and protein and mRNA expression of SULT1A, SULT1B, SULT1C, SULT1E, and SULT2A families in a variety of human fetal and adult tissues revealed that SULTs were expressed in the human fetus at levels equivalent to or higher than

the adults [175]. SULT1B1 was expressed at high levels in the fetal small intestine, while SULT1C2 was expressed in fetal liver, kidneys, and small intestine but not in the adult liver or colon [175].

24.5 CLINICAL IMPLICATIONS OF DRUG THERAPY DURING PREGNANCY

As discussed above, pregnancy results in physiological changes, development of the placenta and changes related to the development and protection of the fetus. The placenta plays a significant role in drug metabolism and transport of xenobiotics between maternal and fetal compartments. Apart from genetic factors and maternal infections, it is the unwanted transfer of drugs from the mother to the fetus that can affect the latter through different stages of its growth and lead to drug-related birth defects and teratogenicity. Drugs influence the development of the fetus at three stages of pregnancy: (i) fertilization and implantation (from conception to 17 days), leading to the failure of pregnancy, which is generally unnoticed; (ii) organogenesis (18–55 days), wherein deformities in organs can occur; and (iii) growth and development (56 days onwards), where the end result is developmental and functional abnormalities. Toxicity of some drugs depends on the stage at which these are administered.

Numerous drugs prescribed to pregnant women, such as antihypertensives, antiepileptics, anticancer drugs, and anti-inflammatory agents, have the potential to cause birth defects in the fetus after crossing the placenta. Drug-related birth defects are heart malformations, including holes in the heart chambers; premature birth; persistent pulmonary hypertension of the newborn; brain defects; facial and spinal defects and fetal alcohol syndrome. Table 24.5 summarizes the examples of drugs that can cause teratogenic abnormalities.

24.6 CONCLUSIONS

Pregnancy presents additional challenges for safe and efficacious drug administration to the prospective mother. The physiological changes in the body as a whole, modifications in the drug transporters, alterations in expression of DMEs, and the presence of polymorphic forms make the prediction of pharmacokinetics and pharmacodynamics of any given medication difficult. Added are the ethical concerns with respect to the safety of the fetus, so hurdles exist in testing and following the paths taken by drugs in pregnant women. This is the reason for the relatively limited research in the field. There is a need for improvement in preclinical models for evaluating the contribution of DMEs and transporters early in the drug development. This may help to design and develop safer drugs, with reduced fetal exposure.

ACKNOWLEDGMENT

The authors wish to thank Deepak Suresh Ahire and Ninad Ramesh Varkhede (NIPER, SAS Nagar) for their help in the literature search and compilation of data.

TABLE 24.5 Drugs Administered to Pregnant Mothers (under Various Disease Conditions) during Different Trimesters and Their Teratogenic Effect on Fetuses

Drugs Crossing Placenta	Trimester	Fetal Birth Defect and Toxicity	References
Selective serotonin uptake inhibitors	First trimester	Omphalocele, craniosynostosis, congenital heart defects, laterality defects, conotruncal defects, atrioventricular defects, right ventricular outflow tract obstruction defects, left ventricular outflow tract obstruction defects, septal defects, anomalous pulmonary venous return.	176,177
Female sex hormones	First trimester (taken unknowingly)	Cardiovascular birth defects	178
Lamotrigine	First trimester	Orofacial cleft, ventricular septal defect, bilateral hip dislocation, club feet	179
Folic acid antagonists	Second and third months	Cardiovascular defect	180
Bendectin	First trimester	Isolated cleft palate, cleft lip with or without cleft palate, heart defects	181
Tumor necrosis factor antagonists	NS	Vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities association	182
Tranquilizers (meprobamate or chlordiazepoxide)	First 42 d	Teratogenic	183
Cocaine	NS	Embryonic or fetal vascular disruption	184
Aspirin	First trimester	Teratogenic	185
Methamphetamine	First and second trimesters	Teratogenic	186
Acetaminophen	First trimester	Gastroschisis	187
Trimethadione	NS	Malformed ears, cleft palate, cardiac defects, urogenital malformations, and skeletal abnormalities	188
Carbamazepine	NS	Spina bifida	189

Abbreviation: NS, not specified.

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