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Ali S. Faqi *Editor*

Developmental and Reproductive Toxicology

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Dedication

This volume is dedicated to Somalia and to the suffering people of Somalia. In addition, I dedicate this to my parents, my elder brother Abdulqadir Said Faqi, my dear Yasmine Allas, and my colleague Lisa Heimsath.

Preface

Developmental toxicity is defined as the study of adverse effects on the developing organism that may result from exposure to drugs/chemicals prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation.

The thalidomide disaster is widely believed to be the catalyst that promoted regulatory agencies around the world, including the US FDA, to initiate requirements for new drugs to be thoroughly tested in animals prior to being sold in the marketplace.

At that time, developmental toxicity studies conducted in animals were inappropriately designed and insufficient to detect a teratogenic signal.

We currently rely on animal testing to predict the potential for drugs or chemicals to cause developmental toxicity in humans. Rodents (rats and mice) and rabbits are the most relevant species used in developmental toxicity testing, dogs and minipigs are rarely used, and nonhuman primates may be used for biologics, especially for monoclonal antibodies.

Manifestation of developmental and reproductive toxicity may include adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, structural abnormalities, premature reproductive senescence, and modifications of other functions that are dependent on the integrity of the reproductive systems.

Evaluation of developmental and reproductive toxicology endpoints is an integral part of the safety assessment process for compounds with potential use in women of childbearing age or females that might be exposed during pregnancy as well as men of reproductive potential.

This volume covers metabolism and drug-drug interactions during pregnancy, critical periods of developmental toxicology, in vivo and alternative methods to assess potential developmental toxicity for drugs and chemicals, and effects of chemicals on testes and mammary glands. The in vivo assessments are guideline-driven and are required for submissions for product approval.

On the other hand, alternative methods for developmental toxicity testing have been sought because of the pressure to reduce the number of animals used in health research. Alternative in vitro methods include cell cultures, zebra fish, c-elegans, organ cultures, and embryo cultures and embryonic stem cells. These test systems can provide invaluable information and decrease the number of animals used in studies. The design of in vitro alternatives with good predictivity of in vivo effects is challenging, as embryo-fetal development is a continuous process of a precisely orchestrated sequence of events and any alternative assay in the field of developmental toxicity represents only part of the complexity of the whole developing conceptus and its maternal environment. Currently, the alternative methods are not used for regulatory submissions but mainly for screening and mechanistic studies.

Finally, I would like to thank all the authors/coauthors for their hard work and timely contributions. Likewise, I would like to extend my sincerest thanks and appreciation to David Casey and the entire Springer publishing team who worked tirelessly in the publication of this volume.

Mattawan, MI, USA *Ali S. Faqi*

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Metabolism and Drug–Drug Interaction in Pregnant Mother/Placenta/Fetus

Ali S. Faqi and Karsten A. Holm

Abstract

The pregnant woman and the presence of the fetus pose many challenges for proper and effective drug administration. The variety of physiological changes that takes place during pregnancy coupled together with the variety in the responses of the cytochrome P450 enzymes in terms of induction and inhibition as well as the presence of polymorphic forms which may be present and the influence of the drug transporters make predicting the pharmacokinetics and pharmacodynamics of any given drug difficult. Treatment and dosage during pregnancy and lactation with drugs such as antibiotics, antivirals, antiepileptic, anticancer, and antipsychotic medications all need to be evaluated carefully to minimize the occurrence of adverse effects due to possible excessive exposure or a lack of efficacy due to possible underexposure. In addition, as more literature data becomes available about the role of efflux transporters such as Pgp, BCRP, and MRP3 and uptake transporters OCT3 and OCTN1 in pregnancy and in the fetus with prescribed medications this information will need to be used in the evaluation. Therefore, for drugs with a narrow therapeutic window or those with marked pharmacologic or toxicological outcomes that are also cleared predominantly by a single CYP450 or handled by a single transporter, the need for systemic monitoring of plasma concentration to monitor exposure is warranted, at least during the initial days of starting a medication.

Keywords: Drug–drug interaction, Drug disposition, Pregnancy, Lactation

1 Introduction

Sixty-five percent of pregnant women in the USA take one or more drugs during their pregnancy. This does not include dietary supplements or vitamins [1].

During pregnancy the effect of drugs may very differently due to several pregnancy-induced changes in drug disposition thus making the efficacy and toxicity of drugs used by pregnant women difficult to predict. Two factors influencing both drug efficacy and disposition are the drug-metabolizing enzymes and drug transporters. Among the more influential drug-metabolizing enzymes are the enzymes of the cytochrome P450 family (CYP450s) as these enzymes are centrally involved in the disposition of the majority of drugs, they exist in many genetic variations and are regulated by multiple mechanisms allowing for their induction and/or inhibition.

In vivo studies have shown that the activity of several hepatic cytochrome P450 enzymes, such as CYP2D6 and CYP3A4, is increased during pregnancy, whereas the activity of others, such as CYP1A2, is decreased. Likewise, the activity of some renal transporters, including organic cation transporter and P-glycoprotein, appears to be increased during pregnancy [2].

The multiple forms of the CYP450s and their activities have been described in detail in numerous reports and reviews [3–5] and are touched on briefly in this chapter. The drug transporters are a newer area of intense research into the complexity of factors influencing drug pharmacology and disposition due to their integral role in drug absorption, exposure, elimination and thus an additional source of drug–drug interactions. The pharmacokinetic changes due to genetic polymorphisms and drug–drug interactions involving transporters can often have a direct impact on the therapeutic safety and efficacy of many important drugs [6]. The transporters studied and described to date are primarily from the major organs involved in drug uptake and disposition such as the GI tract, liver, kidney, and brain as described by Borst et al. [7].

The P450 metabolic pathways through their actions on drugs, endogenous compounds and concomitantly administered medications are a major source of drug–drug, drug–diet, and drug–disease/condition interactions; consequently, functional variability in this complex system can have pronounced consequences in suboptimal therapeutic response or enhanced toxicity [8]. The regulation of the numerous CYP450s is becoming better understood as research in this area continues. The genetic factors and physiological processes controlling CYP450 levels and their induction/inhibition properties are well documented [9]. Additionally, the effects of various nutritional and a disease state such as fasting, diabetes, malnutrition, and alcohol abuse on these systems has been examined and the changes in CYP450s have been discussed [8].

However, there is not much information available about changes in the CYP450s and transporter systems during pregnancy and lactation in the human female as this is an area of more recent investigation and just beginning to be understood. Understanding the physiological and biochemical factors that change in the human female during pregnancy and how they influence pharmacokinetic factors, the CYP450s and transporters is important as medication during pregnancy is common, but specific information about the changes in how these medicines are processed as a result of pregnancy or what the drug exposure is to the mother, placenta, and fetus is not fully known or understood. An accurate understanding of the pharmacokinetics and metabolism of drugs during pregnancy is essential for the safe and optimal drug therapy for the mother and fetus, thus, it is important to have a full understanding of how pregnancy influences drug disposition

factors for better therapeutic outcomes and better predictions of the pharmacokinetic changes of drugs and their effects in pregnant women as well as the fetus. This will allow better prediction of pharmacokinetic changes of drugs in pregnant women. Therefore, the goal of this review is to present what is known about these enzyme and transporter systems and how they change in women during pregnancy and lactation, in the placenta and in the fetus. In addition, the review also discusses any known drug–drug interactions in the pregnant mother/placenta and the fetus.

1.1 Drug Disposition Changes During Pregnancy and Lactation

The pharmacokinetics of various drugs may be profoundly altered during different stages of pregnancy, parturition, and lactation due to numerous physiological and biochemical changes that takes place during pregnancy. During pregnancy the physiological changes include plasma volume expansion and increases in extracellular fluid space and total body water; decreased plasma albumin concentration; a compensated respiratory alkalosis; increased cardiac output with regional blood flow changes; increased renal blood flow associated with increased glomerular filtration; changes in hepatic drug-metabolizing enzymes; and reduction in intestinal motility, increased glomerular filtration rate, and reduced plasma albumin concentration [10]. The increases in plasma volume and total body water may increase the volume of distribution and thereby increase the dose requirements that are necessary to sustain therapeutic drug levels [11].

These changes begin in early gestation but are most pronounced in the third trimester of pregnancy. More maternal physiologic changes occur intrapartum with some normalizing themselves within 24 h of delivery, while others are more prolonged only returning to normal some 12 weeks postpartum [12]. All these changes modify drug distribution, metabolism, and elimination. As a result, the exposure and disposition of many medicines may be altered during pregnancy and the resulting clinical efficacy and toxicity of these drugs can be difficult to predict or can lead to serious side effects. An increase in body weight during pregnancy may result in a decrease in dose per kilogram and thus a potential for a significant lowering of a drug's steady state concentration and thus possible suboptimal treatment.

Additionally, gastrointestinal absorption or bioavailability of drugs may vary due to changes in gastric secretion and motility.

Multiple hemodynamic changes such as an increase in cardiac output, blood volume, and renal plasma flow may affect drug disposition and elimination [13]; these changes in pharmacokinetic parameters should be considered when dosing antiarrhythmic agents in pregnant women [14]. Absorption of drugs may be decreased by nausea and vomiting associated with pregnancy, especially in the first trimester [15]. There are also increases in hormone levels, particularly estrogen, progesterone, placental growth

hormone, and prolactin which have multiple effects particularly on the drug-metabolizing enzymes. One possible effect of the hormonal change is on absorption, the increased plasma progesterone concentrations during pregnancy corresponds to decreases in gastrointestinal motility, with associated prolonged gastric emptying and intestinal transit times which may lead to delayed drug absorption and reduced peak concentrations [16]. Indeed an in-depth understanding in hormonal regulatory mechanisms is warranted for systematic understanding and prediction of the changes in hepatic drug metabolism during pregnancy [17].

Additional absorption changes for weak acid and basic drugs are due to increased gastric pH due to reduced gastric acid secretion which may affect the ionization and absorption of week acids and bases [18]. The increase in blood and total body water volumes can alter the volume of distribution for various drugs. These changes may affect drug disposition and elimination, and can cause an increase or decrease in the terminal elimination half-life of drugs.

1.2 Enzyme Influences During Pregnancy and Lactation

The enzymes of the cytochrome P450 family (CYP450s) have a central role in the pharmacokinetics and metabolism of most medicines in clinical use today. They have been extensively studied ever since there discovery in the 1950s. The majority of CYP enzymes are found in the liver, although other organs such as the gastrointestinal mucosa, skin, lung, brain, and kidney also have significant CYP expression and functional activity [19].

Pollutants and toxicants passing from the mother to the fetus may damage developing organ systems. The human fetal liver is both a potential target organ and a critical defense against exposure to such chemicals. Exposure of the fetus to pollutants/toxicants is associated with significantly altered transcript expression, with the more marked response in the male potentially affecting levels of endogenous factors involved in fetal growth [20].

The activities and nomenclature have been better defined over the last 20 years. Although there are more than 100 CYP genes in humans, there are only about 10 gene products that are important to monitor in preclinical and clinical development for potential drug–drug interactions as reported by Huang et al. [21], namely, CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, and 3A5. These CYPs have the potential for not only inhibition and induction but also genetic polymorphisms that can produce clinically important outcomes. Several of the drug-metabolizing enzymes are polymorphic, having more than one variant of the gene.

A prospective cohort study of 293 women, who delivered singleton live births in Sapporo, Japan, was conducted to estimate the effects of maternal smoking and genetic polymorphisms on infant birth weight and length. Birth weight and length were

significantly lower among infants born to continuously smoking women having the aryl hydrocarbon receptor (*AhR)* wild type genotype the *CYP1A1* variant genotype or the *GSTM1* null genotype indicating that maternal smoking in combination with maternal *AhR*, *CYP1A1*, and *GSTM1* genetic polymorphisms may adversely affect infant birth size [22].

The CYP2D6 enzyme is perhaps the most widely recognized polymorphic enzyme with a recessive poor metabolizer (PM) phenotype resulting when individuals carry two null alleles, yielding either a completely metabolically inactive protein, or no protein [23]. Although the CYP isozymes generally have similar structural and overlapping functional properties, each form has key structural differences resulting in distinct functional properties creating a distinct pattern of metabolic reactions for given substrates. Although CYP2D6 mRNA is detectable in the fetus, however, CYP2D6 protein expression remains mostly undetectable during pregnancy. The CYP2D6 protein concentration rises only a few days after birth [24], but remains low during the first month of life (about 20 % of adult's levels [25]. During the lactation (newborn) period a low level of CYP2D6 activity occurs, independent of genotype that functionally results in all new born being poor metabolizers, as a result, clearance of CYP2D6 substrates are expected to be low for almost all infants. In order to prevent drug accumulation or toxicity individualization of dosing is necessary in infants [23]. The variability of CYP2D6 activities in infants older than 1–2 weeks was largely found to be related to genetic variability [26].

With the additional dimension of genetic polymorphisms there is an increased basis for interindividual differences in the pharmacologic efficacy and side effects of drugs as well as their toxicological and carcinogenic potential. The variability associated with the CYP450 enzymes between individuals result in marked differences in responses when the same drug and the dose are administered to different individuals [12].

In addition to the genetic polymorphism found in CYP2D6, this has been also found in the CYP2C family, specifically 2C8, 2C9, and 2C19 [27].

The expression of CYP3A4 is low during pregnancy and at birth. However, it is the primary hepatic CYP expressed postnatally and is involved in the metabolism of over 75 % of commonly used drugs [23]. CYP3A7 is the major CYP isoform detected in embryonic, fetal, and newborn liver with a shift between the CYP3A7 and CYP3A4 occurring after birth [25].

Loss of consciousness was reported in neonates receiving coadministration of erythromycin (an inhibitor of CYP 3A4) with midazolam [28]. Drug–drug interactions can occur if a drug acts as an inducer or inhibitor of a CYP450 enzyme and significantly alters the function of that enzyme or if an individual has a polymorphic variant form of a CYP450 enzyme. The degree of induction or

inhibition of CYP 3A4 might be influenced by the developmental changes which could further enhance the drug–drug interactions in an immature system.

Regarding changes found in the CYP450 system in pregnant adult women, it has been shown that the changes are variable and affect only a few of the CYP450 enzymes. It has been demonstrated that the activity of the CYP2C subfamily, CYP2D6 and CYP3A4 enzymes increase, while in contrast, the activity of CYP1A2 decreases [29, 30]. The study by Wadelius et al. [30] on CYP2D6 activity involved 17 pregnant women phenotyped into 3 groups with 4 as poor metabolizers, seven as heterozygous extensive metabolizers and six as homozygous extensive metabolizers with dextromethorphan in late pregnancy and 7–11 weeks after parturition. During pregnancy, the metabolic ratio of dextromethorphan and dextrorphan was significantly reduced ($p = 0.0015$) in the homozygous and heterozygous extensive metabolizers, consistent with increased CYP2D6 activity. In contrast, the poor metabolizers showed an increased metabolic ratio during pregnancy. This study finding was consistent with a previous study finding which found a marked increase in the metabolism of the CYP2D6 substrate metoprolol during pregnancy. Because both studies found an increase in CYP2D6 activity during pregnancy, it was suspected that pregnancy somehow causes the induction of the CYP2D6 enzyme. The findings of Davis et al. and Wadelius et al. [29, 30] have been recently confirmed in a study by Tracy et al. [31] which also showed increases in CYP2D6 and CYP3A4 activity and a decrease in CYP1A2 activity. In this study 25 subjects completed the study conducted at several stages of pregnancy, 14–18 weeks, 24–28 weeks and 36–40 weeks, and again at 6–8 weeks after delivery. The enzyme activity results from the 3 phases of pregnancy were compared with the postpartum period. It was found that CYP1A2 activity decreased progressively during the pregnancy relative to the postpartum period with activity reductions of 33, 48 and 65 at 14–18 weeks, 24–28 weeks, and 36–40 weeks, respectively. CYP2D6 activity increased over the course of the pregnancy relative to the postpartum period with increases of 26, 35 and 48 % at 14–18 weeks, 24–28 weeks, and 36–40 weeks, respectively. CYP3A4 activity increased consistently and similarly at each phase relative to the postpartum period with increased activity between 35 and 38 %. Thus, pregnancy can cause opposing actions on the CYP450 system with increases in CYP2D6 and CYP3A4 activity and a decrease in CYP1A2 activity [31]. Recently, increased Cyp3A4 expression; unchanged Cyp2A5 expression and decreased Cyp1A2, Cyp2C37, Cyp2D22, Cyp2E1, and Cyp3A11 was reported in mice during pregnancy Also expression of CYPD22 and CYP2 E1 isoforms correlated with that of peroxisome proliferator-activated receptor PPARα in the mouse livers, suggesting potential involvement of PPARα in downregulation of the

P450 expression during pregnancy [32]. In addition, they found that the expression of Cyp2D22 and Cyp2E1 isoforms directly correlated with that of peroxisome proliferator-activated receptor (PPAR) α in the mouse livers, which led them to suggest potential involvement of PPARα in downregulation of the P450 expression during pregnancy. It is fair therefore to conclude that any dosing adjustment during pregnancy will depend on the medication and the enzyme involved in its metabolism.

Another important aspect is the formation of toxic metabolites that could lead to birth effects. For example, a genetic defect in arene oxide detoxification seems to increase the risk of the baby having major birth defects in epileptic women treated with phenytoin [33]. Shanks et al. [34] developed a murine embryo culture model to study the potential contribution of enzymatic bioactivation to the teratogenicity of phenytoin. Their result suggest that the embryo can enzymatically bioactivate embryotoxically significant amounts of phenytoin, and that bioactivation and embryotoxicity is further enhanced, by an exogenous P-450 system, implicating a possible maternal contribution to phenytoin teratogenicity. A literature review performed on pharmacogenetics of drug induced birth defects found that direct relationship between pharmacogenetics and drug-induced birth defects exits for folate metabolism, oxidative stress caused by phenytoin exposure and drug transporters in the placenta [35].

It has been also been suggested that an increased metabolic conversion of valproate (VPA) to its toxic metabolites including 2-propyl-4-pentenoic acid (4-en) is involved in the mechanism of VPA teratogenicity at higher doses and concentrations [36].

The impact of development and CYP2C9 polymorphisms on neonatal therapeutics can be explained by the interindividual variability for AUC values reported when ibuprofen and indomethacin are used for treatment of ductus arteriosus in neonates. Although indomethacin had a higher volume of distribution in the very preterm baby; clearance from the blood stream occurs more quickly in babies more than 1–2 weeks. In addition markedly longer half-life was observed for Ibuprofen [37].

Although the impact of ontogeny for Phase II enzymes is less studied than phase I enzymes; however, the understanding of their developmental profiles is essential to recognizing the acquisition of metabolic competence in the neonate and its potential therapeutic implications [38]. Glutathione S-transferase (GST) A1 and A2 were identified in human fetal liver tissues during gestation as early as 10 weeks gestational age with adult levels not reached until 1–2 years. For GSTP1, the fetal kidney expression pattern at less than 35 weeks gestational age was similar to that observed for GSTA1/A2. In fetal tissue greater than 35 weeks of age, expression was restricted to collecting tubules and the distal loop of Henle [38]. The presence of GST isoforms in urinary epithelia, digestive tract,

and respiratory tract highlights the importance of GST in detoxification reactions at a very early age and suggests that the embryo is capable of metabolizing drugs [23]. Maternal exposure to these chemicals that induce GST including non-nutrient xenobiotics found in vegetables and citrus fruits have the potential to alter drug metabolism during pregnancy and lactation [23]. The tragedy of Gray Baby Syndrome was the result of failure to recognize the impact of development on the glucuronidation of chloramphenicol and its implications to age related individualization of therapy. The gray baby syndrome occurred in premature and newborn infants receiving high or unmodified doses of chloramphenicol and this condition can be avoided by reduction of dosage and by monitoring levels of drug in the serum of these infant [39]. Furthermore, mutation of the promoter region of UGT 1 gene has been associated with Gilbert's syndrome, a milder form of congenital unconjugated hyperbilirubinemia [40]. Sulfo-transferase (SULT1A3) activity is absent in human liver, but expressed at high levels early in fetal development, and decreases significantly in the late fetal and early neonatal development [41].

Changes in phase II drug-metabolizing enzyme expression during development, as well as the balance between phase I and phase II enzymes, can significantly alter the pharmacokinetics for a given drug or toxicant. Understanding the ontogeny of drug-metabolizing enzymes in the neonate is very important for defining the dosage regimens suitable for children and for limiting the risk of accumulation leading to adverse effects and toxicity.

1.3 Transporter Influences During Pregnancy

The drug transporters are another significant determinant in drug bioavailability and exposure. The first transporter identified was P-glycoprotein (Pgp) in 1976 [42]. Since then about 25 different transporters have been identified. The transporters can be divided into three classes. Two classes are considered uptake transporters, the SLC or solute-linked carrier transporter family and the SLCO or solute-linked carrier organic anion transporter family. The third class, the efflux transporter family, is denoted as ABC or ATP-binding cassette transporter superfamily. Notable members of this efflux family are Pgp, the multidrug-resistant proteins (MDR), the multidrug resistance associated proteins (MRPs) and the breast cancer resistant protein (BCRP) [43]. The distribution of the transporters, representative substrates, inhibitors, and inducers are also given. As shown by Shugarts and Benet [44] the intestine expresses several transporters controlling the uptake such as MCT1 (monocarboxylate transporter protein), PEPT1 and 2 (peptide transport protein), OATP 1A2 and 2B1 (organic anion transporting protein), OCT3 (organic cation protein), and others. There are several efflux transporters including Pgp, several MRPs, BCRP, MCT1, and ENT 1 and 2 (equilibrative nucleoside transporter) proteins. The liver also expresses several uptake and efflux

transporters. The hepatic uptake transporters from the blood stream include the OCTs 1 and 2, OAT2, OATPs 1B1, 1B3, 2B1 AND 1A2, NTCP (sodium-taurocholate co-transporting protein), and several MRPs 3, 4, and 5. The majority of the hepatic efflux transporters remove their compounds into the bile canaliculi, Pgp, MDR3, MRP2, BCRP, and BSEP (bile salt export pump), while one type removes compounds to the blood stream, the MRPs 3, 4, and 5 [45].

The changes in transporters in the adult female following pregnancy are not clearly understood as yet. The variety of important medications given during pregnancy such as anticancer agents, antiviral agents, and cardiovascular drugs such as warfarin can have their pharmacokinetics, their absorption, disposition, metabolism, and elimination affected in a number of ways based on the activity of the individual transporters involved or the cytochrome P450 enzymes as discussed above. While the mother's exposure and drug disposition is controlled by her own complement of cytochrome P450 enzymes, transporters, and internal hormonal and other chemical signaling systems, the drug exposure to the developing embryo and fetus is controlled primarily by the placenta and the ability of the fetus itself to handle the individual medicine given to the mother through its own complement of cytochrome P450 enzymes as discussed below.

A large number of known functional drug transporters have been found in human placenta [46]. Transporter knockout animal studies have shown the role of drug transporters in protecting the fetus from chemical effects [47]. The protection is in part due to the presence of various efflux transporters in the placenta. The effect of placental transporters in effluxing drugs such as glyburide and numerous protease inhibitors from the fetal circulation offers the potential to manipulate the passage of drugs across the placenta [48]. It is important to take into considerations, that placental transporters are vital in modulating the exposure of the fetus to drugs and, therefore, the efficacy and toxicity of such drugs towards the fetus [49]. Some of these transporters are under hormonal regulation in the placenta. Vore and Leggas [50] reported that ABCG2/BCRP expression is regulated by Estradiol and progesterone in BeWo cells, a human trophoblastic cell line.

1.4 Enzyme and Transporter Influences in the Fetus and Placenta

The placental has the ability to metabolize drugs in early pregnancy. Indeed the placenta expresses a wider variety of enzymes during the first trimester than at term [51]. Depending on the substrate, this metabolic action may have significant clinical implications on how it affects the fetus [52]. Also the developing fetus has been shown to express a number of CYP450 enzymes during its development and thus is fully capable of metabolizing endogenous and xenobiotic compounds and drugs it is exposed to. The CYP450 enzymes found to be present in the fetal liver include CYPs 1A1, 1B1,

2C8, 2D6, 2E1, 3A4, 3A5, and 3A7 after the embryonic phase (after 8–9 weeks of gestation) [23]. Xenobiotic metabolism activity was also found to be significant earlier, during organogenesis (before 8 weeks of gestation). Extra hepatic tissues such as the kidney and adrenals also contain substantial levels of CYP enzymes and can thus also exhibit metabolizing activity. The adrenals are involved in the metabolism of hormones of fetal or placental origin to help maintain and protect the fetus during gestation. The polymorphic expression of CYP3A5 and the variability of CYP3A7 expression in fetal liver were demonstrated by Hakkola et al. [53]. This suggests the existence of interindividual differences in the metabolism of xenobiotics at the prenatal stage which may contribute to individual pharmacological and/or toxicological responses in the fetus.

The placenta is also an extremely important organ for the mother and fetus. The human placenta oxidizes several xenobiotics and it represents a critical barrier from toxic agents as well as an essential organ to provide the fetus with nutrients and appropriate gas exchange during gestation. It is also active in drug metabolism and drug transport. CYP1A1, 2E1, 3A4, 3A5, 3A7, and 4B1 have been detected in the term placenta. Although little is known about phase II enzymes in the placenta, however, uridine diphosphate glucuronosyltransferases, have been detected suggesting a significant role of this enzyme in placental drug detoxification [54]. From studies in women examining the effects of smoking and found they found that placental CYP1A1 is highly inducible in pregnant women who smoke, in addition to maternal hepatic CYP1A1 and it is the most important metabolizing enzyme of the placenta for which relevant inducible activity has been demonstrated throughout pregnancy [55]. Aromatase, CYP19, and cholesterol side-chain cleaving, CYP11B genes and proteins are catalytically active in human placenta throughout the pregnancy [56].

Transport proteins play an important role in the adsorption, distribution, and elimination of a wide variety of drugs. It is therefore, comprehensible that transporter-based drug interactions can occur in the clinic. Transporter-based drug interactions in the clinic may be inhibitory, inductive, or both, and may involve influx or efflux transporters [57]. The existence of uptake and efflux transporters in organs responsible for drug biotransformation and excretion gives transporter proteins a unique gatekeeper function in controlling drug access to metabolizing enzymes and excretory pathways [44]. The presence of efflux transporters, P-glycoprotein (Pgp), the breast cancer resistance protein (BCRP), and the multidrug resistance associated proteins (MRP) in the placenta has been implicated to offer the fetus protection from medication taken during pregnancy because of their location on brush border membranes of the placenta syncytiotrophoblast [58].

Transporters for 5-HT (SERT) and NE (NET) are also expressed at the apical surface of the placenta and regulate

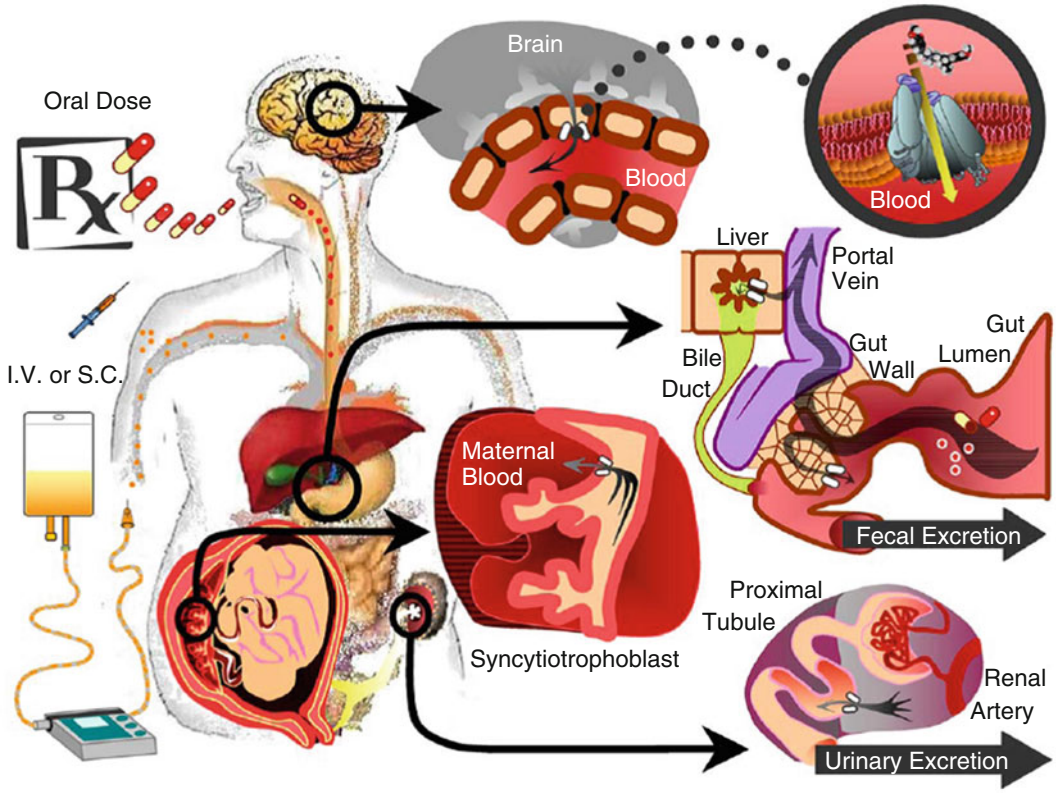

Fig. 1 In humans, P-gp is present in several tissues important for drug absorption, distribution, and elimination, such as the apical membrane of intestinal epithelial cells, the canalicular membrane of the hepatocytes, the capillary endothelial cells of the brain, the apical membrane of the placental syncytiotrophoblasts, and the apical membrane of the renal proximal tubular cells. In these tissues, P-gp functions as an efflux pump, preventing the entry of xenobiotics into these tissues (from ref. [57])

extracellular concentrations of monoamines. Some of the members of the organic anion transporters are also expressed at the basolateral surface of the syncytiotrophoblast [59]. The expression profile of these transporters varies with advancing gestation. P-gp has been shown to decline near term, leaving the fetus susceptible to potentially developmental toxic drugs commonly administered to pregnant women [60].

In the placenta, P-gp is located on the maternal-facing membrane of the syncytiotrophoblasts (Fig. 1) [58], and has been shown to play a significant role in protecting the fetus from xenobiotics [49]. However, studies in pregnant Mdr1a/b (+/+) mice, produced increase in fetal drug distribution following oral administration of the Pgp inhibitors, PSC833 or GF120918, thus indicating that the Pgp protective barrier can be ablated through pharmacological means [61].

These proteins are members of the ABC or ATP-binding cassette transporter superfamily [62]. Solute carrier (SLC) and

ATP-binding cassette (ABC) transporters play also pivotal roles in the transport of both nutrients and drugs into breast milk, thus drug–nutrient transport interactions at the lactating mammary gland are possible [63].

While most have been found to have mainly physiological substrates there are a number of drugs that also gain access to the fetus through transport across the placenta. As discussed by Hodge and Tracy [64] due to changes in many physiological parameters, the variability in the activity of the maternal drug-metabolizing enzymes as well as the influence of the drug transporters in the placenta, the exposure, efficacy, and toxicity of many drugs used by pregnant women can be difficult to predict. Transporters play an important role in exposure of the embryo/fetus to drugs with teratogenic potential during pregnancy, although the significance of placental transporters on human fetal drug exposure is almost an unstudied field so far.

1.5 Resulting Implications in Drug Disposition (DMPK) During Pregnancy

The pregnant woman presents many changes for proper drug administration as discussed above. The variety of physiological changes, the variety in the responses of the cytochrome P450 enzymes in terms of induction and inhibition as well as the presence of polymorphic forms which may be present and the influence of the drug transporters make predicting the pharmacokinetics and pharmacodynamics of any given medicine difficult. There is a lack of full information on these changes and influences that needs more investigation. Because experimenting on humans is limited the need for better animal models, in vitro systems and predictive software is needed. During pregnancy opposing changes in drug metabolism are reported to occur. This includes decreased activity of CYP1A2 and increased activity of CYP2D6 and CYP3A [31]. The CYP1A2, CYP2D6, and CYP3A enzymes are shown to be important in the metabolism of several drugs that are administered during pregnancy of coexisting conditions. Inhibitors of CYP1A2, which plays a role in metabolism of clozapine and olanzapine, include fluvoxamine and grape juice in large quantities; cigarette smoke is considered to be an inducer of enzymes. Inhibitors of CYP3A4 include erythromycin, carbamazepine, rifampin, and glucocorticoids. Women with epilepsy do have increased risks for maternal and fetal complications as children born to mothers taking antiepileptic drugs (AEDs) are at increased risk for findings of fetal anticonvulsant syndrome. In this situation the risks associated with drug exposure to the fetus and newborn need to be balanced against the risks incurred by seizures, and knowledge of pharmacokinetic alterations becomes particularly important for AED optimization. Pregnancy can affect the pharmacokinetics of AEDs at any level from absorption, distribution, metabolism, to elimination. The effect varies depending on the type of AED. The most pronounced decline in serum concentrations is seen for AEDs that are

eliminated by glucuronidation (UGT), in particular lamotrigine where the effect may be profound [65]. The apparent clearance of lamotrigine increases by 50–90 % in pregnancy, requiring dosage adjustment to prevent exacerbation of seizures [66].

These risks can be considerably reduced with careful selection of AED treatment regimens. Prescribing AEDs for women during their childbearing age should include the constant consideration of pregnancy, planned or unplanned [67].

Drug interactions involving antiviral agents mostly reflect shared toxicity with other agents (e.g., neutropenia with ganciclovir and zidovudine, pancreatitis with didanosine and alcohol), although renal excretion or hepatic metabolism may be implicated. Given the possibility of severe adverse reactions and drug interactions, antiviral chemotherapy should only be used for potentially serious virus infections during pregnancy [68].

Maternal ethanol consumption during pregnancy and lactation inhibits the hepatic metabolism of drugs such as chlorpromazine which require glucuronidation for their detoxification. This ethanol-mediated inhibition is largely exerted through the decrease in the NAD-dependent conversion of UDP-glucose (UDPG) to UDP-glucuronic acid, (UDPGA) [69].

In the fetus, important factors influencing drug metabolism are the variety of CYP450s that exist, some polymorphic, and some with changing activity in opposing directions thus presenting complicating situations on what to expect pharmacokinetically and pharmacodynamically relative to the situation in the nonpregnant state. The placenta is a very active and integral tissue in the fetal exposure to drugs. With the presence of both several CYP450s and drug efflux transporters, and there may be others as yet unknown, the placenta plays a very active role controlling the exposure of the fetus to drugs taken by the mother. The opinion on the implications for exposure and disposition is mixed. Depending on the drug and the enzyme and transporter involved the clinical response may be significant or uneventful. Therefore, for drugs with a narrow therapeutic window or those with marked pharmacologic or toxicological outcomes that are also cleared predominantly by a single CYP450 or handled by a single transporter, the need for systemic monitoring of plasma concentration to monitor exposure is warranted, at least during the initial days of starting a medication. In addition, improved understanding of transplacental drug transfer and metabolism will result in further enhancement of the clinical treatment of fetal diseases/conditions.

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