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EXPERT REVIEW

The Placental Barrier: the Gate and the Fate in Drug Distribution

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ABSTRACT Optimal development of the embryo and the fetus depends on placental passage of gases, nutrients, hormones, and waste products. These molecules are transferred across the placenta via passive diffusion, carrier-mediated cellular uptake and efflux, and transcytosis pathways. The same mechanisms additionally control the rate and extent of transplacental transfer of drugs taken by the pregnant mother. Essentially all drugs cross the placenta to a certain extent, and some accumulate in the placenta itself at levels that can even exceed those in maternal plasma. Hence, even drugs that are not efficiently transferred across the placenta may indirectly affect fetal development by interfering with placental function. In this article, we describe key properties of the placental barrier and their modulation by medications. We highlight implications for pharmacotherapy and novel approaches for drug delivery in pregnant women and their fetuses.

KEY WORDS drug transporters · maternal-fetal pharmacology · placenta · placental transfer · pregnancy

ABBREVIATIONS

ABC	Adenosine triphosphate binding cassette
BBMVs	Placental brush-border membrane vesicles
BCRP	Breast cancer resistance protein
CNT	Concentrative nucleoside transporter
CYP	Cytochrome P-450
ENT	Equilibrative nucleoside transporter
FcRn	Neonatal Fc receptors
LAT	L-type amino acid transporter
MDR	Multidrug resistance protein
MRP	Multidrug resistance-associated protein
NET	Norepinephrine transporter
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT, OCTN	Organic cation transporter
P-gp	P-glycoprotein
RFC	Reduced folate carrier
SERT	Serotonin transporter
SLC	Solute carrier
UGT	Uridine diphosphate glucoronosyltransferase

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INTRODUCTION

Extensive evidence for the permeability of the placenta existed long before the thalidomide disaster. As long ago as 1904, JW Ballantyne, a teratologist in Edinburgh, listed "varieties of fetal morbid states", including alcoholism, lead-poisoning and morphine-poisoning (1). Sulfonamide drug transfer to the fetus was reported in the late 1930s (2,3), followed by studies in the 1940s and 1950 that demonstrated transplacental transfer of many other drugs (4). The damaging effect of maternal rubella on the fetus was proven by NM Gregg in 1941 (1). However, until the 1960s drugs were prescribed freely during pregnancy, based on the belief that the placenta is a perfect barrier against harmful influences in the environment (1). Moreover, studies on the placental transfer of hormones and nutrients in pregnant women utilized radiolabeled compounds as substrates (5–7).

The placenta plays a significant role in fetal and adult health, and placental pathology is implicated in all common obstetric complications, including preeclampsia and intrauterine growth restriction (8–10). When pregnant women are treated with medications, the placenta is not only the fetal gatekeeper but is also by itself a potential target to their therapeutic and adverse effects. The consequences of fetal (and placental) exposure to medications can be benign or involve structural or behavioral teratogenicity, or even termination of pregnancy, and are often unknown (11). Furthermore, neurodevelopmental and other defects may be detected long after the drug has been on the market. The pregnancy outcomes depend on intrinsic drug effects and the duration, length and extent of exposure.

In this review, we present the current understanding of placental fate and effects of drugs. To paraphrase Alfred Goodman et al., we describe what the placenta does to the drug (placental pharmacokinetics) and what the drug does to the placental barrier (placental pharmacodynamics) (12). The focus is on the human placenta, but we also present studies conducted in animal models.

THE GATE: HOW SUBSTANCES ARE TRANSFERRED INTO AND ACROSS THE PLACENTA

The placenta is formed from the zygote at the start of pregnancy and has the fetal genetic composition. During most of the first trimester of pregnancy maternal blood flow to the placenta is limited, and maternal–fetal exchange takes place via the extracoelomic fluid. By 12 weeks of gestation, the exocoelomic cavity disappears, the amniotic cavity fills the entire uterine cavity, and maternal blood perfuses the placenta. At term, maternal blood supply to the placenta is approximately 30% of her cardiac output (13).

The mature human placenta is a discoid organ, weighing approximately 500 g. It is divided into several cotyledons, each representing an independent functional vascular unit. Placental cotyledons contain branched fetal villous trees, bathed by maternal blood (10,14,15). The villous trees are separated from maternal circulation by an epithelium-like layer, the villous trophoblast. At the end of the first trimester of pregnancy, all villi are covered by a two-layered trophoblast epithelium, consisting of the cytotrophoblast and the syncytiotrophoblast (15). As the pregnancy proceeds, the cytotrophoblast layer partially disappears and the syncytiotrophoblast layer is progressively thinned. At term, a single syncytiotrophoblast layer separates maternal blood from fetal capillary endothelium (10,14).

The syncytiotrophoblast is considered the functional part of the placental barrier. A single placenta has a single syncytiotrophoblast, which covers all villous trees and comprises a continuous layer without lateral cell borders (15). The syncytiotrophoblast is a polar layer with a basal membrane facing the fetal side and a microvillous apical membrane in direct contact with maternal blood. The microvilli provide a surface amplification factor of 5–7 which facilitates solute transfer across the placenta (14,15). Yet, the syncytiotrophoblast may function as a diffusional barrier. Carrier proteins and cellular enzymes can either restrict or facilitate substrate transfer across the placenta. A non-fenestrated endothelium which lines the fetal vessels throughout gestation further reduces paracellular transport between mother and fetus (14,15). Three main processes mediate the transplacental passage of nutrients, hormones, waste products and drugs across the intact placental membranes: passive diffusion, carrier-mediated transport and transcytosis.

PASSIVE DIFFUSION

Passive diffusion is the predominant route by which many drugs cross the placenta, and applies mostly to hydrophobic molecules of less than 600 Da. High molecular weight drugs such as insulins and heparins are not transported to the fetus in significant amounts (Fig. 1) (16–18). Theoretically, the unbound and unionized concentrations of such drugs should be similar in maternal and fetal circulation (19). However, the total concentrations of drugs that simply diffuse across the placenta (or their metabolites) in fetal blood and tissues may exceed maternal blood levels (Fig. 1). The pH of fetal plasma is lower as compared to that of the mother, by 0.1 of a pH unit, and weakly basic drugs may accumulate in the fetus, especially during fetal distress and acidosis. Drug binding to fetal proteins may form a reservoir from which the drug is slowly released, thereby contributing to longer retention of the drug in the fetal compartment and extended effect on the fetus (20). The diffusion rate of solutes that rapidly diffuse across the placenta such as inhalation anesthetics is influenced by the rate of placental blood flow ("flow-limited"). Placental blood flow increases throughout pregnancy, and, together with the increase in placental surface area and the reduction in the trophoblast's thickness, can result in accelerated passive diffusion of drugs as pregnancy progresses (21). Placental blood flow can be affected by various conditions, including medications taken by the mother. As an example, some inhalation anesthetics can affect their own transfer due to their effect on maternal respiratory system and circulation (4).

CARRIER-MEDIATED TRANSPORT

Placental carriers mediate the uptake of hormones and nutrients from maternal blood into the fetus and the removal of metabolites back to maternal blood, and take part in the
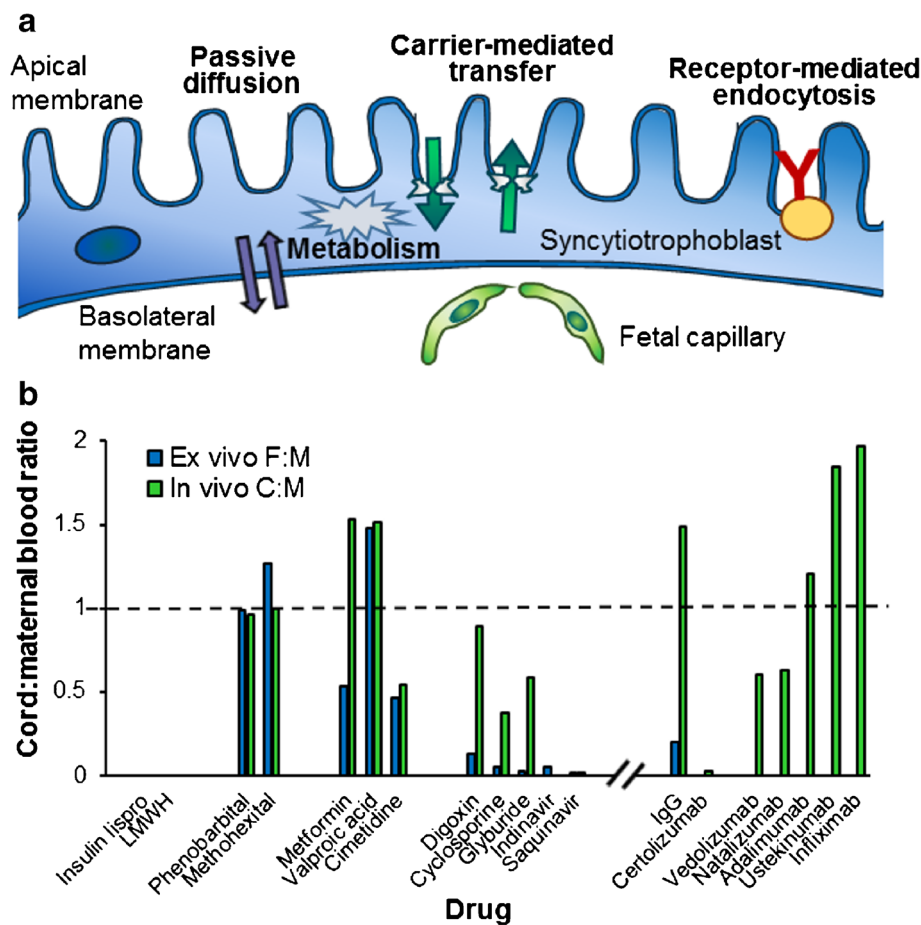
Fig. 1 Mechanisms of transplacental transfer of drugs. (**a**) Schematic diagram showing the major mechanisms contributing to the passage of drugs into and across the syncytiotrophoblast. Drugs and their metabolites can cross the placenta by passive diffusion, carrier-mediate transfer (facilitated diffusion or active transport), or transcytosis. Within the syncytium, drugs can undergo metabolism. (**b**) Maternal to fetal concentration ratios of representative drugs known to be transferred across the placenta. The drugs are grouped based on known mechanisms of their placental transfer, as shown in (**a**). Drug transfer was measured *ex vivo* in the perfused human cotyledon model (fetal to maternal ratio; F:M) and *in vivo*, in cord and maternal plasma (cord to maternal ratio; C:M). Insulin and low molecular weight heparins are large molecules that are not transferred to fetal blood at significant amounts. Phenobarbital and methohexital rapidly diffuse across the placental membranes. Metformin, valproic acid and cimetidine are predominantly substrates of uptake carriers. Digoxin, cyclosporine, glyburide, indinavir and saquinavir are substrates of P-glycoprotein, the breast cancer resistance protein (BCRP), or both (although uptake transporters are also involved in their transplacental distribution). Values of drugs which are primarily efflux transporter substrates are typically less than unity. IgG and therapeutic IgG-based antibodies are transferred across the placenta by receptor-mediated transcytosis (via FcRn receptors), unless they are based on the AB fragment only (certolizumab). Because transcytosis is a slow process, perfusion studies tend to underestimate their cord:maternal concentration ratios. Note that the transplacental transfer of vedolizumab, natalizumab, adalimumab, ustekinumab and infliximab has been reported only *in vivo*. LMWH, low molecular weight heparin. The fetal:maternal ratios of insulin lispro, phenobarbital, methohexital, metformin, valproic acid, digoxin, and glyburide were corrected for maternal and fetal/neonatal protein binding and blood pH (16). References are provided in Supplementary Material.

homeostasis of placental tissue itself (21). The impact of a carrier on substrate transfer across the placenta would be substantial only if this transporter is the predominant route of placental transfer of the drug (21). Carrier proteins share common features such as saturation kinetics and the ability to be competitively inhibited (14), but may differ from each other with respect to substrate selectivity, placental localization, and transcriptional regulation. Carriers can facilitate the transmembranal transfer of substrate drugs down concentration gradients (facilitated diffusion) or against them (active transport). Uptake carriers are involved in substrate influx into the syncytium and fetal capillary cells, whereas efflux carriers export their substrates from cells. Some carriers can exhibit

bidirectional substrate transport. Most placental carrier proteins are members of two major transporter superfamilies, ABC (adenosine triphosphate binding cassette) and SLC (solute carrier) transporters (22,23).

Nutrients and other essential compounds may be transferred across the apical and basolateral membranes of syncytiotrophoblasts by carriers which are relatively substrate-specific, such as those involved in the transfer of folic acid (vitamin B9), including the reduced folate carrier (RFC; *SLC19A1*) and the proton-coupled folate transporter (*SLC26A1*) (24). Although such carriers are not likely to be major contributors to transplacental drug transfer, they can become drug targets, as described below. In other cases,

placental carriers may be "polyspecific" and significantly contribute to drug disposition (25). For example, substrates of the L-type amino acid transporter (LAT1; *SLC7A5*) include, in addition to thyroid hormones, gabapentin, melphalan, baclofen, methyldopa, and methyltyrosine (26). Placental carriers have been shown to play key roles in the distribution of many other compounds essential for fetal development and placental function, such as monoamines nucleosides and carnitine, as described below (27).

Transporters of the Adenosine Triphosphate Binding Cassette Superfamily

ABC transporters are efflux pumps which depend on energy derived from ATP hydrolysis and function to remove substrates from cells or their membranes. Many placental ABC transporters are located on the maternal-facing membrane of the syncytiotrophoblast, a position suitable for drug removal from the placenta towards the maternal circulation (28). Accordingly, the fetal concentrations of drugs which are predominantly substrates of efflux transporters are usually lower than in maternal plasma (Fig. 1). The most studied placental ABC transporters and likely the most clinically relevant ones are P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) (23). Functional activities of several multidrug resistance proteins (MRPs) have also been identified in the human placenta.

P-gp (MDR1)

P-gp is expressed in humans on the apical membrane of syncytiotrophoblasts and on villus maternal and fetal endothelium. P-gp is encoded in humans by the *ABCB1* gene (29). In rodents, two homologs genes, *Abcb1a* and *Abcb1b*, encode for the corresponding Mdr1a and Mdr1b proteins (30). P-gp substrates are generally lipophilic molecules, of which many are cationic, but several neutral of anionic compounds are also P-gp substrates. Substrate drugs include HIV protease inhibitors, immunosuppressive drugs, and chemotherapeutic compounds such as anthracyclines, vinca alkaloids and tyrosine kinase inhibitors (31). P-gp has been detected in syncytiotrophoblast cells throughout gestation, but expression of its mRNA and protein decreases with gestational age (32,33). Inter-individual variability in P-gp-mediated transport has been suggested to result, as least in part, from single nucleotide polymorphisms of the MDR1 gene, but the importance of such polymorphisms at the human placenta has yet to be established (34,35).

The role of P-gp in fetal protection was first demonstrated in variants of a CF-1 mouse strain containing a defective *Mdr1a* gene. Following exposure of pregnant mice to an isomer of the pesticide avermectin, cleft palate was observed in all fetuses homozygous for P-gp deficiency and 30% of

heterozygous fetuses. The homozygous wild type fetuses were insensitive to avermectin (36). In fetuses devoid of both *Abcb1* genes, the concentrations of [^{3}H]digoxin, [^{14}C]saquinavir, and paclitaxel were 2.4, 7, and 16-fold higher, respectively, then in wild-type fetuses of the same dams (37). In the same study, pharmacological inhibition of P-gp in pregnant wild type mice produced a similar increase in drug distribution to that observed with genetic knockout of the *Abcb1* genes, indicating that placental P-gp can be completely inhibited in mice by pharmacological means. A lesser extent of placental P-gp inhibition was achieved in pregnant non-human primates using [^{11}C]verapamil as the P-gp substrate and cyclosporine as the inhibitor (38). Further analysis of the data obtained from a larger set of animals demonstrated that, in the absence of functional P-gp, tissue blood flow limits the distribution of [^{11}C]verapamil across the macaque placenta (39). That analysis also highlighted the importance of flow-normalized distribution clearance (K_1) as a measure of placental P-gp activity.

In humans, ethical and logistical considerations largely prevent the determination of placental drug transfer until delivery, when a single cord blood sample can be obtained. Typically, the cord-to-maternal concentration ratios of P-gp substrates are below unity, but the time of sampling with regard to drug ingestion by the mother can affect the ratio. *Ex vivo* and *in vitro* models which utilize human placentas have been reviewed by Myllynen and Vähäkangas (40). Among these, perfused human placentas provide the only opportunity to investigate placental transfer of substances in organized human placentas (16). Such studies allow measurement over several hours of drug transfer between compartments that represent the maternal and fetal circulations under controlled conditions. The relative contribution of individual transporters to drug transfer can be inferred from comparing drug passage in the presence and the absence of selective transporter inhibitors. The perfusion studies highlighted the importance of P-gp in the human placenta at term, by demonstrating that P-gp inhibition can enhance substrate transfer to the fetal compartment by up to 10-fold (Fig. 2). However, little is known about the role of placental P-gp during the course of 9 months of the human pregnancy.

The Breast Cancer Resistance Protein

Similar to P-gp, placental BCRP (*ABCG2*) has been localized to the brush border (apical) membrane of syncytiotrophoblast cells (41). BCRP is expressed in the human placenta throughout pregnancy but its levels may vary (28). In addition, BCRP exhibits polymorphism that can alter its expression and potentially its protective role in the placenta. Kobayashi *et al.* studied the relationships between *ABCG2* polymorphisms and BCRP expression in 100 human placentas. They reported on lower BCRP protein expression in placentas homozygotes for the A421 allele than in those for the C421 allele. The

Fig. 2 Effect of P-gp inhibition on drug transfer across perfused human cotyledons. In each study, the maternal-to-fetal transfer was measured at the presence or the absence of selective P-gp inhibitors. [a] The perfusion study was conducted at physiological albumin concentration (30 and 40 g/L). [b] Perfusion at low albumin concentration (10 g/L). Data are presented as fold change in substrate distribution to the fetus. References and the inhibitors utilized in each study are listed in Supplementary Material.
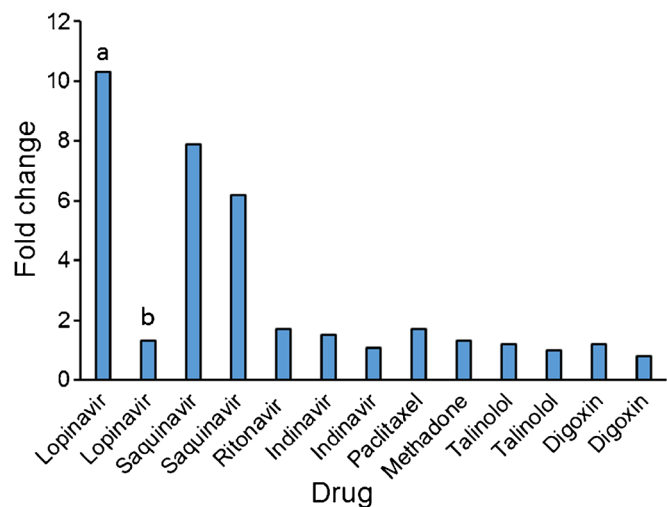
predominant allelic expression pattern of BCRP in placental samples was found to be biallelic (42). In a study in the Han Chinese population that compared the association between *ABCG2* polymorphisms and isolated septal defects, more cases than controls were carriers of the 34G > A polymorphism. *ABCG2* mRNA and protein expression of the GG genotype was significantly higher than that of the AA genotype in the placentas of the study participants (43). BCRP has additionally been suggested to protect placental trophoblasts themselves against cytokine- and ceramide-induced apoptosis (44).

Many BCRP substrates are sulfate and glucuronide conjugates, but BCRP can also transfer unconjugated drugs, including methotrexate, mitoxantrone, topotecan, dipyridamole, nitrofurantoin and glyburide (28). Drugs such as ritonavir, saquinavir, nelfinavir, and nicadipine and cyclosporine can inhibit BCRP (45–47).

The discovery that murine BCRP is an important contributor to the bioluminescence of the luciferase substrate D-luciferin *in vivo* paved the road for the use of D-luciferin and its derivatives as probes of BCRP activity at the blood-brain barrier (48) and the placenta (49) in transgenic mouse models.

Multidrug Resistance-Associated Proteins

MRPs are predominantly organic anion transporters but in addition transport neutral organic compounds. The substrate and inhibitor selectivity of individual MRPs partially overlaps with that of other MRPs, P-gp, BCRP, and organic anion transporters (28,50). Importantly, folic acid and its antagonist, methotrexate, are substrates of several MRPs expressed in the human placenta (31).

MRP1 (*ABCC1*) is expressed on fetal blood vessel endothelia and, at lower levels, at the basal membrane of term human syncytiotrophoblasts (51). Some expression has also been detected at the apical layer of syncytiotrophoblasts (52). This pattern of expression suggests that MRP1 primarily removes

compounds from fetal blood (35). MRP1 substrates are anionic glutathione, glucuronide and sulfate conjugates of endogenous substances such as bilirubin, 17β estradiol and prostaglandins, but also unconjugated compounds, including folic acid, methotrexate, saquinavir and ritonavir (31). MRP1 levels were found to be significantly higher in term human placentas than in first trimester placental samples (53).

MRP2 (*ABCC2*), unlike MRP1, is expressed at the apical human syncytiotrophoblast membrane (52), but the substrate specificity of the two transporters is very similar (35). MRP2 mRNA expression at the human placenta is lower than that of MRP1 (54), but may be induced under pathological conditions and related treatments, e.g. in women with intrahepatic cholestasis of pregnancy treated with ursodeoxycholate (55).

The human placenta expresses several other MRPs whose contribution to drug transfer has yet to be clarified, including MRP3 (*ABCC3*) (56), MRP4 (*ABCC4*) (55) and MRP 5 (ABCC5). MRP5 substrate selectivity is unique as it includes cyclic nucleotides (57).

Transporters of the Solute Carrier Superfamily

SLCs known to be expressed in the placenta and involved in transplacental drug transfer include organic anion transporting polypeptides, organic anion transporters, organic cation transporters, monoamine transporters and equilibrative nucleoside transporters. The involvement of SLC-mediated transplacental transfer varies across drugs (Fig. 1).

Organic Anion Transporting Polypeptides (OATPs)

Several members of the OATP subfamily are expressed on the placenta. These include OATPs 2B1 (*SLCO2B1*), 4A1 (*SLCO4A1*), and, to a lesser extent, 1A2 (*SLCO1A2*) (54). OATP2B1 is localized at the basal membrane of the syncytiotrophoblast (58), whereas OATP4A1 is

predominantly expressed on the apical membrane (59). The placental OATP isoforms are involved in the transmembrane transport of prostaglandins, thyroid hormones, steroid hormone metabolites, and drugs, including fexofenadine, saquinavir, glyburide, imatinib, methotrexate (60) and repaglinide (61). Basolateral OATP2B1 and apical BCRP may act in concert to shuttle steroid sulfates from fetal to maternal circulation (62).

Organic Anion Transporters (OATs)

OAT4 (*SLC22A11*) is the most abundant OAT on the human placenta, and is expressed on the basal surface of syncytiotrophoblasts (63). OAT4 is involved in the transport of steroid sulfates, steroid precursors for estrogen synthesis and several drugs, including zidovudine (64).

Organic Cation Transporters

Organic cation transporters include the potential-sensitive OCTs and the proton gradient-driven carnitine transporters OCTNs. The predominant OCT in the human placenta is OCT3 (*SLC22A3*), which mediates substrate uptake at the basolateral side (65). OCT3 exhibits high affinity for monoamines and is considered to be an extraneuronal monoamine transporter (66). It may play a role in catecholamine clearance from fetal circulation (27) and release of acetylcholine from the placenta (67). OCT3 has been suggested to be involved in the transplacental transfer of metformin, a cationic and highly hydrophilic drug (68). However, metformin transport was not shown to be inhibited by the OCT inhibitor cimetidine (69). OCT3 may contribute to vectorial transport of organic cations across the placenta by mediating their uptake from the basolateral membrane (fetal side). Their subsequent removal from cells across the apical membrane may be mediated by other mechanisms, such as efflux by ABC transporters.

OCTN1 (*SLC22A4*) and OCTN2 (*SLC22A5*) are expressed at the maternal-facing membrane of syncytiotrophoblasts, where they can facilitate carnitine transfer from maternal blood to the placenta and the fetus (27,70). Drug substrates of OCTN 1 and 2 include verapamil and quinidine (71).

Nucleoside Transporters

Nucleosides are highly hydrophilic molecules, which depend on carriers for crossing membrane barriers. Two families of nucleoside transporters have been described in humans, equilibrative transporters (ENTs; *SLC29*) and concentrative transporters (CNTs; *SLC28*), and several members of these families are enriched in the placenta (72,73). Significant expression of ENT1, ENT2, and CNT2 mRNAs and ENT1 and ENT2 proteins was detected in term human placentas. The ENT1 protein was localized to the brush-border membrane with positive staining in endothelial cells of blood vessels. ENT2 staining was less intense than that of ENT1, and was predominantly cytoplasmic (73). The substrates of nucleoside transporters are purine and pyrimidine nucleosides, but also several related anticancer and antiretroviral drugs, including 6-mercaptopurine, cytarabine and gemcitabine (74). In mice, Ent1 affects the rate but not the extent of ribavirin accumulation in the fetus (75).

Monoamine Transporters

The serotonin transporter (SERT; *SLC6A4*) and the norepinephrine transporter (NET; *SLC6A2*) are expressed on the maternal-facing membrane of syncytiotrophoblasts and mediate monoamine uptake into the placenta (76,77). Amphetamine and methamphetamine compete with endogenous monoamines for binding to the carrier active site and enter placental cells instead of the monoamine substrates (78). Amphetamine and methylphenidate have nanomolar affinity for NET and micromolar affinity for SERT. Another attention-deficit/hyperactivity disorder medication, atomoxetine, binds both NET and SERT at nanomolar concentrations (79). Whether these drugs are NET or SERT substrates is unknown. Additionally, a variety of antidepressants are established inhibitors of monoamine transporters (78,80). Their effects on placental SERT and NET have yet to be elucidated.

ENDOCYTOSIS AND EXOCYTOSIS

Endocytosis consists of several mechanisms, including pinocytosis (fluid-phase endocytosis), phagocytosis (engulfment and destruction of extracellular material), and receptor-mediated endocytosis. The latter involves selective internalization of specific extracellular ligands into cytoplasmic vesicles through their interactions with specific receptors. Particularly, IgG or IgG-based antibodies bind with high affinity to the neonatal Fc receptors in the acidic environment (approximately pH 6) of the endosome. Binding prevents their transfer into the lysosome, and they can be transported in coated vesicles across the trophoblastic layers and released into the fetal circulation (or back into maternal plasma) at physiological pH (81). The rate of endocytosis-mediated transfer is determined by several factors, including membrane fluidity, vesicle mobility in the cytosol, and, in the case of receptor-mediated endocytosis, the rate of receptor turnover (82). Additional examples for placental receptors include folate receptor alpha (*FOL1*) and megalin. Megalin (*LRP2*) is most extensively expressed on the apical (lumen-facing) surface of renal proximal tubular epithelial cells, and is involved in the endocytosis of vitamin B12 (83). Megalin-mediated endocytosis has been suggested as the primary mechanism for renal aminoglycoside

accumulation and toxicity and was shown to be involved in gentamycin uptake by BeWo cells (84). Hence, endocytosis can contribute to the accumulation of gentamicin in the human placenta (85) and be involved in gentamicin's transfer to fetal blood. Gentamicin's transfer across the placenta has been profiled in a recent clinical study (NCT02427932; clinicaltrials.gov). Findings from this study can contribute to understanding of the factors that govern gentamicin's passage across the placenta. Although, in most cases, transcytosis does not have a significant effect on the extent of transfer of small-molecule drugs, it is relevant for two emerging treatment approaches, namely therapeutic antibodies and drug-containing nanoformulations such as nanoparticles and liposomes.

Antibodies and related products, including antibody–drug conjugates, are the fastest growing class of therapeutic agents (86,87). The most commonly used therapeutic antibodies are of the IgG family (87,88), which are handled by the placenta similarly to naturally occurring maternal IgG antibodies. Transport is mediated by Fc receptors which become functional at week 13 of gestation (89). IgG transport is bidirectional, possibly as a means of achieving homeostasis of IgG within the fetal circulation. Fab' fragments, which do not bind to Fc receptors, can also be transported across the placenta, but transport is significantly less efficient (88). The rate of transport increases as the pregnancy progresses and is thought to be most efficient in the third trimester, during which 80% of transfer occurs (88,90). In one study, fetal concentrations of IgG at gestational weeks 17–22 were only 5–10% of the maternal levels, but exceeded the maternal levels at term (91). Likewise, the levels of therapeutic antibodies in cord blood may be higher than in the mother at the time of delivery (90,92). For example, in a study of 31 pregnant women with inflammatory bowel disease receiving infliximab, adalimumab, or certolizumab pegol, the concentrations of infliximab and adalimumab (IgG1 antibodies) were higher in infants at birth and their cords than in their mothers (160% and 153%, respectively; drug treatment was stopped weeks before delivery). In comparison, the median cord level of certolizumab, a PEGylated Fab' fragment of a humanized monoclonal antibody, was only 3.9% of that of the mother (90) (Fig. 1). Its concentrations in fetal circuit were below the limit of quantification in 5 of 6 human placentas perfused *ex vivo* (93). Similarly, in the perfused human placenta model, minute amounts of abciximab (a Fab fragment of an IgG$_1$ monoclonal antibody) were detected in the fetal circuit and attached to the trophoblastic surface of the placental villi, to maternal platelets and to residual blood platelets found focally in the fetal capillaries. However, it was estimated that abciximab transfer is unlikely to result in biologically significant occupancy of its platelet receptors and pharmacologic inhibition of platelet aggregation in the fetus (94).

Therapeutic antibodies can be detected in the infant serum more than 6 months after birth (88). In one infant, infliximab concentration of 0.03 mg/mL was detectable at 12 months of age (92). It is often advised that pregnant patients on biologic therapy will take their last dose early in the third trimester. In addition, the current recommendation is to wait at least 6 months or until drug levels are undetectable before giving any live vaccines to these neonates exposed in utero to biologics due to potential immune suppression (95).

Nanomaterials are defined as having at least one dimension between 1 and 100 nm, although larger (submicron) structures are often encompassed as well (96). Nanomaterials can be uptaken by the placenta with their content potentially delivered to the fetus. Small liposomes and nanoparticles (<60 nm) may be uptaken into placental trophoblasts and capillary endothelium via coated vesicle-mediated pinocytosis (97,98). In addition, nanoformulations may undergo phagocytosis by a large population of resident macrophages present in the placenta (99). More recently, paracellular passage has been suggested as a transfer mechanism for very small nanoparticles (100). Enhanced uptake and passage of nanoparticles was observed when placental integrity was hampered by inflammation (101). The placental transfer of various types of nanoformulations and their effects on the fetus have been reviewed by Keelan *et al.* (96) and will be described here in brief.

Liposomes were among the first nanoformulations to be evaluated as a pharmaceutical carrier and as such, have been extensively investigated with regard to transplacental transfer. In the rat placenta, tissue-weight normalized uptake of liposomal inulin was similar to that in the liver (102). Liposomally-entrapped [^{3}H]penicillin, [^{14}C]inulin, [^{3}H]mthotrexate and [^{3}H]rivoflavin were localized much more in the placenta compared with the free substances (5.6-fold, 5.0-fold, 4.6 and 2.9-fold, respectively). No intact liposomes were found to be transported across the placenta, but their content was transferred to the fetus as free molecules. Liposomal [^{14}C]riboflavin, [^{3}H]methotrexate, and [^{14}C]penicillin were transferred to the fetus more than the free molecules (8.8-fold, 7.5-fold, and 4.2-fold, respectively). Placental uptake of liposomes depended on their phospholipid composition, and negative liposomes were localized in rat and rabbit placentas more than neutral and positive liposomes (102). Likewise, anionic liposomes containing carboxyfluorescein were taken up by cultured human term trophoblasts more avidly than neutral and cationic liposomes and the free carboxyfluorescein (103). In perfused human placentas, liposomal thyroxine (T4) crossed the placenta to a greater extent than free thyroxine, which was metabolized in the placenta to T3 (104).

Perfused human placentas have been used to demonstrate placental uptake and transfer to the fetal circulation of additional types of nanoformulations, including polystyrene particles with diameter up to 500 nm (105), silica nanoparticles (106), and fluorescently tagged PAMAM dendrimers (100). Placental transfer ranged with the particle type and size. For

example, the concentration of 50 nm polystyrene beads in the fetal circuit was 49% of the concentration in maternal circuit, whereas when 500 nm beads were used, nearly all particles were retained in the maternal circulation or placental tissue. The concentration of the 500 nm beads detected in the fetal circulation was nearly 30-fold lower as compared to that of the 50 nm beads (105).

PLACENTAL DRUG METABOLIZING ENZYMES

The human placenta expresses enzymes that catalyze both phase I (drug oxidation, reduction and hydrolysis) and Phase II (conjugation) reactions. Placental cytochrome P450 (CYP) isoform proteins include 1A1, 2E1, 3A4, 3A5, 3A7, 4B1 and 19 (107,108). At the mRNA level, the major isoforms detected in the placenta are placental aromatase (CYP19) and CYP11A (109). Additional phase I enzymes detected at term placentas include alcohol dehydrogenases, epoxide hydrolases and N-acetyltransferases (110). Placental phase II enzymes include uridine diphosphate glucoronosyltransferases (UGTs), glutathione S-transferase, epoxide hydrolase, N-acetyltransferase, and sulphotransferases (110). For instance, in a study of 12 term human placentas, expression of UGT2B4, 2B7, 2B10, 2B11 and 2B15 mRNA was observed in all the placentas, although with great between-placenta variability in expression levels. UGT2B1 and 2B7 were additionally detected at the protein level and were localized to the syncytiotrophoblast (111). Deconjugation reactions can also take place in the placenta, e.g., by glucuronidases, as was demonstrated for the xenoestrogen bisphenol A in a sheep model (112).

The type and the amount of placental drug metabolizing enzymes change during pregnancy. For instance, CYP3A7 in the human placenta is induced during pregnancy (113), whereas UGTs are present at the placenta throughout pregnancy (111). In mice, almost all the studied placental *CYP* genes were upregulated during mid-pregnancy (gestational day 10) and levels decreased by mid- to late pregnancy (114).

Drugs which have been shown to undergo significant placental metabolism include structural analogues of endogenous compounds, such as zidovudine (115) and dideoxyinosine (116), but also other compounds such as oxcarbazepine (117,118). Placental CYP19 is involved in the metabolism of glyburide (119), buprenorphine (120), and methadone (121). Olanzapine (122) and zidovudine (123) have been shown to be conjugated to *N*-glucuronide *ex vivo*, in the perfused cotyledon model. The extent to which the placental metabolic barrier limits fetal exposure to most drugs appears to be minor compared to that of the maternal liver. Yet, it may contribute to the formation of fetotoxic reactive metabolites (124). Nuclear receptors may be involved in upregulation of placental enzyme expression. For example, aryl hydrocarbon receptor ligands induced the expression of *CYP1A2* mRNA in human term placental trophoblast cultures (125).

DISTRIBUTION KINETICS

The intensity and duration of fetal effects of drugs depend the dose taken by the mother, maternal and fetal pharmacokinetics, and individual factors such as pharmacogenetics, concurrent disease states, and concomitantly taken medications. Another key determinant of fetal drug exposure is the rate and extent of drug distribution across the placenta. Some drugs equilibrate rapidly across the placental membranes whereas other have slower distribution, e.g. due to saturable carrier-mediated uptake or endocytosis. Accordingly, the fetus has been suggested by Gerhard Levy to have the pharmacokinetic characteristics of a shallow or deep compartment, respectively (126). In the latter case, the maximum drug concentration in the fetus is lower and the post-distribution fetal: maternal drug concentration ratio is higher than when the drug distributes rapidly across the placenta. Hence, the maternal dosing regimen may significantly affect fetal exposure. After a single, rapid intravenous bolus of the drug, it may not extensively distribute to the fetus before its concentrations decline in maternal plasma. However, when the drug is administered repeatedly or continuously, it can accumulate in the fetus with time, and its effects may be significant for up to a few hours (20). For example, the fetal:maternal concentration ratio of pethidine increase with time and exceed 1 after approximately 4 h, although by this time the concentrations are low in both mother and cord blood (127). Studies in isolated cotyledons may underestimate the *in vivo* cord blood:maternal blood concentration ratio of the drug if a distributional steady state is not achieved during the perfusion experiment (e.g., cyclosporine and likely therapeutic antibodies, as described above; Fig. 1). Such compounds may also slowly accumulate in placental tissue itself, as was demonstrated by us for indocyanine green in perfused human placenta (Fig. 3) (128). Hydrophilic drugs may never reach distributional equilibrium because the fetus rapidly excretes them into the amniotic fluid. Such compounds are swallowed by mature fetuses and may concentrate in the fetal intestinal lumen. For example, babies born to mothers treated with hexamethonium suffered from paralytic ileus (20).

Compared with abundant data on drug transfer to the fetus, less is known about their concentrations in the placenta. Most of the few studies that evaluated placental drug concentrations were conducted in term placentas, although some utilized placentas obtained during early pregnancy terminations. The available information indicates that some drugs can accumulate within placental tissue and achieve higher concentrations than in maternal plasma. In a study that compared the concentration of gentamicin given to treat chorioamnionitis in
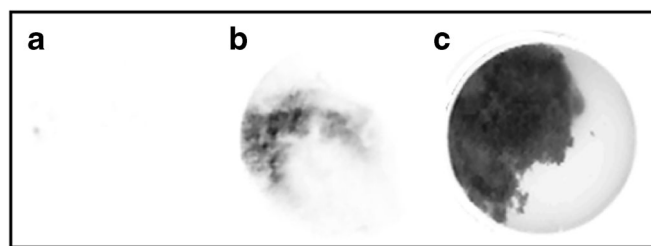
Fig. 3 Time-dependent accumulation of the near infrared marker indocyanine green in human placentas during *ex vivo* perfusion of placental cotyledons. Indocyanine green was added to the maternal compartment and cotyledons were perfused for up to 3 h. Tissue samples were washed three times in PBS before *ex vivo* near infrared imaging. Samples are from a cotyledon that was not exposed to indocyanine green (A) or cotyledons exposed for 2 h (B) or 3 h (C).

maternal blood, cord blood, and placental membranes, placental gentamicin level was about four- and six-fold higher in placental membranes than that in maternal and cord blood, respectively (Fig. 4) (85).

THE FATE: HOW DRUGS AFFECT THE PLACENTAL BARRIER

Because placental concentrations of some drugs may be high enough to exert pharmacological activity, their potential direct effects on the placenta cannot be ignored. Specifically, by modulating placental barrier function, a drug can affect the distribution of an essential compound or that of another drug into the fetus or placenta itself. Practically any placental pathway may be affected by medications of various chemical structures and pharmacological classes (Table I). Even drugs that produce very low levels in the fetus such as heparins can affect trophoblast function. For instance, heparins were demonstrated to be beneficial in the prevention of placenta-mediated complications of pregnancy (e.g., by direct proangiogenic effect on the placenta) (139). Examples of drugs that can interfere with the barrier function of the placenta include

antiepileptic drugs, corticosteroids and antiretroviral protease inhibitors.

As a group, antiepileptic drugs are among the most common teratogenic medications prescribed to women of childbearing age (140). Harmful effects of exposure to antiepileptic drugs *in utero* include fetal loss, intrauterine growth restriction, and congenital malformations (141). The risk of major congenital malformations was consistently shown to be two-to-four times as high with the use of valproic acid compared with the use of other antiepileptic drugs such as carbamazepine and lamotrigine (141–143). Valproic acid was also associated with impaired cognitive outcomes of the offspring (144,145), increased risk of autism spectrum disorders (146,147) and diagnosis of attention deficit hyperactivity disorder (ADHD) (148). Many antiepileptic drugs cross the placenta by passive diffusion. Valproic acid is exceptional, as its mechanism of placental transfer appears to involve a proton-linked saturable transport system (149,150). Another exception is gabapentin which is transported in JEG-3 cells by LAT1 (151) and has been suggested to act as a placental LAT1 inhibitor (152). Antiepileptic drugs can affect additional placental targets. We recently evaluated the effects of valproic acid, phenytoin, carbamazepine and lamotrigine on carrier expression in BeWo cells (153). Valproic acid-treated cells expressed half

Fig. 4 Drug accumulation in the human placenta *in vivo*. Data are shown as placenta:maternal plasma concentration ratios. Concentrations of antibiotics were measured in women treated for chorioamnionitis. (**a**) Early pregnancy. (**b**) Late pregnancy/term. 10-OH-CBZ, 10-hydroxy-10,11-dihydrocarbazepine. References are provided in Supplementary Material.
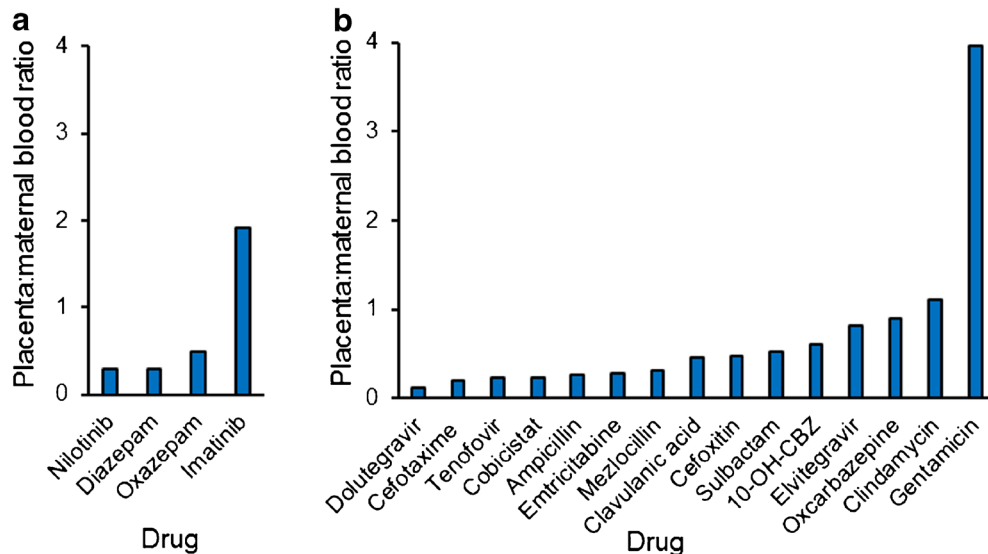
Table I Effects of Drugs on the Distribution of Essential Compounds in Models of the Human Placenta

Compound	Drug	Model	Effect	Suggested mechanism (s)	Reference
Monoamines					
Serotonin	Fluoxetine	BBMVs, Jar cells	Reduced serotonin uptake and reduced paroxetine binding	Inhibition of the serotonin transporter	(129)
Norepinephrine	Desipramine	Rat trophoblasts	Reduced norepinephrine uptake	Antagonisms of the norepinephrine transporter	(130)
Carnitine	Valproic acid	Human BBMVs	Reduced carnitine uptake	OCTN2 inhibition	(131, 132)
	Phenytoin	Human BBMVs	Reduced carnitine uptake	OCTN2 inhibition	(132)
	Tiagabine	Human BBMVs	Reduced carnitine uptake	OCTN2 inhibition	(132)
	Gabapentin	Human BBMVs	Reduced carnitine uptake	OCTN2 inhibition	(132)
	Vigabatrin	Human BBMVs	Reduced carnitine uptake	OCTN2 inhibition	(132)
	Topiramate	Human BBMVs	Reduced carnitine uptake	OCTN2 inhibition	(132)
	Ciprofloxacin	BeWo cells	Reduced carnitine uptake	OCTN2 inhibition	(133)
	Gatifloxacin	BeWo cells	Reduced carnitine uptake	OCTN2 inhibition	(133)
	Ofloxacin	BeWo cells	Reduced carnitine uptake	OCTN2 inhibition	(133)
	Levofloxacin	BeWo cells	Reduced carnitine uptake	OCTN2 inhibition	(133)
	Grepafloxacin	BeWo cells	Reduced carnitine uptake	OCTN2 inhibition	(133)
	Verapamil	Human BBMVs	Reduced carnitine uptake	OCTN2 inhibition	(131)
Folic acid	Valproic acid	ELISA with FRa,FRb, or bFBP printed plates, HEK293T cells	Reduced binding of folic acid, 5-methyltetrahydrofolate, s-folinic acid to folate receptors	Noncompetitive inhibition of the high affinity folate receptors	(134)
	Labetalol	Isolated villous cytotrophoblasts	Reduction in folic acid uptake, acute	Modulation of the expression of FA placental transport systems	(135)
	Atenolol	Isolated villous cytotrophoblasts	Reduction in folic acid uptake, chronic	Modulation of the expression of FA placental transport systems	(135)
Amino acids					
L-arginine	Aspirin	Perfused placentas of women treated with aspirin and un-treated women	Altered transport kinetics of L-arginine	Increased transport affinity and reduced capacity	(136)
Glycine	Haloperidol	JAr cells	Reduced glycine uptake	Noncompetitive inhibition of glycine transporters 1 & 2	(137)
	Clozapine	JAr cells	Reduced glycine uptake	Noncompetitive inhibition of glycine transporter 1	(137)
Total amino acids	Dexamethasone	BeWo cells	Reduced levels of total amino acids	Downregulation of SLC7A5 expression via GR-mediated transrepression	(138)

BBMVs placental brush-border membrane vesicles

the levels of RFC mRNA and protein and up to 2.7-fold higher levels of BCRP mRNA and protein, and displayed greater BCRP activity than cells treated with the vehicle. Changes in transporter expression were also observed in cells treated with phenytoin, carbamazepine, and lamotrigine. Results from pregnant mice treated with valproic acid (200 mg/kg/day for four days) confirmed some of the *in vitro* findings and pointed to a potential effect of valproic acid on the functionality of the placental barrier (154). Valproic acid and phenytoin, as well as several other antiepileptic drugs, have additionally been shown to significantly inhibit OCTN2-mediated carnitine uptake (Table I) (131,155). This can lead to carnitine deficiency in both the placenta and the fetus. Carnitine supplementation is recommended for certain populations of patients with epilepsy, including infants receiving valproic acid, but is not routinely given to pregnant women treated with antiepileptic drugs (132,156).

Glucocorticoids are administered to women at risk of preterm birth to accelerate fetal lung maturation (157). Because of the clinical need and the inverse correlation between placental sensitivity to glucocorticoids and placental P-gp expression, several studies evaluated the effects of glucocorticoids on the expression of P-gp and other ABC transporters. In guinea pigs betamethasone (1 mg/kg) given on gestational days 40/41 and 50/51 (length of gestation 59–72 days (158)) resulted in a significant decrease in placental Abcb1 mRNA and protein expression (159). However, the same group later observed in mice up-regulation by dexamethasone (0.1 mg/kg or 1 mg/kg, given daily for one week) of placental Abcb1a mRNA and P-gp protein expression. These changes were not

accompanied by reduced exposure of the "fetal unit" (the fetus, amniotic fluid and intact fetal membranes) to [^{3}H]digoxin (160). In another study in rats, dexamethasone (repeated administration of 1 mg/kg for 9 days beginning on day 11 after conception) induced *Abcb1* expression in fetal liver and brain but not in the placenta (161). In primary human cytotrophoblasts isolated from full term placentas, dexamethasone and betamethasone significantly induced ABCB1 mRNA expression by around 4-fold but did not affect the expression of *ABCG2* and *ABCC* 1–5, 10, and 12 (162). P-gp expression was also studied in placentas collected from 53 women presenting with threatened preterm labor. In that study, P-gp mRNA and protein expression were not affected by the timing of antenatal glucocorticoids but expression was lower in placenta from small-for-gestational age infants than in appropriately grown infants (163). In another study, in placentas derived from female fetuses, high-dose (1 mg/kg) dexamethasone significantly downregulated *Abcg2* mRNA expression and inhibited Bcrp1 function (164). Other reported effects of glucocorticoids on the placenta include lower placental CYP19 mRNA content and aromatase activity in betamethasone-treated women (165) and reduced placental system A amino acid transporter activity *ex vivo* in women who were at risk of preterm labor and received glucocorticoids but delivered at term (166).

Antiretroviral therapy during pregnancy can treat maternal HIV infection and reduces the likelihood of HIV transmission to the fetus. Recommended treatment regimens for pregnant women include combinations of antiretroviral drugs of several pharmacological classes (167). Among these, atazanavir and lopinavir boosted with ritonavir are currently the first-line protease inhibitors in pregnancy. Indinavir, nelfinavir, and saquinavir exhibit unreliable placental transport (168), but can affect the expression of placental transporters. In human cytotrophoblast cells saquinavir significantly increased both expression (to a 2-fold extent) and functionality (by 18%) of P-gp. In the same study, nelfinavir increased P-gp functionality (by 23%) as a result of its dissociation from caveolin-1. Nelfinavir additionally reduced hCG secretion by 30% (169). Interestingly, P-gp expression in term placentae was greater in HIV-1-infected women receiving pharmacotherapy than in uninfected controls (170).

OUTLOOK

Drugs are usually given to pregnant women to treat the mother, but may be used to manage pathological conditions of the fetus (171) or the placenta (172). Awareness of the principles that govern maternal-fetal pharmacokinetics can minimize unnecessary exposure of the fetus to drugs or help optimize drug delivery to the fetus or the placenta. For instance, when valproic acid is given to pregnant women, it is assumed that

"flatter is better". That is, the teratogenic risk is related to the peak plasma concentration of the drug in maternal plasma (173). *Ex vivo*, valproic acid readily distributes across the human placenta, reaching distributional equilibrium within 1.5 h (174). Accordingly, it is generally recommended to use a prolonged-release formulation of valproate when given to pregnant women, although this assumption is based solely on a study in mice (175). Alternatively, transnasal administration of valproic acid has been shown in rats to reduce systemic exposure to the drug (176) and may be an optimal delivery route in pregnant women. Carrier inducers or inhibitors can additionally modulate the placental pharmacokinetics of drugs (21), although the effect of the modulator on carriers at drug-eliminating organs may offset those on the placenta (177).

Reduced placental and fetal exposure to drugs, or, in other cases, enhanced drug delivery to the placenta and the fetus may be also achieved by the use of nanosized drug carriers. Even without targeting molecules, nanoparticles may accumulate in the placenta, but effective drug delivery strategies require the development of targeted nanoparticle-based drugs specifically, e.g. for the treatment of trophoblast tumors or infections. For example, doxorubicin-loaded nanocells were constructed with the ability to target trophoblastic tumors via surface decoration with an antibody that binds the epidermal growth factor receptor (EGFR, highly expressed on the placental surface) (178). Although current literature suggests that the risk of fetal exposure and toxicity following maternal use of nanoformulations is low, it is not negligible (96). Ongoing studies evaluate nanoparticles as potential means for drug delivery in pregnant women (NCT02199756 and NCT02720887; clinicaltrials.gov).

The application of the newer 'placenta on chip' technologies could allow assessing the *in vitro* transfer of drugs and drug formulations across the human placental barrier. The model is created in a multilayered microfluidic system that enables co-culture of human trophoblast cells and human fetal endothelial cells that reproduce the formation of microvilli and the syncytialization of trophoblasts (179).

CONCLUSIONS

The placenta affects not only pregnancy, but lifelong health. Throughout pregnancy, it provides the varying developmental needs of the embryo and the fetus. To fulfill this function, the placenta is equipped with carriers, enzymes and transcytotic pathways that regulate exchange of essential compounds between the mother and the fetus. Medications are not only transferred to the fetus via these mechanisms, but can also modulate their functional activity, thereby indirectly affecting fetal development. Understanding drug pharmacokinetics and pharmacodynamics in the placenta is a first step

towards improving therapeutic regimens in pregnant women and developing strategies that may protect the fetus and the placenta from adverse drug effects. Alternatively, drugs and drug delivery forms can be designed to specifically target the placenta and fetus.

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The authors have no commercial or financial relationships that could be constructed as a potential conflict of interest.

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