Review Article

Placental Drug Transfer and Fetal Drug Exposure: Emerging Pharmacokinetic Approaches for Rational Pharmacotherapy in Pregnancy

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ABSTRACT

Medication use during pregnancy is common, yet pregnancy-specific pharmacokinetic and fetal exposure data remain limited. Placental drug transfer is often described as a barrier phenomenon, but the placenta is better understood as a dynamic interface that integrates passive diffusion, transporter-mediated influx and efflux, placental metabolism, maternal and fetal blood flow, and fetal distribution and elimination. Maternal physiological changes alter systemic drug exposure and therefore the amount of drug presented to the placenta, while gestational maturation changes placental structure, transporter localization, and fetal clearance. Recent studies have strengthened quantitative approaches to fetal exposure prediction, particularly through integration of ex vivo human placental perfusion with maternal–fetal physiologically based pharmacokinetic (PBPK) models. Transporter-informed approaches using relative expression factors have also demonstrated the potential to predict fetal exposure for selected P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates. At the same time, microphysiological placenta models and placenta-on-a-chip systems are being developed to address limitations of conventional trophoblast models and term placental tissue. Important uncertainties remain, including limited direct fetal concentration data, incomplete characterization of gestational-age-dependent transporter function, variability in ex vivo perfusion methodology, and uncertainty in transplacental clearance parameters. This review summarizes current evidence on the determinants of placental drug transfer, pregnancy-associated pharmacokinetic changes, placental transport and metabolism, experimental models, and computational approaches, with emphasis on how recent advances can improve mechanistic interpretation and support rational maternal pharmacotherapy while avoiding overinterpretation of predicted fetal exposure.

Key words: Pregnancy, Placenta, Fetal Drug Exposure, Pharmacokinetics, Placental Drug Transfer, Transporters, PBPK, Maternal–Fetal Pharmacology.

Pregnancy is associated with important physiological changes that can alter drug pharmacokinetics. Changes in plasma volume, total body water, plasma protein concentrations, renal function, and hepatic drug metabolism may affect drug absorption, distribution, and elimination [1,2]. These changes can modify maternal drug concentrations and may consequently influence fetal drug exposure. Medication use during pregnancy is often necessary for the treatment of maternal diseases, infections, and pregnancy-related conditions. Therefore, understanding drug disposition during pregnancy is important for achieving effective maternal treatment while considering potential fetal exposure [1,2].

The placenta is the main interface between the maternal and fetal circulations and plays an important role in determining the extent of fetal exposure to drugs. The placenta should not be considered only as a passive barrier. Drugs can cross the placenta by passive diffusion and through carrier-mediated transport, while placental transporters and metabolic enzymes can modify the amount of drug reaching the fetal circulation [3–5]. The extent of placental transfer depends on several factors, including drug molecular size, lipophilicity, ionization, protein binding, maternal drug concentration, placental blood flow, transporter activity, and placental metabolism [3–6]. Placental drug transporters, including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance-associated proteins, and several solute carrier transporters, may influence fetal exposure [3–5]. However, the presence of a transporter in placental tissue does not necessarily indicate that it has a major functional role in controlling fetal drug concentrations. Transporter localization, substrate specificity, activity, and gestational age must also be considered [3–5]. In addition, maternal physiological changes during pregnancy can alter systemic drug exposure and thereby change the amount of drug available for placental transfer [1,2].

Access this article online	
Received – 24th July 2025 Initial Review – 27th July 2025 Accepted – 30th August 2025	Quick Response Code

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Direct measurement of fetal drug concentrations is difficult because fetal sampling is limited for ethical and practical reasons. Therefore, different experimental and computational approaches have been developed to study placental drug transfer. In vitro placental and trophoblast models can provide information about drug permeability and transporter activity, while ex vivo human placental perfusion models allow assessment of drug transfer across intact placental tissue [7,8]. Maternal–fetal physiologically based pharmacokinetic (PBPK) models can further integrate experimental and clinical data to estimate maternal and fetal drug concentrations [7–10].

Despite these advances, important gaps remain in the quantitative prediction of fetal drug exposure. Available data on placental transporter function, gestational-age-dependent changes, placental metabolism, and fetal drug disposition are still limited [3–10]. This review summarizes the major determinants of placental drug transfer and fetal drug exposure, including pregnancy-related pharmacokinetic changes, passive and transporter-mediated drug transport, placental metabolism, experimental approaches, and maternal–fetal PBPK modeling. It also discusses current limitations and emerging approaches for improving the prediction and interpretation of fetal drug exposure during pregnancy.

2. PLACENTAL INTERFACE AND DETERMINANTS OF DRUG TRANSFER

The syncytiotrophoblast constitutes the major cellular interface between maternal blood and the fetal capillary network. Across this interface, drug movement is determined by the physicochemical properties of the compound and by the anatomical and molecular characteristics of the placenta. Recent physiological analyses highlight molecular size, lipid solubility, paracellular pathways, membrane polarity, and transporter localization as important determinants of net transfer [11]. The consequence is that the placenta can simultaneously restrict, facilitate, and metabolize drug movement rather than acting as a simple one-directional filter.

Passive diffusion remains important for many small molecules. Lipophilicity, molecular size, ionization, and the unbound fraction influence membrane partitioning and the concentration gradient available for transfer. However, these descriptors are insufficient when a drug is a substrate for placental transporters or when placental metabolism is substantial [12,13]. Protein binding is particularly important because the unbound fraction is generally the fraction available for diffusion and transporter interaction. Maternal and fetal protein binding can also differ, making total concentration ratios difficult to interpret. The ABC transporter family includes P-gp (ABCB1) and BCRP (ABCG2), while the SLC superfamily contains numerous uptake and exchange transporters. Their functional effect depends on which membrane is involved, the direction of transport, substrate specificity, transporter abundance, and competing pathways [14,15]. Recent transporter-informed PBPK work illustrates this principle: proteomics-based scaling of P-gp and BCRP activity has been used to predict fetal-to-maternal unbound exposure ratios for selected substrates with clinically observed term data [16]. Such studies are important because they move the field from descriptive transporter expression toward quantitative estimates of transporter contribution. Gestational age adds another layer of complexity. Placental structure, vascularization, transporter expression, and transporter localization evolve during pregnancy. A model based solely on term tissue can therefore misrepresent exposure earlier in gestation, when organogenesis and developmental susceptibility may be greatest [9,17]. Emerging studies that manipulate trophoblast differentiation and vascularization to reproduce early-to-late placental development may help address this limitation [18].

3. PREGNANCY-ASSOCIATED CHANGES IN MATERNAL PHARMACOKINETICS

Changes in maternal physiology determine the drug concentration presented to the placenta. Plasma volume and total body water increase during pregnancy, whereas albumin concentration generally decreases. These changes can increase the apparent distribution volume of some drugs and increase the unbound fraction of highly protein-bound compounds. Renal blood flow and glomerular filtration also increase, often increasing clearance of drugs that are predominantly eliminated by filtration [2-5]. Hepatic metabolic pathways do not change uniformly: individual CYP and other enzyme pathways may increase, decrease, or remain relatively stable. The effect must therefore be evaluated for each drug rather than assumed from a general rule. Recent pregnancy PBPK studies demonstrate the practical importance of these changes. Models have been used to predict maternal and fetal concentrations of anti-infective drugs, antiepileptic therapy, antihypertensives, and other medicines [19-22]. For example, bottom-up PBPK models incorporating maternal, fetal, and placental physiology predicted maternal and fetoplacental concentrations of cefazolin, cefuroxime, and amoxicillin during pregnancy [19]. Similar integration of clinical data and model physiology has been applied to carbamazepine [20]. A model for famotidine predicted lower exposure in mid- and late pregnancy than in non-pregnant adults while also illustrating the uncertainty associated with limited clinical data [21].

These studies support a key distinction: maternal pharmacokinetic change and placental transfer are related but not interchangeable. A reduction in maternal total concentration may coexist with a different change in unbound concentration, and fetal exposure is further modified by placental transfer and fetal clearance. Accordingly, maternal therapeutic drug monitoring, when used, should be interpreted

in relation to drug-specific exposure–response information rather than treated as a direct surrogate for fetal concentration [5,7].

4. PLACENTAL TRANSPORTERS AND METABOLISM

Transporter biology is one of the most intensively studied determinants of placental drug disposition. P-gp and BCRP have received particular attention because their localization can support efflux away from the fetal compartment for selected substrates. Yet the term "fetal protective transporter" can be misleading if used without specifying membrane localization, substrate, and gestational age. Recent mechanistic work emphasizes that transporter abundance alone cannot establish a rate-limiting role in transplacental transfer [9,10].

Quantitative proteomics and functional scaling are increasingly important. In a 2024 study, an efflux-ratio/relative-expression-factor strategy predicted term fetal exposure for glyburide, imatinib, and nelfinavir within two-fold of observed fetal-to-maternal unbound exposure ratios [16]. This represents a useful advance because it links in vitro transporter activity to human placental abundance and then to an exposure metric that can be evaluated against clinical observations. Nevertheless, the approach is validated mainly for selected drugs and term exposure; extrapolation to other compounds or earlier gestation requires additional evidence. Placental metabolism can further alter the amount and chemical form of drug reaching the fetus. Recent comprehensive reviews describe passive transfer, transporter-mediated transfer, and placental biotransformation as interacting processes rather than isolated mechanisms [11]. The quantitative importance of metabolism remains compound-specific, and active metabolites may complicate interpretation. For this reason, a mechanistic assessment should distinguish parent-drug transfer from total pharmacologically relevant exposure. There is also growing interest in targeted placental delivery. Recent reviews describe nanoparticle, peptide, antibody, and other targeting strategies intended to concentrate therapy in placental tissue for disorders such as pre-eclampsia and fetal growth restriction [23,24].

These approaches are conceptually distinct from conventional maternal drug administration: the objective is to modify tissue distribution deliberately rather than simply characterize unintended fetal exposure. Their clinical translation will require rigorous assessment of placental specificity, maternal exposure, fetal exposure, and developmental safety.

5. EXPERIMENTAL MODELS FOR STUDYING PLACENTAL TRANSFER

No single experimental model reproduces all determinants of human fetal drug exposure. Conventional trophoblast cultures are useful for controlled permeability, uptake, efflux, and mechanistic studies, but they simplify tissue architecture and blood flow. Ex vivo human placental perfusion retains organized villous structure and separate maternal and fetal vascular circuits, allowing direct measurement of transplacental transfer under controlled conditions [12,25].

The major limitation of ex vivo perfusion is methodological variability. A literature review of 135 human placental perfusion studies identified substantial differences in preparation, control, perfusion, drug exposure, and reporting parameters, limiting direct comparison between laboratories [25]. Standardized viability checks, flow conditions, leakage assessment, and transparent reporting are therefore essential if perfusion data are to serve as quantitative inputs for PBPK models. Microphysiological systems provide another route toward improved human relevance. A systematic review of placenta-on-a-chip studies identified a range of devices and cell sources and found that some systems could reproduce key characteristics of the placental barrier while allowing investigation of drug transport [26]. A separate evaluation of a microphysiological human placental barrier model further demonstrated the feasibility of using engineered systems to study drug transfer [27]. These platforms may allow better control of cell composition and dynamic exposure than static cultures, but they remain models and require validation against human tissue and clinically observed exposure. Animal studies remain useful for whole-organism pharmacology and developmental outcomes, but interspecies differences in placental architecture, transporter expression, metabolism, and gestational development constrain direct extrapolation to humans [28]. The most informative strategy is therefore complementary: mechanistic cell systems for specific processes, human placental tissue for tissue-level relevance, animal models for integrated biology, and clinical observations for validation.

6. PBPK MODELING AND QUANTITATIVE PREDICTION OF FETAL EXPOSURE

Maternal–fetal PBPK modeling offers a framework for integrating the heterogeneous evidence generated by these experimental systems. A mechanistic model can represent maternal physiology, placental transfer, fetal distribution, and immature fetal clearance while allowing parameters to vary with gestational age [13-15]. This is particularly valuable because direct fetal sampling is ethically and practically limited, especially during early pregnancy [7].

Recent studies demonstrate increasing sophistication. PBPK models have integrated ex vivo placental perfusion data to predict fetal exposure to doravirine and crizotinib [29,30]. Other models have predicted fetal and maternal concentrations for multiple drugs using gestational changes in maternal, placental, and fetal physiology [19]. The methodological direction is important: rather than treating placental transfer as an empirical fixed ratio, investigators are increasingly

attempting to represent transplacental clearance as a mechanistic component that can be tested against observed data. However, PBPK predictions are not measurements. Their reliability depends on the quality of physiological parameters, drug-specific clearance estimates, transporter activity, protein binding, fetal distribution volumes, and assumptions about gestational maturation. A 2024 study evaluating alternative approaches to estimate transplacental clearance for vancomycin illustrates the sensitivity of fetal predictions to the method used to parameterize placental transfer [31]. Regulatory-oriented reviews similarly conclude that pregnancy PBPK models can capture exposure trends for several drugs, but model performance is not uniformly adequate for magnitude of change or all clinical settings [32].

Good practice therefore requires independent verification, sensitivity analysis, transparent reporting of parameter uncertainty, and clear separation of observed data from model-derived predictions. The most defensible use of PBPK is to integrate evidence and explore plausible exposure scenarios, identify data gaps, and guide study design, not to replace human observations when those observations are feasible. An additional advantage of model-based analysis is the ability to separate uncertainty in maternal exposure from uncertainty in placental transfer. For example, fetal-to-maternal unbound concentration ratios can be estimated for transporter substrates and explored across gestational ages, providing a quantitative description of how placental efflux may alter fetal exposure [20]. Generic fetal PBPK models are also beginning to represent fetal organs rather than treating the fetus as a single homogeneous compartment. A 2024 cefuroxime model predicted concentrations in fetal plasma, amniotic fluid, and several fetal organs, while the authors emphasized the need for additional clinical validation [17].

These developments are relevant because toxicity and pharmacological response are often tissue-specific. A fetal plasma concentration may therefore be an incomplete surrogate for fetal organ exposure. The appropriate level of model complexity should nevertheless be matched to the available data; adding compartments or transporter parameters that cannot be supported experimentally may increase apparent sophistication without improving predictive reliability. Model qualification should therefore remain an iterative process in which each new parameter is linked to an identifiable biological process and evaluated against independent observations.

7. CLINICAL INTERPRETATION AND RESEARCH PRIORITIES

The presence of a drug in fetal blood or tissue does not by itself establish fetal toxicity. Clinical interpretation depends on dose, duration, gestational timing, fetal concentration, pharmacological target, developmental biology, and the maternal indication for treatment [6,7]. Conversely, low measured fetal concentrations do not necessarily imply absence of biological effect if a drug accumulates in placental tissue, has a long tissue half-life, or produces active metabolites. A central research priority is therefore better linkage between exposure and outcome. Human pregnancy pharmacokinetic datasets remain uneven, and many drugs lack sufficient data to support confident dose adjustment [8].

More prospective pharmacokinetic sampling, standardized maternal and cord-blood collection, quantitative placental measurements, and careful recording of gestational age and dosing history would strengthen model calibration and validation. The next generation of studies should combine three layers of evidence: first, quantitative characterization of drug-specific permeability, transporter activity, and metabolism; second, gestational-age-specific human placental physiology; and third, clinical maternal and fetal concentration data. Newer organ-on-chip and microphysiological models may contribute particularly useful information for early gestation, where direct human sampling is most constrained [26,27]. Spatial and single-cell approaches may also improve understanding of transporter localization, although transcript abundance should not be assumed to equal functional protein activity [9].

Finally, the field should move toward standardized reporting of placental transfer metrics. Terms such as placental transfer ratio, fetal-to-maternal concentration ratio, and unbound fetal-to-maternal exposure ratio are not interchangeable. Explicit definition of the metric, sampling time, gestational age, protein binding, and whether the measurement is total or unbound will improve comparability across studies.

CONCLUSION

Placental drug transfer is a dynamic, gestation-dependent process governed by drug physicochemical properties, maternal exposure, placental anatomy, transporter localization and function, placental metabolism, vascular exchange, and fetal disposition. Recent PubMed-indexed research has strengthened the evidence base for combining human placental experiments with quantitative PBPK approaches and has expanded the use of microphysiological models for mechanistic investigation. At the same time, important uncertainties remain, particularly for early gestation, transporter function, transplacental clearance, and direct fetal concentration data.
For rational pharmacotherapy in pregnancy, the practical goal is not simply to minimize fetal exposure. Effective maternal treatment may be essential, and fetal exposure must be interpreted in the context of developmental timing, pharmacological action, and maternal benefit. The strongest path forward is an evidence-integration framework in which experimental measurements, clinical pharmacokinetics, and mechanistic models are used together, with uncertainty explicitly reported. Such an approach can improve the scientific

basis for maternal dosing, fetal exposure assessment, and the design of pregnancy pharmacology studies.

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How to cite this article: Haridoss N K. Artificial Intelligence in Pediatric Medication Safety: Opportunities for Detecting Dosing Errors and Adverse Drug Reactions. Indian J Pharm Drug Studies. 2025; 4(3):89-94.

Funding: None *Conflicts of Interest: None Stated*