Drug Dosing during Pregnancy- Opportunities for Physiologically Based Pharmacokinetic Models

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Abstract
Drugs can have harmful effects on the embryo or fetus at any point during pregnancy. Not all the damaging effects of intrauterine exposure to drugs are obvious at birth, some may only manifest later in life. Thus, drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus. Dosing of drugs during pregnancy is often empirically determined and based upon evidence from studies of non-pregnant subjects, which may lead to suboptimal dosing, particularly during the third trimester.

This review collates examples of drugs with known recommendations for dose adjustment during pregnancy, in addition to providing an example of the potential use of PBPK models in dose adjustment recommendation during pregnancy within the context of drug-drug interactions.

For many drugs, such as antidepressants and antiretroviral drugs, dose adjustment has been recommended based on pharmacokinetic studies demonstrating a reduction in drug concentrations. However, there is relatively limited (and sometimes inconsistent) information regarding the clinical impact of these pharmacokinetic changes during pregnancy and the effect of subsequent dose adjustments. Three examples were described to show how pregnancy PBPK can facilitate and guide dose assessment throughout gestation.

Keywords
Pregnancy, Physiologically-based pharmacokinetic model, Dosing adjustmentFetal exposure

Background

Pharmacotherapy plays a major role in obstetrical care throughout pregnancy. The total avoidance of pharmacological treatments is often not feasible as pregnant women frequently require therapeutic intervention for pregnancy-related conditions and those unrelated to their pregnancies that require ongoing or episodic treatment (e.g., asthma, epilepsy, hypertension). Such pharmacotherapy requires knowledge of the proper dosing in order to achieve the appropriate drug concentrations for efficacious management of the condition and to prevent poor fetal outcomes associated with poor maternal disease control. However, there are still vast gaps in pharmacology information and evidence for appropriate dosing of medications in pregnant women [1,2]. The rates of prescription drug use in pregnancy, excluding prenatal vitamins, were reported to be about 44% in Denmark and Finland, 85% in Germany and 93% in France [3]. The frequency of using these prescription drugs during pregnancy is higher during first trimester as many women may not be aware of their pregnancy during this time, but also during the third trimester due to the development of new gestational-related conditions, amplifying of underlying pre-pregnancy conditions or preparation for caesarean section. It is also intuitive to minimize drug exposure or intake during early gestational weeks, when the teratogenic window is at its highest sensitivity.

Currently, there is a paucity in data for prescribers and patients to make informed decisions as to the proper selection and appropriate dosing of many drugs used during pregnancy [4]. Many drug labels advise not to take these drugs due to absence of safety data. Despite these warnings, many older drugs, due to their long history of use and track record of safety profiles in non-pregnant patients, are prescribed off-label. A review of surveys among developed countries indicated that the percentages of use of contraindicated medicines in pregnancy ranged from around 1% in Denmark to 5% in USA, while the percentage of use of overall harmful drugs ranged from 2% in Italy to 59% in France [3]. In a UK study, about 24% of drugs prescribed to pregnant women were off-label and 16% were of high risk [5]. In a French study, about 28% of drugs prescribed to pregnant women were off-label; 22% were considered high-risk, and 7% were contraindicated medications [6]. Likewise in the USA, about 23% of pregnant patients received at least one off-label drug. When prescriptions were grouped per trimester, about 94% of these prescriptions were during the third trimester [7]. It should however, be pointed out that unlicensed or off-label use may be necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience as it increases the prescriber's professional responsibility and potential liability. Unfortunately, the recommended doses and dosing intervals for off-label drugs may be inaccurate because they are based on the pharmacokinetics usually determined in healthy "male" volunteers. However, it is worth nothing that clinical practice habits and labelling can differ between countries; for example, doxylamine is off-label and seldom used in France but is on-label in the USA for nausea/vomiting during pregnancy (see [6]).

Challenges in dosing pregnant patients

Historically, pregnant women are actively excluded from drug development clinical trials, and, if pregnancy does occur, the usual procedure is to discontinue treatment and remove the patient from the study. Such challenges have led to the status quo that the number of medicinal products currently labelled for use during pregnancy is

limited, which translates into current clinical practice which results in doses for pregnant women being based upon adult doses. Pregnant women, however, do not exhibit pharmacokinetics of typical subjects recruited onto clinical trials, and often pregnancy results in the processing of medications differently to that of men [8,9]. This difference is a result of well-known physiological changes that take place during pregnancy [10], such as differences in enzyme activities, cardiac output, tissue blood flow, renal function, body fluids and development of new feto-placental unit (Figure 1). These factors limit our ability to establish safe and effective doses for pregnant patients, making the establishment of safe and efficacious doses based on data obtained under different physiological statuses difficult. This is primarily manifested through the impact on numerous pharmacokinetic processes, such as drug metabolism, increasing distribution volume, and addition of the growing feto-placental unit [11,8].

For drugs with a narrow therapeutic window, an increased clearance during pregnancy can lead to sub-therapeutic concentrations and worsening disease control. Ideally, pregnant patients should receive drugs that have been appropriately evaluated for their use in this population. In 2004, the US Food and Drug Administration (FDA) released a guidance describing a framework for designing and conducting PK/PD studies in pregnant women with recommendations on how to assess the influence of pregnancy on drugs PK/PD and what to consider when designing and conducting PK studies in pregnant women [12]. The FDA has also increased pregnancy investigation requirements and has given recommendations on how and when to include pregnant women in drug development clinical trials [13]. Furthermore, FDA replaced the pregnancy categories letters from all human prescription drug and biological product labels with meaningful information about the risks of using a drug during pregnancy [14]. The gestational age dependency in PK/PD may require direct investigations through clinical studies, or indirect investigations through the application of a model-based approach.

The role of physiologically-based pharmacokinetic models

The combined effects of multiple physiological parameters during pregnancy on drug kinetics can be augmented or partially/totally cancel each other out. For example, the reduction in albumin concentration and the increasing in CYP3A4 activity, together with the rise in cardiac output during pregnancy (Figure 1) has led to increased midazolam clearance [15], a drug that is normally classified as intermediate hepatic extraction ratio in adult healthy volunteers. The increasing clearance with gestational age can easily push this compound to high extraction ratio region during the third trimester, a situation that has been seen in the paediatric population [16]. Such increases in clearance during pregnancy, together with the increasing volume of distribution (Figure 1), should result in lower drug exposure in pregnant women compared with their non-pregnant counterparts and hence higher doses are required to achieve similar exposure [17].

Pregnancy can increase the distribution volume of drugs to different levels depending on the stage of pregnancy and the physico-chemical properties of the drug. Physiological parameters include, but not limited to, changes in the level of binding proteins, expansion of intravascular fluid, accumulation of fat, growth of the feto-placental organs, composition of different organs, changes to the blood flow and induction of transporter expressions. Expansion of plasma volume can increase distribution volume and lower the peak and steady-state concentrations of hydrophilic drugs if the dosing is unchanged [18]. Reduction in plasma binding protein can increase the free

fraction of highly protein-bound drugs such as midazolam, valproic acid and phenytoin and increase their distribution to the extravascular space. Current pregnancy PBPK models integrate such physiological changes with physico-chemical properties of the drug such as lipophilicity, changes in drug free fraction, affinity to cellular components and transporter kinetics, to describe the change to the drug distribution volume during pregnancy and partitioning into different tissues using different predictive methods [19,20].

A unique situation during pregnancy is the induction of CYP2D6 resulting in depletion of CYP2D6 substrates such as, dextromethorphan [21], paroxetine [22] and metoprolol [23] from the plasma of pregnant women, who are extensive and ultra-rapid CYP2D6 metabolizers. Depending on whether the parent drug or the metabolite is the pharmacologically active substance, differences in genotype can have different effects on maternal plasma concentrations of the active drugs during pregnancy, leading to therapeutic and safety consequences. In addition, the activity of CYP1A2 decreases as a function of gestational age [24] along with an increase in CYP2D6 activity. Together these phenomena can partially cancel the effect of each other on drug metabolism, as demonstrated by the relatively consistent systemic exposure for propranolol during pregnancy [25]. However, this also depends on the contribution of these enzymes to the overall clearance, for example if the subject is an ultra-rapid metabolizer with respect to CYP2D6, then the impact of CYP2D6 on propranolol clearance will be dominant and dose increase may be required. Conversely, CYP1A2 is the dominant metabolizing enzyme for theophylline clearance in non-pregnant subjects, but toward the end of pregnancy this can lead to a decreasing metabolic clearance increased exposure. This has been observed in two of six pregnant women at third trimester [26] and required dose reduction. The fact that not all patients did not require dose reduction can be attributed to the increasing compensatory effect of renal clearance with gestational age. Therefore, pregnancy partially converts a proportion of theophylline clearance from hepatic metabolic clearance to renal with advancing gestational time. Due to such a dynamic nature during pregnancy, the implementation of pregnancy physiologically based pharmacokinetic (PBPK) models catering for such physiological changes and their mutual effects with pharmacokinetic processes, is a necessary step in maternal drug development and therapeutics.

Pharmacogenomics-bases dosing strategy

Over the last few years, there has been a substantial rise in the number of new drugs that carry pharmacogenomic information about metabolizing enzymes/transporters in labelling to provide clinicians with the information they need to adjust the dose appropriately[27]. Such information also may suggest considering alternative drugs, if the patient is already under medication and there is an expectation of risks from drug-drug interactions. For the pregnancy population, it is still unclear how maternal/placenta phenotypes can affect the safety and efficacy profile of the drug to the mother herself and to the fetus in the presence of myriad physiological adaptations. Currently, determination of fetal pharmacogenomic information is not part of pharmacotherapeutics and unlikely to be significant as the expression of fetal enzymes and transporters are very low, if not absent. Clinical applications of prenatal pharmacogenomics could include both prospective testing to identify pregnancies likely to have significantly altered placental transfer, allowing for changes in dosing and medication selection to optimize safety and efficacy, as well as retrospective testing to identify whether the fetus has been previously

exposed to significant risk [28]. Understanding the impact of maternal genotypes on the drug exposure can help to describe part of interindividual variability in drug kinetics, contribute to better understanding the impact of physiology, and further guide if dose adjustment is required [29,30,22]. The interplay effect of pregnancy and CYP2D6 phenotypes may have clinical implications for CYP2D6 drug substrates with a narrow therapeutic range or low therapeutic index. Because the effect may vary from drug to drug, any such treatment warrants a re-evaluation of the dose when a woman becomes pregnant.

Current status of pregnancy PBPK applications

Modelling and simulation tools, so far, have been applied to predict "gestational pharmacokinetics" with the aim to determine safe and efficacious doses more efficiently. Population pharmacokinetics plays an important role in this area due to the nature of the limited number of samples that can be collected from each pregnant patient and also to the strength of this approach in borrowing information from different patients to derive a conclusion from sparse data [31-35]. While population pharmacokinetic approaches can be applied to understand the changes in PK during pregnancy if observed concentration data exist, its application to investigate new drugs and dosing proposals is challenging. In addition, mapping and extrapolating the obtained results beyond the data used to derive the model to understand the highly dynamic physiological status during pregnancy is questionable.

The PBPK approach is another tool that enables prediction of drug exposure in pregnant women based on preclinical data on drug kinetics and physicochemical properties and inclusion of gestational age-related changes in physiological parameters. The major benefit of pregnancy PBPK models is the incorporation of gestational age-dependent changes in patient physiology (e.g., cardiac output and feto-placental unit) and the activities of metabolizing enzyme and drug transporters in combination with the possibility to disentangle aspects of inter-subject variability that stems from phenotypes or biometric differences (Figure 2). Furthermore, these approaches offer the possibility to comprehend non-linearity in drug pharmacokinetics, in addition to enabling extrapolation to different populations or assessing drug interactions.

Building a pregnancy PBPK model should be seen as "add-ins" on top of the normal PBPK for non-pregnant women, through incorporating physiological changes during pregnancy as continuous functions linked to the baseline values of the physiological parameters, such as bodyweight, cardiac output and metabolic changes. The required parameters for building PBPK model is highly depend on the granularity of the model and/or on the aim of the model. A detailed PBPK model needs more parameters than a simple PBPK model depending on the mechanism of the physiological features to be captured in the model.

For example if the pregnancy PBPK model is evaluating the maternal plasma pharmacokinetics for renally eliminated drugs via glomerular filtration, then gestational-dependent changes in renal functions are of major interest. If the aim of the model is to investigate the maternal plasma pharmacokinetics of renally drugs eliminated via filtration and active processes, then the model should include parameters that describe the changes in transporter kinetics in addition to changes to the passive processes that my occurs during pregnancy. The model can be complex if the aim is to investigate kinetics of drugs that also undergo metabolism where there are temporal changes to the activity of the involved metabolizing enzymes. The pregnancy PBPK model can be more complex

if the aim is to investigate the transplacental passage of drugs known to be affected by placental transports or metabolizing enzymes and in PBPK terms this model requires permeability-limited models where (saturated or unsaturated) kinetics can be evaluated [36]. The complexity of the model can be further increased if the model is developed to assess the fetal systemic or organ exposure, where detailed physiological parameters are required for describing the growth of fetal organs, their blood perfusions and compositions [37-39]. Differences in the structure of the basline (non-pregnant) and dynamic (pregnant) PBPK models have been reviewed [40,41]. Furthermore, within a PBPK model, different predictive tools, which further challenge the possibility of mapping the model parameters.

Due to the physiological complexity, pregnancy PBPK models by nature should retain a level of complexity to reflect the dynamic status but without losing their potential capabilities. This complexity in pregnancy PBPK model is often associated with uncertainty in the model parameters. Preclinical and nonclinical data can contribute to better understanding of the system and reduce the model uncertainty. For example, experimental data from human placental perfusion experiment can be used to parametrize the placental diffusion parameters within the PBPK model [42]. An alternative way to parametrize the trasplacental permeability is the use of cell lines permeability data [36]. Quantification of gestational-dependent placental transporters expression and in vitro experiment of cell lines allows expansion of the model to further facilitate the investigation of transporter kinetics at different gestational age. while, in vitro kinetics of transporters and metabolizing enzymes can be used as assumed as same in nonpregnant women, the in vivo metabolism can be different in pregnant women due to the perturbation in the media such as the reduction in binding protein levels and other factors known to affect protein kinetics such as the elevation of plasma free fatty acids. In vitro measurement of unbound drug in maternal plasma as well as in umbilical cord plasma is important PBPK parameter not only for drug kinetics, but also in order to assess drug safety to the mother and her fetus

So far, the pregnancy PBPK model has been primarily applied to predict any alteration in drug kinetics during pregnancy after being validated for adequate prediction in non-pregnant subjects (see examples in Table I). The increasing applications of pregnancy-PBPK models has aided in building confidence around this approach. These applications can guide dosage adjustment to achieve a target therapeutic window (concentration or exposure), usually adopted from non-pregnant women (or men) and assuming the exposure-response relationship is valid. While this can be a safe assumption for some drugs with wide therapeutic windows, it can be hazardous for antiarrhythmics and the majority of CNS acting drugs [43]. Pregnancy may alter drugs response due to specific receptor alterations from the nonpregnant state (Smiley 1996) or increase drug sensitivity which may lead to increase adverse effects over non-pregnant individuals or to the fetus [44,45]. Even at doses that have been shown to be safe for the mother, prolonged use of benzodiazepines, specially, near term is contraindicated because of neonatal toxicity and withdrawal symptoms.

Examples of pregnancy PBPK model applications

Quetiapine

Quetiapine is an atypical antipsychotic drug used for management of bipolar disorder in adults and during pregnancy [46,47]. Quetiapine is mainly metabolized by cytochrome P450 enzyme CYP3A4 (approximately 80%) with minor contributions attributable to CYP2D6 [48]. Both enzymes are induced during pregnancy [24]. The increase in drug clearance during pregnancy reflected the observed lower plasma concentrations of quetiapine compared to postpartum level and that pregnant patients may need higher doses to maintain consistent plasma concentrations and efficacy. A pregnancy PBPK approach has been applied to optimise the required dose throughout gestation by targeting a therapeutic range of 50–500 ng/ml [49]. The model was validated using non-pregnant population data and then checked for it is performance in during pregnancy using therapeutic drug monitoring data. The pregnancy PBPK predicted decrease in trough concentration during pregnancy compared with non-pregnant subjects and proposed higher dosing 500-700 mg twice daily to achieve the target therapeutic window.

Chloroquine

Chloroquine has been used for the treatment of malaria and for prophylactic treatment during pregnancy when in the judgment of the physician the benefit outweighs the potential risk to the fetus. The Zika virus infection during pregnancy can lead to reduced fetal brain tissue, ocular damage, congenital contractures, restriction in body movement and other birth defects of the new born infant to infected mother [50]. In vitro studies have highlighted that chloroquine is capable of inhibiting Zika virus endocytosis in brain cells [51,52] and in mice [53,51]. The drug has not been approved for this indication.

Pregnancy PBPK approaches have been applied to develop a predictive model for chloroquine exposure to identify an optimal maternal/fetal dosing regimen to prevent Zika virus endocytosis in brain cells by targeting a therapeutic chloroquine plasma window of 0.3-2 μM [54]. The PBPK model was first validated using 13 non-pregnancy and 3 pregnancy clinical studies to ensure that the model captured chloroquine pharmacokinetics during pregnancy. The pregnancy PBPK model was then run for current chloroquine dosing regimens used in rheumatoid arthritis, systemic lupus erythematosus, and malaria to assess their ability to target the therapeutic window. These dosing regimens identified that weekly doses used in malaria were not sufficient to reach the lower therapeutic window, while daily doses of 150 mg of chloroquine enabled targeting to within therapeutic window. This was partly a result of the longitudinal physiological changes during gestation highlighted in Figure 3, in addition to alterations in the contribution of each CYP isozyme metabolic pathway (fraction metabolism by each CYP isozyme: fmCYP) towards chloroquine metabolism. This was exhibited as a reduction in the fmCYP for 3A4 and 2C8 and increase in 2D6. The final dosing regimen proposed loading doses of 600 mg on day 1, 300 mg on day 2 and 3, and 150 mg thereafter and illustrates a framework where pregnancy PBPK modelling can be used to support repurposing of medicines in pregnancy.

Piperaquine

Piperaquine is an antimalarial drug that has gained interest for use during pregnancy in response to increasing resistance towards sulfadoxine-pyrimethamine. The availability of in-vitro metabolic clearance data is limited for piperaquine with CYP3A4 identified as the major metabolic pathway and CYP2B6 playing a minor role [55]. In many developing countries, co-infection with HIV is common during pregnancy making pregnant women more

vulnerable to the complication of malaria, such as anaemia, placental parasitemia and low birthweight [56]. The fact that these women need HIV treatment, usually combined therapy, the potential of interaction between HIV drugs, anti-malarial drugs and the physiological changes due to the gestation that can affect the drugs kinetics, can result in highly complex clinical situation. Yet, little is known about the impact of HIV mediated drug-drug interactions on piperaquine PKs during pregnancy and whether prior knowledge can be extrapolated from an ethnic population to others. The pregnancy PBPK approach has been used to predict PKs in non-pregnant and pregnant patients, which was validated in distinct customised population groups from Thailand, Sudan and Papua New Guinea [57]. First the piperaquine PBPK model was built and verified in Caucasian non-pregnant healthy subjects. The piperaquine PBPK model was then parameterised using physiological parameters from the three target populations and verified for capturing the drug kinetics in non-pregnant women.

The ethnic-dependent piperaquine PBPK model was then applied to predict the drug kinetics during pregnancy in the target populations assuming the trajectories for pregnancy parameters for these three populations are similar to those in Caucasian pregnant women and baseline is only ethnic-dependent, where data available. The pregnancy PBPK model for these populations was used to assess the impact of efavirenz (CYP3A4 induction) or ritonavir (CYP3A4 inhibition) on piperaquine concentration. Their results indicated no significant differences piperaquine concentrations during pregnancy with a predicted AUC_{ratio} in the range 0.56-0.8 and 1.64-1.79 for efavirenz and ritonavir, respectively, over GW 10-40 gestational weeks. No dosing adjustment was suggested for piperaquine in these drug-drug interaction scenarios [57], probably due to the fact that the effect of the inducer on CYP3A4 is partially counteracted by the effect of the inhibitor. It is also worth mentioning that while antiretroviral-mediated drug-drug interaction (DDIs) could significantly alter piperaquine PKs due to other reasons, the framework followed in this assessment indicate the promising field of pregnancy PBPK model applications.

Paroxetine: genotype-based dosing

Paroxetine is a selective serotonin reuptake inhibitors (SSRIs) and is used to treat conditions such as major depressive disorder, social anxiety disorder, anxiety disorder and obsessive-compulsive disorder [58,59]. Its primary metabolism route is trough CYP2D6 with smaller contributions from CYPs 3A4, 1A2, C219 and 3A5 [60]. In addition, paroxetine is known to be a mechanism-based inhibitor of CYP2D6 [61-63]. Aside from the aforementioned physiological changes associated with gestation which impacts upon drug pharmacokinetics, a consequence of the longitudinal increase in the activity of CYP2D6 during gestation results in a 50 % decrease in paroxetine plasma levels [59,64-67,21]. This is further confounded by the polymorphic nature of CYP2D6, which results in an approximate 7-fold difference in paroxetine clearance between the extensive metabolism (EM) and poor metaboliser (PM) phenotypes [68,63]. Given the risks of poor control of mental health to both mother and fetus, coupled with post-natal risks of neonatal withdrawal syndrome and particularly persistent pulmonary hypertension of the new-born (PPHN) [69] [70].

The pregnancy PBPK modelling approach was used to provide a clinically relevant dose titration strategies [71] when considering the CYP2D6 phenotype status patients by targeting a paroxetine plasma window of 20-60 ng/mL [72,73]. The PBPK model workflow validated the pregnancy model through: (i) 3 single dose and 2 multiple dosing studies in non-pregnancy subjects; (ii) non-genotyped pregnant subjects throughout gestation and (iii) genotyped (EM, PM and UM) pregnant subjects at the mid-point of each trimester. With knowledge of the plasma therapeutic range, this approach allowed dose optimisation across gestation specifically for EM, PM and

UM phenotypes targeting this therapeutic range, and culminated in a requirement for daily doses in-excess of the standard 20 mg dose throughout gestation. For each trimester (T), a dose titration was required for EM (T1: 30 mg; T2: 40 mg; T3 40 mg), PM (T1: 20 mg; T2: 30 mg; T3 30 mg) and for UM (T1: 40 mg; T2: 40 mg; T3 40 mg). Using the pregnancy PBPK modelling approach, this study highlights how precision dosing could be implemented within clinical practice with polymorphic CYP isozymes to support optimisation of drug therapy.

Efavirenz: genotype-based dosing

The first-line treatment for acquired immune deficiency syndrome (AIDS) often includes non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTI) [74]. Within these treatment approach, the NNRTI efavirenz commonly utilised as a first-line agent in most regimens at a dose of 600 mg daily. Efavirenz is predominantly metabolised by CYP2B6 [75] and is an inducer of CYP3A4 [76,77]. Efavirenz has a linear pharmacokinetics behaviour, and steady-state plasma concentration are reached within 7 days [78]. It is a standard first-line treatment in paediatrics or pregnancy population groups [79] [80]. Several important CYP2B6 SNPs have been identified to have a significant impact on drug metabolism with, in some cases, up to 50% higher frequencies in some populations [81,82].

CYP2B6 is highly polymorphic with at over 100 identified SNPs [83] [84], with the **1/*1* genotype considered as wild-type carrier and the **6/*6* genotype (poor metaboliser phenotype) being prominent in about 15-40% in Asians and more than 50% in African-Americans population [85-87]. Furthermore, the **6/*6* genotype can often result in a 2-3-fold higher efavirenz plasma concentration [88,89,82,90], and hence an increased ability to induce CYP3A4 [77,91,92].

Given the sparsity of studies considering efavirenz pharmacokinetics in pregnancy and the lack of knowledge on the impact of the poor metaboliser phenotypes during gestation, a pregnancy PBPK modelling approach was utilised [74] aimed at assessing the impact of CYP2B6 phenotypic status efavirenz dosing during the third trimester in order to assess the suitable of a recently recommend lower daily dose (400 mg) [75]. This study demonstrated an approximate 2-fold decrease in poor metaboliser clearance when compared to extensive metabolisers, with 1.4-fold increase in peak plasma concentration [74]. This pregnancy PBPK study demonstrated that approximately 57 % extensive metaboliser patients in trimester 3 possessed trough concentration below the lower therapeutic target of 1 mg/L, suggesting a 400-mg dose may lead to a significant number of extensive metaboliser patients being sub-therapeutic, and highlights the importance of pregnancy PBPK modelling in assessing the complex interplay between longitudinal physiological changes during gestation and the pharmacogenomic risks associated with genotype/phenotype pregnant patient groups.

Fetal Exposure

The application of PBPK models to describe fetal exposure have been reported for many drugs, including emtricitabine, tenofovir, nevirapine, midazolam, theophylline, darunavir, dolutegravir, zidovudine and acetaminophen (Table 1). In most of these examples, transplacental transfer parameters were estimated from the ex-vivo human placenta perfusion experiments and then were implemented in pregnancy PBPK models that have been developed in both non-pregnant and pregnant women. Model verifications were done by comparing observed

maternal and cord blood concentrations to predicted concentrations. For examples, the fetal PK profiles for three antiretroviral drugs, emtricitabine, tenofovir and nevirapine were predicted after scaling ex vivo parameters from perfuming a human cotyledon to the whole placenta and then integrating within pregnancy PBPK models developed for these drugs [76,77]. Both emtricitabine and tenofovir are renally cleared compounds, while nevirapine is metabolized by the cytochrome CYP3A4, CYP2B6 and CYP2D6 pathways. was developed to predict maternal and fetal pharmacokinetics (PK). Models prediction for maternal and fetal systemic exposures are given in Figure 4.

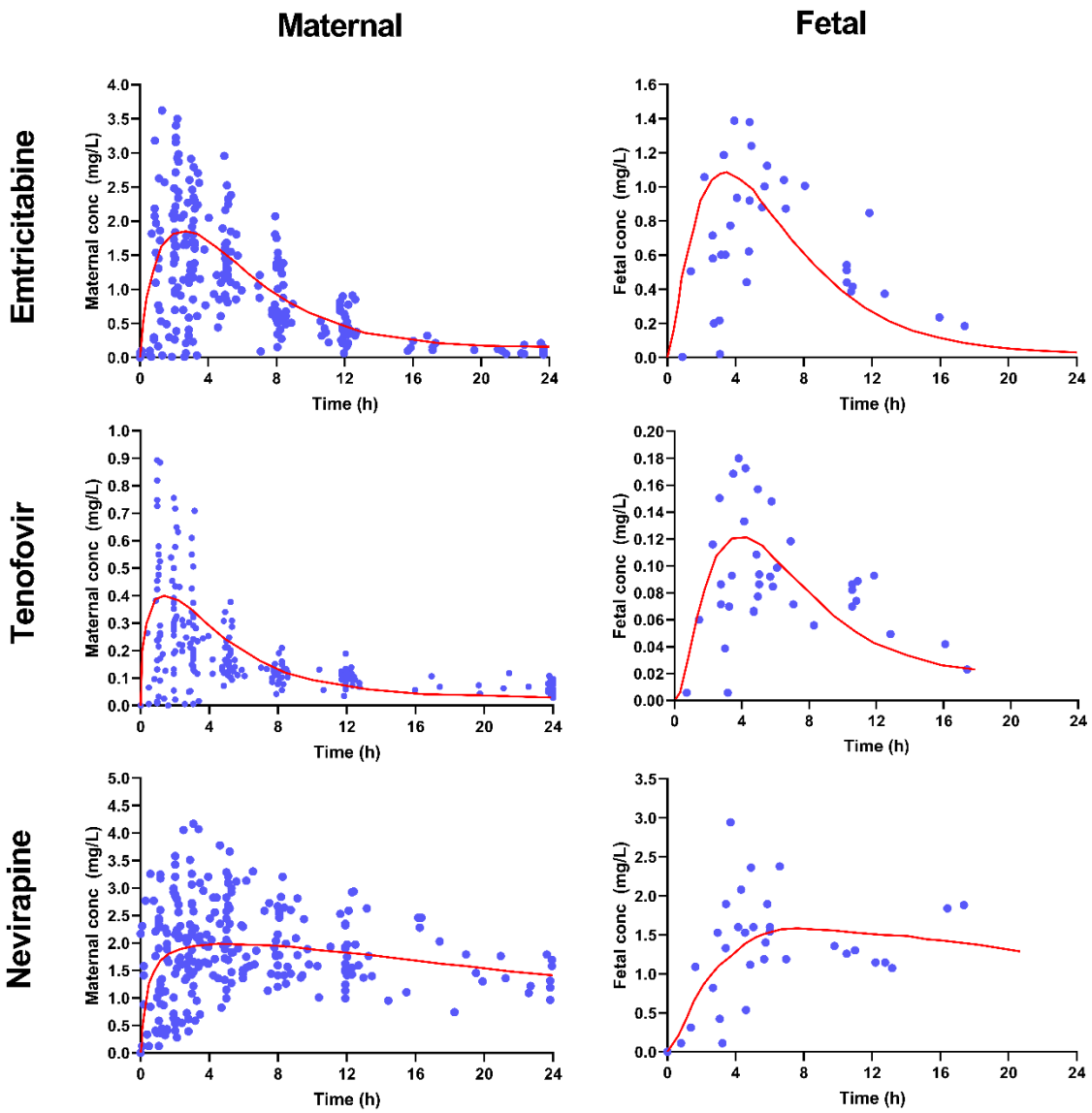

Figure 4: Maternal and fetal concentrations of emtricitabine, tenofovir and nevirapine [76,77]. Squares represent observed data; circles represent fetal (umbilical) data at delivery; Lines represent PBPK predictions for an average subject.

Assessment of maternal dose based on fetal target

Darunavir administered once daily (QD) or twice daily (BID) to treat and prevent human immunodeficiency virus (HIV) during pregnancy. Darunavir is approximately 94% protein bound, mainly to a-1-acid glycoprotein. Biotransformation is almost exclusively mediated by CYP3A4. Clinically, darunavir is coadministered with the potent CYP3A4 inhibitor ritonavir,to reduce darunavir clearance and maintain higher plasma concentrations throughout the dosing interval [78].

Pregnancy PBPK approaches was applied to develop a predictive model for both maternal and fetal darunavir systemic exposure at term in the presence of the inhibitor [79]. Data from ex vivo human placental perfusion experiment were integrated and used within the pregnancy PBPK model to parameterize the transplacental clearances of darunavir. The developed model was then verified against observed maternal and umbilical cord concentration during delivery. The verified feto-maternal PBPK model was then used to simulate and evaluate fetal darunavir exposure after different maternal darunavir/ritonavir dosing regimens (Figure 5). A therapeutic target trough concentration of 0.55 mg/L in the umbilical cord was used for darunavir in the presence of ritonavir.

Simulation showed that the standard dosing regimen for darunavir/ritonavir (600/100 mg twice a day) resulted in fetal population trough concentration that is higher or around the half-maximal effective darunavir concentration for a resistant virus (0.55 mg/L). While the standard dosing regimen may provide benefits to the prevention of mother-to-child transmission of HIV, possibly even higher dosing regimens are optimal with regard to fetal benefit, especially in the case of high-risk situations, such as maternal HIV breakthrough at term or if infected women have developed (multiple) resistance to protease inhibitors. Moreover, this study indicates that the experimental placental perfusion data can be integrated with pregnancy PBPK model to simulate fetal drug exposure and assess fetal toxicity or enhance the development of more selectively targeted fetal drug treatments.

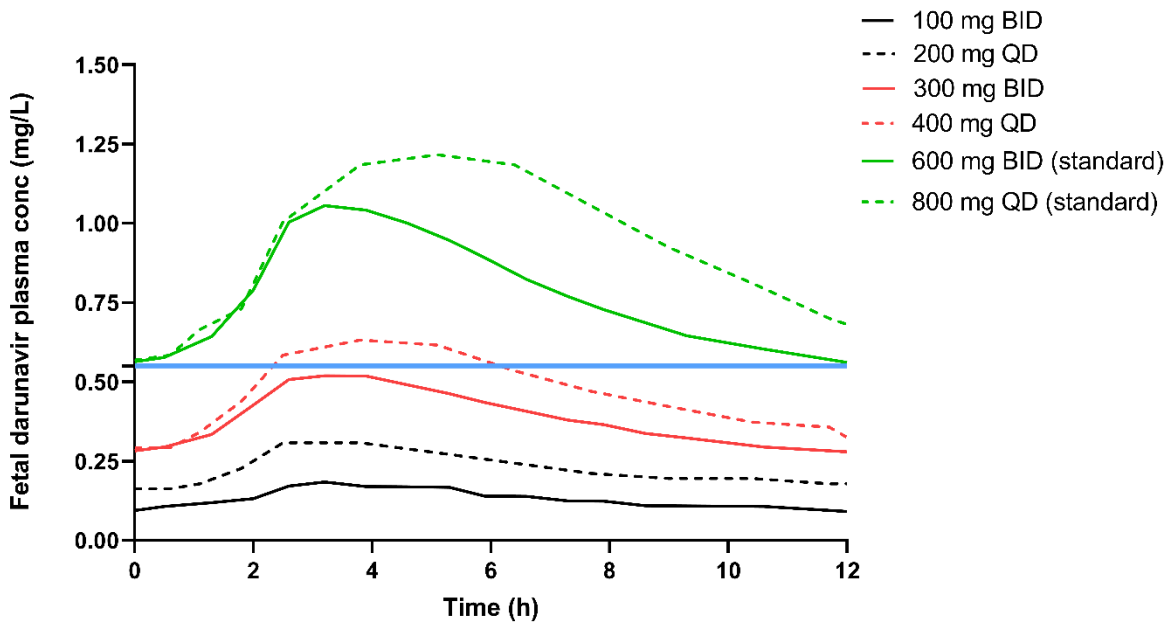

Figure 5. Simulated fetal darunavir concentration-time profiles for several maternal darunavir dosing regimens in the presence of ritonavir, a CYP3A4 inhibitor (Selected profiles around the target trough concentration from [79].

Concluding remarks

The first dose of any drug in pregnant women can be investigated directly by studying the drug kinetics in this population or assessed through PBPK approaches, which have the benefit of accounting for longitudinal changes in the physiological parameters of the model. Dosages of drugs may need to be increased during pregnancy in order to avoid loss of efficacy if the drug is predominantly cleared by renal or/and metabolised by CYP3A4, CYP2D6 and CYP2C9. Other non-CYP450s enzymes reported to induced during pregnancy are uridine diphosphate glucuronosyltransferase (UGT) UGT1A4 and UGT2B7 isoenzymes [8]. It is expected that if the drug elimination is enhanced during pregnancy, then the liability to drug-drug interaction will be lower compared to non-pregnant subjects, which may give an opportunity to pregnant women to benefit from such drugs. On the other hand, dosage of narrow therapeutic window drugs predominantly metabolised by CYP1A2 and CYP2C19 in non-pregnant healthy subjects should be reduced during pregnancy, especially during the third trimester to minimize their potential toxicity. However, these rules might be not straightforward due to the interplay between different factors affecting the clearance, including binding protein, co-medication and co-morbidity. These situations can be assessed by applying a PBPK approach that embraces all these elements and helps to better direct further studies and relax some ethical constrains rising from potential risk of harm to the pregnant women or her fetus(es).

Most current applications of pregnancy PBPK approaches tend to predict plasma concentration-time profiles during pregnancy providing that the non-pregnant prediction is well characterised and the model includes relevant physiological parameters. However, there is lack of robust data around the understanding of physiological changes to phase-II metabolizing enzymes and transporters. There is still a paucity on how and to what magnitude the geno/phenotypes of these proteins can alter the pharmacokinetics during pregnancy. Ideally, establishing dosing regimens for drugs with narrow therapeutic window for pregnant patients according to their phenotypes and at different points during their pregnancy is a forward step toward prenatal precision medicine. Pregnancy PBPK models that have been built and verified with a particular phenotype, can be easily accommodated to predict drug exposure in other phenotypes.

Going forward, it is imperative to assess whether dose adjustment is required during pregnancy, particularly when in vitro to in vivo extrapolation techniques are part of the model approach. The assessment can be more realistic if any prior knowledge on fetal exposure are added into the PBPK model, prior to assessing the dose adjustment or evaluating drug interactions. Given the mechanistic nature of these models, the future for PBPK modelling is promising with many potential opportunities to be explored, particularly with relevant to DDIs.

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Conflict of interest

The Authors declare no conflicts of interest to disclose.

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Table

Table 1. Examples of drugs that have been evaluated for PK changes and dose adjustment during pregnancy and their published pregnancy PBPK models.

Drug (Major elimination pathway)	**Clinical Studies**		**Aim of the published Pregnancy PBPK model**
	Pregnant PK compared to non-pregnant women	**Recommended action**	
Abacavir	Similar PK parameters (AUC, Cmax, half-life) during 3rd trimester to those at postpartum [80,81].	No dose adjustments are required.	NA
Acetaminophen (Glucuronidation, sulphation, P450)	Half-life was significantly lower and CLpo (glucuronidation) was significantly higher during (8-12 GWs) compared to non-pregnant women [82]. CLpo was 58% higher and half-life was 28% lower in pregnant (31-38 GWs) compared to non-pregnant women [83], CLpo (glucuronidation) increases at delivery compared with non-pregnant women [84].	No dose changes due to increased metabolite formation.	Maternal and umbilical cord PK prediction [85]
Acyclovir (Renal)	Similar PK parameters at > 35 GWs to those of non-pregnant adults [86,87]	No dose changes.	Maternal and umbilical cord PK prediction [88]
Amoxicillin (Renal)	During 2nd and 3rd trimesters both renal CL(total) and renal CL (secretion) were 1.6-fold higher than non-pregnant value [89].	Increase dose/more frequent dosing may be needed [89].	NA
Ampicillin (Renal)	Increased renal clearance, lower AUC and shorter half-life during 3rd trimester [90,91].	Increase dose/more frequent dosing.	NA
Betamethasone (Hepatic)	A 1.2-1.6 fold increase in clearance and volume of distribution [92].	Increase dosing frequency for sustained plasma levels [93] or dosing per kg lean body weight to reduce variability [92].	Maternal PK prediction [94]
Buprenorphine (CYP3A4, UGT1A1 and UGT2B7)	Increasing CLpo and decreasing exposure during 18 GWs to term [17,95].	Increase dose.	Maternal PK prediction [96]
Caffeine (CYP1A2)	Decreasing CLpo and increasing half-life with pregnancy progression [97,98].	No (possible dose reduction).	Maternal PK prediction [99-102]
Cefazolin (Renal)	About 1.7-fold increase in systemic clearance during 18-33 GWs [103,104].	Increase dose.	Maternal PK prediction [105]

Cefradine (Renal)	About 1.6–fold increased clearance in systemic clearance during 10-29 GWs [103].	Increase dose [103].	Maternal PK prediction [105]
Chloroquine (CYP2C8, CYP3A and CYP2D6)	Chloroquine and its desethyl metabolite exposure were 25% and 45% lower during 2nd and 3rd trimesters [106]. Similar trend observed during 2nd and 3rd trimesters [107] and early 3rd trimester [108]. This lower exposure was associated with 34% and 80% higher CLpo for chloroquine and its metabolite, respectively [106].	Dose increase may be desirable to achieve similar exposure to non-pregnant women [106].	PBPK evaluation during pregnancy proposing dosing regimens for prevention of Zika Virus disease [54]
Clonidine (Renal, CYP2D6)	About 1.8-fold higher oral CL and shorter t1/2 [64].	Dose increase/increase dosing frequency.	Maternal PK prediction [102]
Cyclosporine (CYP3A4)	Increased oral clearance, lower blood trough levels (C0) during 2nd and 3rd trimesters.	Daily dose increasing during pregnancy [109].	NA
Darunavir (+ ritonavir) (CYP3A4)	Increased oral clearance during second (1.77-fold) and third trimester (2-fold). Increasing darunavir dose from 600 mg BID to 800 mg BID failed to significantly increase darunavir exposure [110].	Increasing dosing frequency [111] or increasing ritonavir dose instead [110].	Maternal and umbilical cord PK prediction [78,79]
Dextromethorphan (CYP2D6, CYP3A4)	CYP2D6 activity increased by 25.6%, 34.8% and 47.8% at 14-18, 24-28, and 36-40 GWs. CYP3A activity increased by 35%-38% during all stages of the pregnancy [24]. Metabolic ratio in extensive metabolizers were reduced by 29% at 36 GWs [21].	No recommendations.	Maternal PK prediction [102]
Diazepam (CYP3A4 and CYP2C19)	CLpo at 9-12 GWs were within normal non-pregnant range [112]. Systemic clearance was similar to non-pregnant women, while half-life was 2-fold longer [113].	No recommendation. Probably due to its high transplacental passage, lower effective dose is recommended to avoid floppy infant syndrome[114].	Maternal PK prediction [101]
Digoxin (Renal)	Lower exposure due to (~60%) increase in renal CL during 28-32GWs [15] and throughout third trimester [115].	An oral loading dose of 0.5 mg/8 h during 24 h followed by a maintenance regimen of 0.5 mg/12 h been recommended to start fetal supraventricular tachycardia treatment [115].	Maternal PK prediction [116]
Dolutegravir (UGT1A1, CYP3A4?)	Slightly higher clearance, and lower AUCss. AUCss, maximum and trough concentrations were 20–50% lower in the 2nd and 3rd trimesters compared to postpartum [117,118].	No dose change was recommendation as trough concentrations in pregnancy were well above dolutegravir EC90.	Maternal and umbilical cord PK prediction [119]
Efavirenz (CYP2B6)	Similar PK during 2nd and 3rd trimesters to those observed in non-pregnant women [120-122].	No dose adjustment is required.	Maternal PK prediction [123]
Emtricitabine (Renal)	Higher CLpo, lower trough concentrations and exposure during 2nd and 3rd trimesters compared to postpartum [124,125].	Observed changes were not sufficiently large to warrant dose adjustment during pregnancy.	Maternal [126,76,116,88] and umbilical vein [76,88] PK prediction.

Fluvoxamine (CYP2D6 and CYP1A2)	Therapeutic drug monitoring (TDM) data from pregnant women throughout pregnancy showing about 14%, 38% and 56% decline in maternal drug serum concentrations during 1st, 2nd and 3rd trimesters, respectively compared to the non-pregnant level [59].	Dose increase of about 100% during the third trimester in order to maintain stable concentrations [59].	NA
Glyburide (CYP3A4, CYP2C9)	CLpo was 2-fold higher during 28–38 GWs compared to non-pregnant value [127].	Higher (double ?) doses may be needed during pregnancy to achieve glycemic control [127].	Maternal PK prediction [128]
Imipenem (renal filtration and dehydropeptidase)	Systemic CL increased by 2.1, and 2.9-fold at 7-11 GWs and 37-41 GWs, respectively compare to non-pregnant women. Similarly, renal CL increased by 2.4 and 2.7 fold, while Cmax reduced by 2.93 and 2.89 fold at at 7-11 GWs and 37-41 GWs, respectively [129].	Adjustment of doses of imipenem may be required.	NA
Indinavir (CYP3A4)	CLpo was 2-fold higher, AUC was 1.2-fold lower and Cmax was 1.7-fold lower than postpartum values [130]. CLpo increased and AUC decreased by 3.7-fold compared with postpartum [131].	An increased dose of indinavir during pregnancy may be preferable to ensure adequate exposure throughout pregnancy [130].	Maternal PK prediction [132]
Indomethacin (Renal, bile, UGT?)	CLpo was 2.2-fold higher during 12–31 GWs than in healthy male subjects [133].	Possible dose adjustment.	Maternal PK prediction [134]
Labetalol (UGT1A1 and UGT2B7)	Increasing CLpo with pregnancy progression from 1.4-fold at 12 GWs to 1.6-fold at 40 GWs [135].	Dose increase/increase dosing frequency [135].	NA
Lamivudine (Renal)	About 22% increase in CLpo between 6 and 39 GWs compared with non-pregnant CLpo [136].	No need for dose adjustment.	Maternal PK prediction [126]
Metformin (Renal)	Similar pharmacokinetic parameters during 10-14 GWs, increased renal clearance by 1.5-fold at 22-26 GWs and by 1.3-fold at 34-38 GWs. Secretion clearance increased by 1.5-fold at 22-26 GWs and by 1.3-fold 34-38 GWs [137]. At 26-38 GW, bioavailability increased by 1.35-fold, 1.6-fold increase in renal CL, and 1.7-fold increase in secretion CL, with no significant change to half-life after 500 mg dose. These fold changes were minimal for the 1000 mg dose [138].	Dose increase maybe required.	Maternal PK prediction [139,116]
Methadone (CYP3A4, CYP2B and renal)	Increase clearance during 1st, second and third trimesters and lower trough concentrations despite the dose were higher during pregnancy compared with postpartum [140]. Higher unbound clearance and lower trough concentrations during pregnancy compared with non-pregnant women [141]. Half-life was 60% shorter than non-pregnant [142].	Increase dose[141], dosing frequency [143] to reduce fetal stress. About 86% of pregnant women required increasing maintenance dose [144].	Maternal PK prediction [128]

Metoprolol (CYP2D6, CYP3A4 and Renal)	CLpo was about 4.4 times higher during 35-38 GW and the exposure exceeded that after pregnancy by a factor of 2 to 13 [145,146]. About 4-fold lower exposure during 34-39 GWs compared with postpartum exposure[147]. CLpo was 1.8-fold and 3.0-fold higher at 22-26 and 34-38 GWs, respectively compared with postpartum clearance, while renal CL was 1.5-fold higher during 34-38 GWs[23].	Dose increase/increase dosing frequency.	Maternal PK prediction [99,101,102]
Midazolam (CYP3A4)	CLpo increased by 2-fold during 28-32 GWs, the exposure reduced by 46% and Cmax was 28% lower of postpartum values, while no change to the half-life [15].	Many need dose increase during second half of pregnancy [15].	Maternal [99,148,116,101,36,149,132] and umbilical cord [36] PK prediction
Morphine (UGT)	Average half-life was 0.5-fold shorter and CLpo was 1.7-fold higher, while distribution volume did not change in parturients than in the non-pregnant women[150].	Possible dose increase.	NA
Nevirapine (CYP2B6, CYP3A4)	CLpo was 22% higher, while exposure, Cmin and Cmax were 19.2%, 18.6%, and 28.5% lower, respectively during pregnancy[30]. Increased CLpo by 30% during 33-42 GWs[31]. No significant changes in PK parameters (AUC and CLpo) during 2nd and 3rd trimesters vs postpartum[151]. PK parameters (C12h, Cmax AUC) were lower during 3rd trimester compared to postpartum [152].	Possible dose optimization based on CYP2B6 phenotypes.	Maternal and umbilical cord PK prediction [77]
Nifedipine (CYP3A4)	Approximately 2-fold lower Cmax and 2.73-fold increase in CLpo during 26-35 GWs [153] compared to non-pregnant women [154] and 2.4-fold at labour [29].	Dose increase/increase dosing frequency [153].	Maternal PK prediction [101,132]
Oseltamivir carboxylate (renal)	The systemic exposure of oseltamivir carboxylate (OC) was reduced approximately 30% and CLpo increased by 40% in pregnant women [35,155]. The CLpo was approximately 66%, 45% and 28% higher during 1st, 2nd and 3rd trimesters, respectively compared with CLpo in non-pregnant women. Half-life of OC was not different between pregnant and non-pregnant women [35].	Increasing the dose and/or dosing frequency of oseltamivir during pregnancy may be necessary to achieve comparable exposure in pregnant and nonpregnant women [35,155].	Maternal PK prediction [139]
Paroxetine (CYP2D6)	There was a drop of 12%, 34% and 51% of the plasma levels during 1st, 2nd and 3rd trimesters compared to the baseline [59].	Dose increase of about 100% during the third trimester in order to maintain stable concentrations [59].	Maternal PK prediction [102]
Phenytoin (CYP2C9)	Phenytoin CLpo increased during pregnancy by 1.9, 2.0, and 2.2-fold during 1st, 2nd and 3rd trimesters compared to postpartum women [156]. Both total and free concentration decreased, while free fraction increased with pregnancy progression [156,157].	Dose increased during pregnancies to maintain therapeutic efficacy [158,159].	Maternal PK prediction [128]
Piperacillin	Cmax was 2-fold lower and systemic CL was 2.8 higher near term compared with non-pregnant patients [160].	Dose increase.	NA
Piperaquine	Similar PK parameters during 2nd and 3rd trimesters to those observed in nonpregnant women [34,161].	No need for dose adjustment.	Evaluation of the impact of HIV mediated drug-drug interactions

(CYP3A4)			on piperaquine PKs during pregnancy in different ethnic populations [57]
Proguanil (CYP2C19)	Reduced formation of cycloguanil metabolite via CYP2C19. Mean cycloguanil Cmax in blood and in plasma at > 36 GWs were 50% lower compared with Cmax after pregnancy [162]. Median dose-adjusted concentration of cycloguanil was 73% lower during 3rd trimester compared with postpartum level [163].	Dose of proguanil should be increased by 50% [163].	NA
Quetiapine (CYP3A4)	Increased CLpo [127]. AUC decreased by 27%, 42% and 18% during 1st, 2nd and 3rd trimesters, respectively compared with postpartum[164].	Dose increasing [165].	Dosing optimisation strategy [49]
Sotalol (Renal)	Systemic CL and CLpo were 1.6-and 1.8-fold higher during 32-36 GWs compared to postpartum. Bioavailability and elimination rate were similar in these two occasions [166].	Possible dose adjustment [167].	NA
Tacrolimus (CYP3A4)	About 39% higher clearance during mid- and late-pregnancy compared to postpartum [168]	Dose increase [168].	Maternal PK prediction [139]
Tenofovir (Renal)	Slight reduction in systemic exposure and trough concentration during the 2nd and 3rd trimesters [169]. Pregnant women had a 39% higher apparent clearance compared to non-pregnant women [170].	Dose increasing from second trimester to delivery [170].	[126,76]
Theophylline (CYP1A2, Renal)	Free CLpo decreased by 1.2 and 1.4-fold during 24-26 and 36-38 GWs, respectively. non-renal CL decreased by 1.6-fold at 36-38 GWs, while most increase in renal CL was 1.8-fold at 24-26 GWs [171]. CLpo was 20-53% lower during last few weeks of pregnancy [26].	Possible dose reduction might be required during the second half of pregnancy, especially for renal impairment women, due to the narrow therapeutic window.	Maternal [36,102] and umbilical cord [36] PK prediction
Zidovudine (UGT2B7, Renal)	No change in the PK parameters during 2nd, and 3rd trimesters and at delivery compared to non-pregnant women [172,173].	No change to the dose.	Maternal and umbilical cord PK prediction [36]

AUC: area under the concentration time profile curve; CLpo: Clearance after oral administration; GWs: Gestational weeks; NA: Not available so far in the public domain.

Figure Legends

Fig 1 Examples of longitudinal variation in different physiological parameters during normal gestation (for more details see [10]). (A) Fold-change in CYP isozyme expression compared to non-pregnant subjects for 3A4, 2D6 and 1A4; (B) Changes in human serum albumin (red line, left y-axis) and α1-acid glycoprotein (green line, right y-axis); (C) Changes in cardiac output (red line) or glomerular filtration rate (GFR) (black line) and (D) changes in plasma volume (black line) or feto-placental unit (red line).

Fig 2 Pregnancy PBPK model input and output components

Fig 3 The impact of gestation on the fraction of chloroquine metabolized by CYP isozymes. Chloroquine metabolism is represented during dosing over 40 weeks of gestation by the fraction metabolism by each CYP isozyme (fmCYP) responsible for chloroquine metabolism, namely CYP 2C8, 2D6 and 3A4 [54].