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*The Journal of Medical Research 2024; 10(4):90-96*

The Journal of Medical Research

***Short Communication***

JMR 2024; 10(4):90-96
July- August
ISSN:2395-7565

www.medicinearticle.com
Received:11-06-2024
Accepted:14-08-2024
DOI: 10.31254/jmr.2024.10401

# Maternal-fetal physiologically-based pharmacokinetic modeling and CYP2C8 polymorphism impact on imatinib dosing in pregnancy

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## Abstract

Imatinib is first BCR-ABL tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST) in patients. However, the use of this drug in pregnancy is controversial, and critical information is missing for supporting the use during pregnancy. The objectives of the current study were to develop a physiologically-based pharmacokinetic (PBPK) maternal-fetal model to evaluate imatinib pharmacokinetics (PK) in pregnancy, explore the imatinib concentration in different fetal organs and the CYP2C8 polymorphism influence on pharmacokinetics and pharmacodynamics of imatinib in pregnancy. The imatinib PBPK model was built in PK-Sim® and MoBi® which are parts of the open-source software Open Systems Pharmacology (OSP). The fetal model was derived from our previously published model. The observed clinical data for the validation of the imatinib models were obtained from the literature. The current imatinib PBPK model reasonably predicted imatinib concentrations in the adult population and the pregnant population. The ratio of predicted vs observed PK parameters for the adult model ranged from 0.59-0.83 for AUC and 0.54 -0.90 for $C_{max}$ and $C_{min}$. The current model slightly overestimated the imatinib concentration in pregnant individuals in comparison with the clinical observation data, with most clinical observed individual data falling into the 5-95% predicted concentration range (4 of 6, 66.7%). The current model reasonably predicted the umbilical cord concentration of imatinib which compared to the clinical data. All clinical observed individual data fall into the 5-95% predicted concentration range 7 of 7 (100%). In addition, the current model provided predicted imatinib concentrations in different fetal organs such as brain, heart, lung, liver, kidney, muscle, GI and fat. In addition, the CYP2C8 influence to the imatinib concentration was significant, which affects the imatinib dosing in adults and during pregnancy. The current study demonstrated the utility of using PBPK modeling to understand pharmacokinetic differences between adults and special populations, such as pregnant women and their fetuses, indicating that the PBPK modeling can potentially inform or optimize dosing conditions in pregnant people.

**Keywords:** Physiologically-based pharmacokinetics, Imatinib, Maternal-fetal model, Fetal organ exposure, Umbilical cord, CYP2C8 polymorphism, Pregnancy.

## INTRODUCTION

Imatinib is the first small molecule BCR-ABL tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST). [1] Imatinib was approved by FDA in 2001 and started an era of molecularly-targeted cancer therapy.[1] The recommended dose for adult patient with CML in chronic phase is 400 mg orally per day and 600 mg per day for accelerated phase or blast crisis [1].

Some information on the pharmacokinetics (PK) of imatinib is available. The absorption of imatinib is high and the bioavailability is 98% [2]. Plasma concentrations of imatinib reach a peak concentration around 2 hours after oral administration, and the terminal elimination half-life is 18 hours. Imatinib is approximately 95% bound to $\alpha_1$- acid glycoprotein (AAG) [2,3]. The metabolism of imatinib is complicated but is the major pathway of elimination for imatinib. The renal elimination of imatinib is a minor fraction [2]. In addition, imatinib is also a substrate for multiple transporters such as ABCB1, ABCG2 and SLC22A1 [4,5]. At least one of the metabolites of imatinib, N-desmethyl imatinib, is pharmacologically active, but the N-desmethyl metabolite has much less potent pharmacologic activity than that of imatinib.

The major enzyme to metabolize imatinib is cytochrome P450 (CYP) 3A4, but other CYP enzymes such as CYP2C8, CYP3A5, CYP1A2, CYP2D6, CYP2C9 and CYP2C19 also contribute to the metabolism of imatinib. However, those enzymes play a minor role in imatinib metabolism. Imatinib is a competitive inhibitor of CYP3A4 and complicates the metabolism of this drug [6].

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In the long-term use of imatinib, CYP2C8 becomes a major enzyme to metabolize imatinib[7]. CYP2C8*3 and CYP2C8*4 are the major polymorphisms of CYP2C8. CYP2C8*3 has increased metabolic activity of imatinib and CYP2C8*4 has decreased metabolic activity of imatinib. Therefore, the genotypes of CYP2C8 affect the metabolism of imatinib and its exposure. Investigating the influence of CYP2C8 on imatinib PK provides important information for the appropriate dosing of imatinib.

Although imatinib is recommended as chronic treatment for patients with CML, it is not recommended for pregnant women in the FDA drug label. Animal studies have showed that imatinib can cause teratogenic effects in rats, and imatinib was considered to cause fetal teratogenic effects during pregnancy [1]. In addition, one report from the literature indicated a higher birth defect rate in pregnant women using imatinib than in pregnant women not using imatinib. Thus, women of childbearing potential are advised to avoid becoming pregnant when taking imatinib [1].

However, there are some reports in the scientific literature of pregnant patients with CML who have taken imatinib. [8] Some cases of pregnant women on imatinib who gave birth to healthy newborns have been reported in literature [8-10]. All the pregnant women in those studies had a normal childbirth. Thus, it is important to understand whether pregnancy alters the PK and the appropriate dosing of imatinib during pregnancy. Imatinib's therapeutic effect is strongly related to trough concentrations at steady state. The imatinib target concentration was equal to or more than 1,000 ng/ml. For trough concentration limits according to the literature, the maximum standard dose is 800 mg per day and results in a reported trough concentration is 2,960 ng/ml.

Physiologically-based pharmacokinetic (PBPK) modeling is the *in-silico* combination of physiological changes and pharmaceutics information in a compartmental modeling framework allowing the simulation of drug exposure in scenarios that are untested or difficult to test in patients. PBPK modeling has thus been successfully utilized to predict drug exposure in various special populations, including the pregnancy populations [11]. Recently there has been an increasing interest in the utility of PBPK to predict PK changes in pregnant people and their fetuses [12,13]. In view of the sparse information about imatinib PK in pregnant populations, the objectives of this study were to develop a maternal-fetal PBPK model for imatinib in the adult population, and to validate this model with clinical data. Once validated, the model was translated to a maternal-fetal model to study potential PK alterations and drug exposure in pregnant people, umbilical cord and different fetal organs in order to explore the potential changes in imatinib dosing for pregnant women if clinicians elect to use this drug [14].

## MATERIALS AND METHODS

### PBPK modeling

PBPK models were developed using the open-source software suite Open Systems Pharmacology (OSP, version 10) which includes PK-Sim® and MoBi® (https://www.open-systems-pharmacology.org/) [15]. The software R (version 4.3) was used for non-compartmental analysis and graphics creation. Web Plot Digitizer was used to extract data from figures and convert it into numerical format.

Initially a PBPK model of imatinib was built for the adult population following a previously published workflow [16]. The imatinib drug properties, such as molecular weight, lipophilicity, and solubility, were obtained from a literature search and applied to the model as model input parameters. Imatinib is primarily metabolized by CYP3A4, and to a lesser extent by CYP2C8. In the model, the fraction of metabolism via CYP3A4 and CYP2C8 to total metabolism was 60% and 40%, which was based on *in vitro* data from human liver microsomes experiment. For long-term use, the fraction of metabolism of CYP3A4 and CYP2C8 to total metabolism were 35% and 65%, respectively [7]. Imatinib is minorly eliminated renally about 5%, [1,2] and there is no renal elimination was incorporated into the model. The input parameters for the PBPK model for imatinib are listed in Table 1.

Once validated, the adult PBPK model for imatinib was translated to pregnancy model, which was carried out in PK-Sim® and MoBi® following a previously reported workflow [16]. The pregnancy PBPK model was parametrized for a gestational age range of 38 weeks. The following changes in enzyme activity were applied to the pregnancy model of imatinib: no change in CYP3A4 activity due to inhibition of CYP3A4 activity of imatinib. Regarding CYP2C8, the effect of pregnancy on CYP2C8 activity is unclear. One study from Choi et al. indicated that CYP2C8 appear to be increased by about 2-fold during 3rd trimester during pregnancy. Thus, 2-fold increase of CYP2C8 activity was applied to the model. The translation to integrate the fetal model was done in PK-Sim® and MoBi® as described previously [14].

### Clinical data used for model evaluation

Model performance was validated by comparison of simulated to observed clinical data reported in literature. Model suitability was determined in case the simulated vs. observed PK parameters fell within a 2-fold error range.

Studies from the literature were used for the adult model evaluation. Peng et al. study [2] included healthy volunteers who were administered a single oral dose of imatinib of 100 mg and a single iv dose of imatinib of 100 mg. The data from Forrest et al [17]. included CML patients on multiple dose 400 mg once a day. Guilhot et al study [18] included CML patients on multiple dose 300 mg, 400 mg, 600 mg and 800 mg once a day. Ogata et al study [19] included CML patients on multiple dose 300 mg and 400 mg once a day. Li et al study [20] included CML patients on multiple dose 400 mg and 600 mg once a day. The details of the adult PK studies are listed in Table 2. The study by Chelysheva et al. was used to evaluate the pregnancy model of imatinib [8]. This study included several pregnant patients with CML with a gestational age of 35 to 41 weeks receiving imatinib at an oral dose of 400 mg once a day. Further details on the two studies by Chelysheva et al. [8] and the pregnant patients are listed in Table 2.

## RESULTS

The current PBPK model of imatinib could successfully predict the imatinib concentration in non-pregnant adults (Figure 1). The maternal-fetal model reasonably predicted drug exposure in pregnant population, umbilical cord concentration of imatinib as well. (Figure 2). In additional, the model predicted imatinib concentration in multiple fetal organs such as fetal brain, fetal lungs, fetal liver, fetal kidneys, fetal GI, fetal muscle and fetal fat. (Figure 3)

The non-pregnant PBPK model developed for non-pregnant adults described the plasma concentration-time profiles following intravenous and oral administration of imatinib adequately (Figure 1, Table 3). For each of these clinical studies, the ratio of simulated to observed PK parameters is listed in Table 3, showing that the average AUC ratio was 0.71 (0.59-0.83); Cmax ratio was 0.89; Cmin ratio was 0.74 (0.54-0.90). The current model slightly overestimated the clearance of imatinib.

The maternal-fetal PBPK model was the reasonably predicted the plasma concentration and umbilical cord concentration of imatinib during pregnancy (Figure 2). Most of observed data (66.7%) fell in the predicted range (Figure 2A). There were 2 data points out of prediction range. The variability of the imatinib concentration in 3rd trimester of pregnancy was underestimated. The maternal-fetal model also the reasonably predicted the umbilical cord concentration of imatinib (Figure 2B). The 7 of 7 observed data (100%) fell in the predicted range (Figure 2B). In addition, the prediction of fetal organ exposure of

imatinib were showed in Figure 3. The model predicted the imatinib exposure in the fetal organs such as fetal brain, fetal heart, fetal lung, fetal liver, fetal kidney, fetal GI, fetal muscle, fetal fat and other fetal organs. The imatinib concentration in most fetal organs, such brain, kidney, heart, fat, muscle, lung and venous blood, is around 160-170 ng/ml with range of 60-270 ng/ml. The fetal liver concentration of imatinib is 513 ng/ml with range of 193-854 ng/ml. The fetal GI concentration of imatinib is 550 ng/ml with range of 290-758 ng/ml. Unfortunately, there was no clinical data of fetal organ exposure of imatinib available.

**Table 1:** PBPK Model Input Parameters

| **Parameters [unit]** | **Value** | **Reference** |
|---|---|---|
| Molecule weight [g/mol] | 493.60 | Drugbank |
| Lipophilicity [log units] | 3.46 | fitted |
| Solubility [mg/L] | 1 | Drugbank |
| p*K*a value 1 (base) | 8.07 | Drugbank |
| p*K*a value 2 (base) | 3.03 | Drugbank |
| Fraction unbound | 0.05 | FDA label |
| Protein binding partner | α1 – acid glycoprotein | FDA label |
| $Kcat_{CYP3A4}$ [1/min] | 3.00 | fitted |
| $Kcat_{CYP2C8}$ [1/min] | 0.52 | fitted |
| Protein expression profile | RT-PCR | |
| Model for estimating organ-to-plasma partition coefficients | Rogers & Rowland | |
| Weibull dissolution shape | 0.92 | fitted |
| Weibull 50% dissolution time [min] | 240 | fitted |

**Table 2:** Clinical studies used for PBPK Model

| Reference study | Dose | Patient number | Subjects |
|---|---|---|---|
| Non-pregnancy | | | |
| Peng et al. | 100 mg iv, single dose | 17 | Healthy male & female |
| | 100 mg oral, single dose | 17 | Healthy male & female |
| Forrest et al. | 400 mg per day | 70 | CML patients male & female |
| Guilhot et al. | 300 mg per day | NA | CML patients male & female |
| | 400 mg per day | NA | CML patients male & female |
| | 600 mg per day | NA | CML patients male & female |
| | 800mg per day | NA | CML patients male & female |
| Ogata et al. | 300mg per day | 3 | GIST male & female patients |
| | 400mg per day | 4 | GIST male patients |
| Li et al. | 400mg per day | 36 | CML patients male & female |
| | 600mg per day | 10 | CML patients male & female |
| Pregnancy | | | |
| Chelysheva et al. | 400 mg per day | 7 | CML patients at labor |

**Table 3:** PBPK Model Predictions vs Observations of Imatinib in Non-pregnant adults

| | $C_{max}$ [ng/mL] Predicted/observed (ratio) | $C_{min}$ [ng/mL] Predicted/observed (ratio) | AUC [ng*h/mL] Predicted/observed (ratio) |
|---|---|---|---|
| Non-pregnancy | | | |
| Peng et al_iv | -- | -- | 6237/7527 (0.83) |
| Peng et al_oral | 1630/1822 (0.89) | -- | 17482/29607 (0.59) |
| Forrest et al | -- | 959/ 1065 (0.90) | -- |
| Guilhot et al_300mg | -- | 744/1040 (0.72) | -- |
| Guilhot et al_400mg | -- | 974/1200 (0.81) | -- |
| Guilhot et al_600mg | -- | 1374/1935 (0.71) | -- |
| Guilhot et al_800mg | -- | 1685/2690 (0.63) | -- |
| Ogata et al_300mg | -- | 697/934 (0.75) | -- |
| Ogata et al_400mg | -- | 770/1430 (0.54) | -- |

| | | | |
|---|---|---|---|
| Li et al_400mg | -- | 983.66/1325.61(0.74) | -- |
| Li et al_600mg | -- | 1371.22/1550.90 (0.88) | -- |

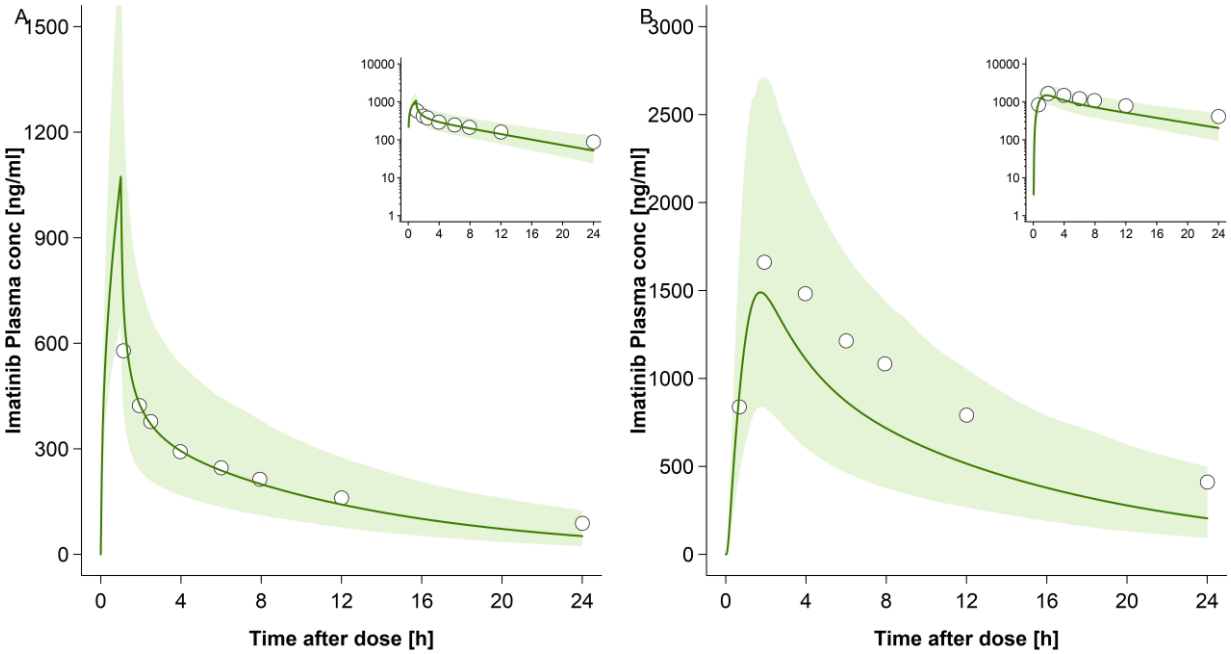


**Figure 1:** PBPK model simulations of imatinib for non-pregnant adults

Plasma concentration-time profiles in the peripheral blood plasma for imatinib. (A) Peng et al. iv study; (B) Peng et al. PO study. Black circles represent the observed mean; the solid line represents the predicted geomean and the shaded area represents the predicted 5$^{th}$ -95$^{th}$ percentile range. Observed data were taken from references listed in Table 2.

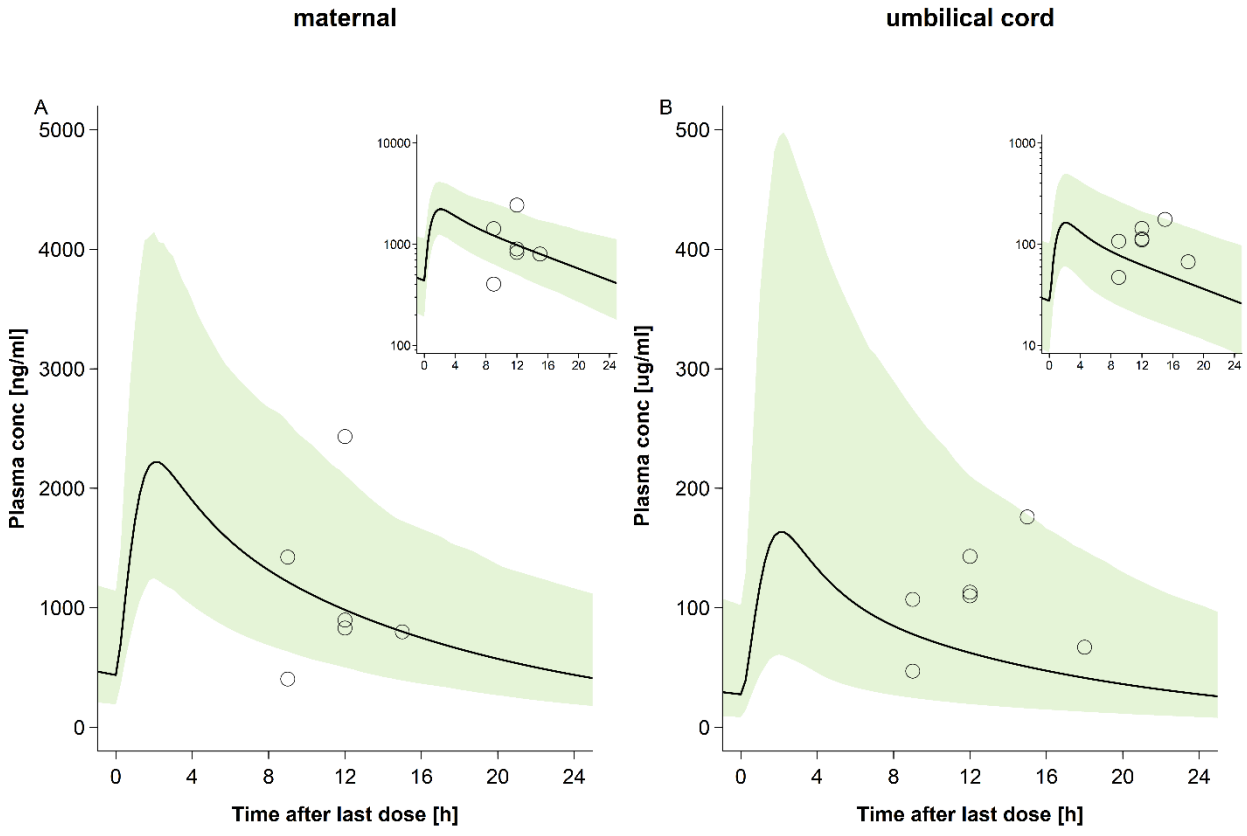


**Figure 2:** PBPK model simulations of imatinib in venous blood and umbilical cord for pregnant population

Plasma concentration-time profiles in the peripheral blood plasma for imatinib. (A) maternal concentration form Chelysheva et al study; (B) umbilical cord concentration from CHelysheva et al. study. Black circles represent the observed mean; the solid line represents the predicted geomean and the shaded area represents the predicted 5$^{th}$ -95$^{th}$ percentile range. Observed data were taken from references listed in Table 2.

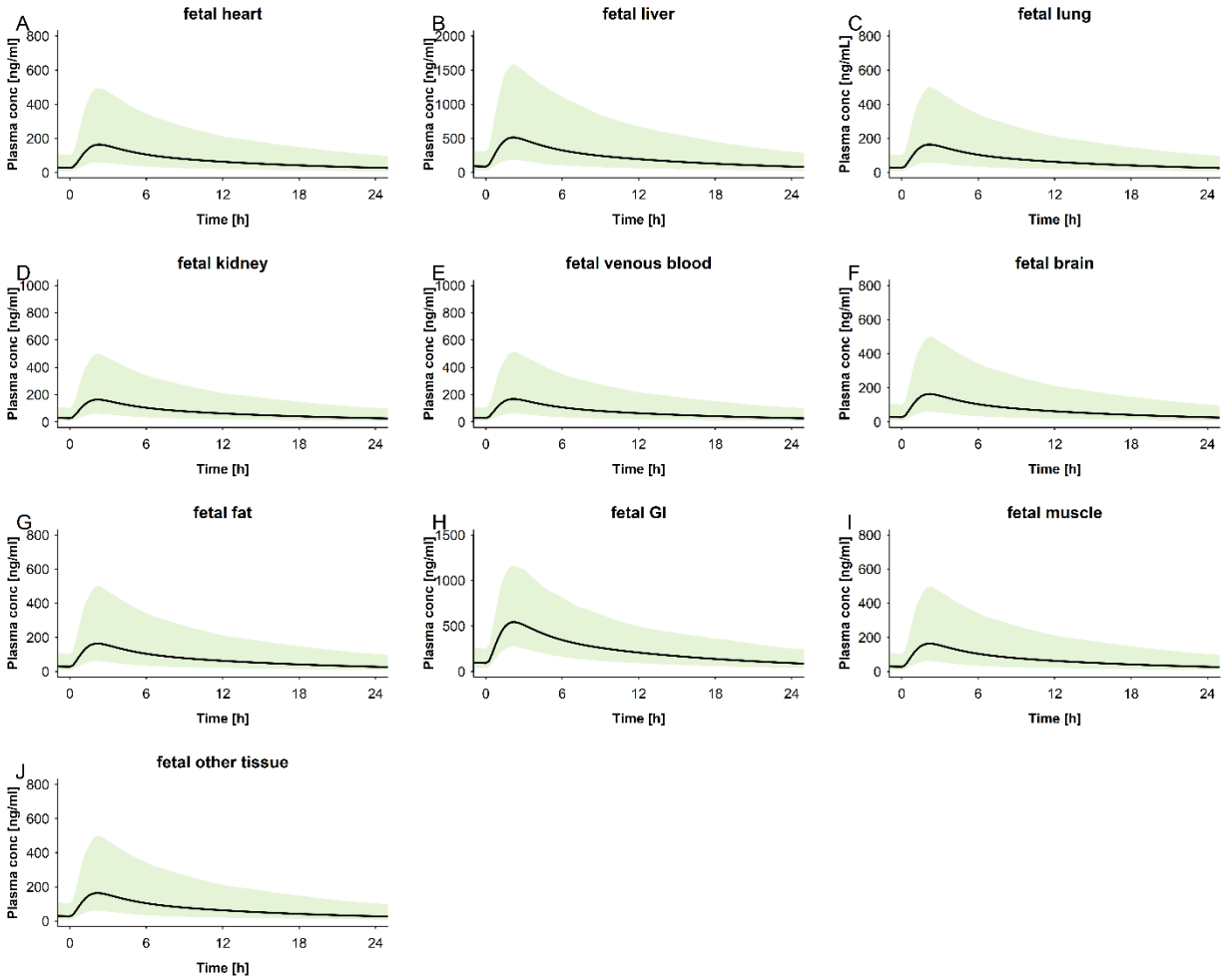


**Figure 3:** PBPK model simulations of imatinib in fetal organs

The solid line represents the predicted geomean and the shaded area represents the predicted 5$^{th}$ -95$^{th}$ percentile range. Observed data was not available.

**DISCUSSION**

PBPK modeling has been widely used in research related to drug exposure in pregnancy. The pregnancy PBPK model is actively used for dosing in pregnancy, considerations for the inclusion of pregnant people in clinical trials, and for maternal fetal drug transfer. The imatinib dosage recommendation currently is 400 mg daily for adult patients [1].

The metabolic pathway for imatinib is metabolism primarily by CYP3A4 and CYP2C8 [7]. The current model of imatinib was developed by integrating the drug properties of imatinib and the characteristics of adult healthy volunteers in clinical studies to build an adult model for imatinib. The pregnancy model of imatinib was transferred from the adult model of imatinib by integrating the model with the anatomic and physiological changes of pregnant women [11]. The fetal model PBPK model was derived from a previously published model which integrates the physiological changes of the fetus during pregnancy [14]. Thus, the maternal-fetal PBPK model of imatinib included pregnancy-specific compartments in addition to the adult model of imatinib, which were specifically fetus, maternal section of placenta, fetal section of placenta, arterial umbilical cord, venous umbilical cord, breasts, amniotic fluid and myometrium compartments [11]. In addition, the fetal model includes multiple compartments which were fetal brain, fetal lungs, fetal liver, fetal kidneys, fetal GI, fetal muscle and fetal fat [14]. Furthermore, the changes of predicted enzymes were applied to the pregnancy model of imatinib.

The adult model of imatinib was evaluated by multiple clinical studies. The adult model of imatinib successfully predicted the plasma concentration of imatinib in non-pregnant adults in comparison to the observed data from the Peng et al [2] intravenous study, but underestimated the plasma concentration of imatinib in comparison to the observed data from the Peng et al. [2] oral study. One of the possible reasons for this underestimation was that there was no information on healthy volunteers' basic information in the Peng study [2], such as age, body weight, body height and so on. The other studies were patient-involved studies which reported only trough concentrations of imatinib, while one study reported the maximum concentration of imatinib. In general, the trough or maximum concentration of imatinib were underestimated. However, imatinib metabolism was complicated due to multiple enzymes involved. In addition, the major metabolic enzyme for imatinib, CYP3A4, was inhibited by imatinib. During the long-term use of imatinib, the other enzyme, CYP2C8, became a major metabolic enzyme for imatinib, which added complexity to PK profile in the drug. Imatinib is also the substrate for multiple transporters such as ABCB1, ABCG2 and SLC22A1 [4,5]. Thus, the variability of imatinib concentration is very high. According to literature reports, the variation of imatinib concentrations is up to 25-fold. Although many studies have been done to investigate the rational for the high variability in imatinib concentrations, no conclusion is apparent.

To date, CYP2C8 polymorphism is considered an important factor for the large variability of imatinib concentrations [7]. The CYP2C8*3 and

CYP2C8*4 are the most common CYP2C8 polymorphisms in Caucasians. CYP2C8*3 has increased enzyme activity and CYP2C8*4 has decreased enzyme activity in comparison with the wild type CYP2C8. According to the model prediction, in patients with CYP2C8*1*3 taking 400 mg imatinib per day, their imatinib trough plasma concentration is 967 ng/ml with range of 176-2932 ng/ml, and patients with CYP2C8*3*3 has even lower imatinib trough plasma concentrations of 799 ng/ml with range of 128-2763 ng/ml. In patients with CYP2C8*1*4 taking 400 mg imatinib per day, their imatinib trough plasma concentration is 1415 ng/ml with range of 290-3369 ng/ml, and patients with CYP2C8*4*4 have even higher imatinib trough plasma concentrations of 1768 ng/ml with range of 482-4322 ng/ml. Thus, the patients with CYP2C8*3 might keep the standard dose of imatinib while the patients with CYP2C8*4 might require a decrease in imatinib dose to 300 mg per day. According to the model prediction, in patients with CYP2C8*1*4 taking 300 mg imatinib per day, their imatinib trough plasma concentration is 1069 ng/ml with range of 234-2600 ng/ml and patients with CYP2C8*4*4 have an imatinib trough plasma concentration of 1342 ng/ml with range of 361-3199 ng/ml.

The maternal-fetal model successfully predicted the maternal plasma concentration and umbilical concertation of imatinib in comparison with observed data. The maternal-fetal model of imatinib was evaluated by six data points from third trimester pregnant women with chronic myeloid leukemia studied by Chelysheva et al. [8]. There were four out six data sets that fell into predicated range. The other two data points probably were the outlyers since the variability was underestimated. The two outlyer concentrations were 404 ng/ml and 2433 ng/ml respectively, which showed a 6-fold difference within only six patients and demonstrated the large variety of imatinib concentrations that are observed. The imatinib clinical data for pregnant patients with chronic myeloid leukemia is scarce with only the observed data from six pregnant patients in one study, so that model performance is difficult to evaluate. Further studies need to be performed.

Using imatinib in pregnant women with chronic myeloid leukemia is not recommended. Moreover, imatinib administration is contraindicated during conception and first trimester due to the cytotoxicity of the drug, which can affect fetal development during the first trimester. Several studies have reported birth defects in newborns when their mother was taking imatinib during the first trimester. However, in the report from Chelysheva et al., [8] there were eight pregnant women who were administered imatinib during pregnancy, and more than half of them had been on imatinib during conception. Four pregnant women on imatinib had standard dose 400 mg per day and one pregnant woman had higher dose 600 mg per day. All patients stopped imatinib after pregnancy was confirmed and later restarted imatinib after the first trimester. Those pregnant women all delivered newborns without any birth defect with a follow up period of a median duration of 22 months and up to 5.5 years.

Although the report from Chelysheva et al. showed positive results of using imatinib during pregnancy, [8] the low patient number in the study cannot support the safe use of imatinib in the first trimester. The current model predicted the imatinib maternal concentration in the third trimester in comparison with the clinical data. According to the predicted results, the standard dose of 400 mg per day could not reach the target trough concentration of imatinib of 1000 ng/ml. The predicted mean concentration is 515 ng/ml with range of 194 -1165 ng/ml, which means that most patients were undertreated since the imatinib trough concentration is significantly related to its therapeutic effects. Theoretically, the imatinib dose should be increased for pregnant women. According to the model prediction, increasing the imatinib dose to 600 mg per day showed a mean trough concentration 728 ng/ml with range of 255 – 1616 ng/ml, and increasing the imatinib dose to 800 mg per day showed a mean trough concentration 896 ng/ml with range of 292 – 2013 ng/ml. However, increasing the imatinib dose causes a significant increase in imatinib concentration in fetal organs, which potentially increases the risk of abnormalities in the fetus. According to the current model prediction, in pregnant women taking imatinib 400 mg per day, the fetal liver concentration could reach 513 ng/ml with range of 193-854 ng/ml.

Previous literature reports demonstrate that birth defects do occur when the pregnant person is taking imatinib 400 mg per day [1]. As a result, an imatinib dose increase should be cautious and done with consideration to the mother's clinical course with close monitoring of the fetus. Pregnant patients with CYP2C8 polymorphism could increase the complexity of imatinib dosing decisions. The pregnant patients with CYP2C8*3 should potentially increase the imatinib dose while pregnant patients with CYP2C8*4 potentially should keep the standard dose. According to the model prediction, in pregnant patients with CYP2C8*1*3 taking 400 mg imatinib per day, their imatinib trough plasma concentration is 339 ng/ml with range of 155-942 ng/ml and pregnant patients with CYP2C8*3*3 have even lower imatinib trough plasma concentrations, 275 ng/ml with range of 128-776 ng/ml. Conversely, in pregnant patients with CYP2C8*1*4 taking 400 mg imatinib per day, their imatinib trough plasma concentration is 600 ng/ml with range of 280-1528 ng/ml and pregnant patients with CYP2C8*4*4 have a higher imatinib trough plasma concentration of 898 ng/ml with range of 434-2198 ng/ml. According to the model prediction, there were no patients with CYP2C8*3 reaching the target concentrations. As a result, the pregnant patients with CYP2C8*3 should potentially increase the dose of imatinib. According to the model prediction, in pregnant patients with CYP2C8*1*3 taking 800 mg imatinib per day, their imatinib trough plasma concentration is 581 ng/ml with range of 227-1628 ng/ml and pregnant patients with CYP2C8*3*3 have a imatinib trough plasma concentration of 477 ng/ml with range of 185-1342 ng/ml. Due to the complexity of PK of imatinib combined with physiologic changes in pregnancy, close monitoring of the fetus is necessary when increasing the dose of imatinib.

One limitation of the current study is that the prediction of metabolism of imatinib focuses on CYP3A4 and CYP2C8. However, there are several other enzymes involved in the metabolism of imatinib such as CYP1A2, CYP2D6, CYP2C9 and CYP2C19. The current study does not include those enzymes. In addition, the current study didn't involve membrane transporters in the imatinib model. Imatinib is a substrate for multiple transporters such as ABCB1, ABCG2 and SLC22A1 [4,5]. Transporters might influence imatinib exposure, which may be the reason that the current model showed underestimated imatinib exposure in comparison to observed data. The most important limitation was the lack of clinical data. Although most of the observed data fell into the predicted range of plasma concentrations of imatinib, the limitation of data to six patients could not provide enough information for established confidence in the maternal-fetal model of imatinib. In addition, all of the data from the pregnant patients were from the end of pregnancy. Further study of imatinib in pregnant patients with chronic myeloid leukemia is needed.

**CONCLUSION**

PBPK modeling is a powerful tool for research and drug development. PBPK modeling has been widely used for studying drug exposure for pregnant people and their fetuses, particularly in the situation in which little clinically observed data is available. The current maternal-fetal PBPK model of imatinib could reasonably predict the plasma concentrations of imatinib during pregnancy and drug exposure in fetal organs. Furthermore, the model was able to predict the changes in the PK of imatinib due to pregnancy and drug concentration in fetal organs. Finally, the current model provided important information on CYP2C8 polymorphisms and their influence on CYP2C8 PK and drug exposure in mother and fetus. In conclusion, the current maternal-fetal PBPK model of imatinib can provide valuable information on imatinib exposure in the pregnant population, particularly the imatinib exposure in fetal organs, and the influence of CYP2C8 polymorphisms

in pregnancy in order to provide valuable information for the use of imatinib when necessary, during pregnancy.

**Conflict of Interest**

The authors declare no conflicts of interest.

**Funding**

None declared.

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