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PBPK modeling of intravenous/oral acetaminophen in healthy and pregnant individuals

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Abstract: **Background**: Drug metabolism may be influenced by pregnancy. Use of acetaminophen (APAP) is prevalent among pregnant women, necessitating the development of effective methods for predicting its *in-vivo* disposition. **Objectives**: A whole physiologically based pharmacokinetic model was developed to predict the pharmacokinetic behavior of APAP following oral or intravenous administration in both healthy subjects and pregnant women across different trimesters (first, second, and third trimesters). **Methods**: Phoenix WinNonlin 8.4 was used to establish the model, which was verified by literature data and the fold error method. Sensitivity analysis was used to identify the factors most sensitive to the model results. **Results**: The model was established successfully. The clearance rate and half-life of intravenous APAP increased during pregnancy and the changes were more obvious with the increase of pregnancy trimesters. Theoretically, adjusting the oral and intravenous doses for pregnant women in the third trimester to 1.23 and 1.16 times those administered to healthy individuals may yield a comparable area under the curve in healthy subjects. According to the sensitivity analysis results, the influencing factors were ranked from largest to smallest as follows: activity of sulfatase > activity of glucuronidase > the constant of the gastrointestinal transport rate > activity of CYP450. **Conclusion**: Pregnancy affects the metabolism of APAP and more attention should be paid to pregnant women in clinical medication.

Keywords: Acetaminophen; Physiologically-based pharmacokinetic model; Pregnant women; Sensitivity analysis

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INTRODUCTION

During pregnancy, pregnant women experience changes in physiological parameters, such as increased cardiac output, which may impact the pharmacokinetic behavior of drugs in the human body. These alterations could potentially lead to reduced drug efficacy and increased toxicity (Beaulac-Baillargeon and Rocheleau, 1994; Pinheiro and Stika, 2020; Brookhuis *et al.*, 2021; Song *et al.*, 2023). Laws often restrict the participation of pregnant women in clinical trials (Brookhuis *et al.*, 2021). Therefore, the pharmacokinetic behavior of drugs in pregnant women is often not comprehensively understood. (Dawes and Chowienczyk, 2001). So, how to solve this problem?

Physiologically based pharmacokinetic (PBPK) models enable accurate prediction and investigation of pharmacokinetics in pregnant women (Macente *et al.*, 2023). The PBPK model employed in this study is a mechanistic bottom-up approach that facilitates scaling from the healthy population to the pregnant population. To date, a total of 18 articles have established PBPK models in pregnant women, encompassing over 30 drugs including indomethacin and caffeine (Song *et al.*, 2023). Certainly, within the past two years, several new reports have emerged (Le Merdy *et al.*, 2024; Liu *et al.*, 2024; Thepaut *et al.*, 2024). The influence of changes in the pharmacokinetic behavior of most drugs during pregnancy on the dose lacks sufficient research (Brookhuis *et al.*, 2021). Understanding the impact of pregnancy on drug pharmacokinetics is crucial for optimizing clinical dosing (Pinheiro and Stika, 2020).

The utilization rate of acetaminophen (APAP) in pregnant women is remarkably high, with approximately 40.5 % of expectant mothers employing this drug at least once during their pregnancy (Beaulac-Baillargeon and Rocheleau, 1994; Brookhuis *et al.*, 2021; Buhrer *et al.*, 2021). During pregnancy, oral administration is often used to relieve symptoms such as headache, back pain and fever. Intravenous administration is mainly used for analgesia during cesarean section and postpartum (Brookhuis *et al.*, 2021). The utilization of APAP in pregnant women is widespread, yet there is a dearth of clinical studies (Mian *et al.*, 2020). The literature reports significant alterations in the half-life, oral clearance and maximum plasma concentration in humans after pregnancy compared to healthy individuals (Rayburn *et al.*, 1986; Beaulac-Baillargeon and Rocheleau, 1994). The available reports are limited. Therefore, if the PBPK model can be employed to anticipate its pharmacokinetic behavior in pregnant women, it would significantly enhance medication safety during pregnancy.

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Then, can the PBPK model be applied to predict the pharmacokinetic behavior of APAP? There was only one searched article so far (Brookhuis *et al.*, 2021). The PK-Sim® software was utilized to fit the model and the optimized physiological parameters were obtained by initially utilizing the measured data from individuals without any health issues. Subsequently, the physiological parameters of pregnant women were further derived by comparing them with reported changes in physiological parameters (such as liver metabolism, intestinal permeability, etc.) between pregnant women and healthy individuals in the existing literature (Mian *et al*., 2020). The results improved as actual data were utilized for fit optimization in healthy individuals. These fits add an artifact to the model. Therefore, the WinNonlin 8.4 software's model mode was used in this study. Initially, a PBPK model in healthy humans was established by incorporating relevant physiological parameters and data on APAP specificity from the literature. Changes in physiological parameters reported in the literature were used to predict its pharmacokinetic behavior across the trimesters of pregnancy, with validation against measured values reported in the literature. Both oral and intravenous models were developed using the same set of physiological parameters to provide clinical evidence regarding its metabolic behavior in pregnant women.

MATERIALS AND METHODS

PBPK model development and validation

The specific modeling process of the PBPK model is described in the Methods of the Supplementary information. See figure S1, table S1 and table S2 for the model structure diagram and related parameters.

Effect of pregnancy on pharmacokinetic parameters

A representative dose (1000 mg) was used to predict its pharmacokinetic behavior within a 12-hour timeframe, following oral or intravenous administration. The pharmacokinetic parameters in the plasma of pregnant women (first, second and third trimesters) were standardized by setting the pharmacokinetic parameters of healthy human plasma as 100 %.

Pregnancy can influence the pharmacokinetic behavior of APAP in humans (Rayburn *et al*., 1986; Beaulac-Baillargeon and Rocheleau, 1994). It is theoretically possible to achieve a dose adjustment that would result in an area under the curve for a pregnant woman that is equal to that of a healthy individual, with the same pharmacological effect. Several experiments were conducted. The $AUC_{0\text{-}\infty}$ values in plasma after adjustment of oral or intravenous dose in pregnant women (first, second and third trimesters). The numbers on the bars are the fold change in the dose during pregnancy compared with the pre-adjustment dose (1000 mg).

Sensitivity analysis

The transit time in the gastrointestinal tract can influence absorption (Abuhelwa *et al*., 2017). Pregnancy affects the enzymatic activity of UGT1A1 and CYP2E1 (Mian *et al*., 2020). The activity of SULT1A1 can be modulated by drugs, disease and other factors (Yalcin *et al*., 2013; Isvoran *et al*., 2022). Therefore, this study aimed to conduct a sensitivity analysis of parameters the constant of gastrointestinal transit time (k_i), the maximum rate of CYP450s ($V_{max,APAP}$), APAP-sulfate ($V_{max,APAP\text{-}S}$) and APAP-glucuronide ($V_{max,APAP\text{-}G}$). Following established methodologies in the literature, these parameters were subjected to threefold or one-third changes based on the model of oral APAP in healthy individuals to observe alterations in its pharmacokinetic behavior (Xu *et al*., 2020).

Data source

The pharmacokinetic data came from data reported in PubMed following oral single-dose or multidose administration to healthy subjects and pregnant women. The pharmacokinetic behavior data of healthy people were obtained from the literature (Iqbal *et al*., 1995; Obodozie *et al*., 2004; Liukas *et al*., 2011; Singla *et al*., 2012; Court *et al*., 2017; Achterbergh *et al*., 2019; Garcia Aguirre *et al*., 2019). Plasma pharmacokinetic data for healthy and pregnant individuals were obtained from references (Rayburn *et al*., 1986; Simpson *et al*., 1988; Macfie *et al*., 1991; Beaulac-Baillargeon and Rocheleau, 1994; Allegaert *et al*., 2015; Nitsche *et al*., 2017).

RESULTS

The results of the tissue distribution prediction are in supplementary information (Fig. S2).

Prediction and validation of pharmacokinetics in healthy subjects

After an oral dose of 500 mg, the predicted plasma concentration in healthy subjects is mostly (33/35) within 0.5-2 times the observed value (Figs. 1a and 1b). After oral administration of 1000 mg, about 83% of the measured values fell within a double error of the observed value (Figs. 1c and 1d). For intravenous administration, most (13/19) predicted values are within 0.5-2 times the observed value after intravenous administration of 1000 mg (Figs. 1e and 1f). Most (5/6) of the poorly predicted values are concentrated in the literature reported by (Singla *et al*., 2012). These results indicate that the prediction is good.

The pharmacokinetic parameters, as shown in table 1, indicate that the majority (25/30) of the predicted values did not exceed twice the error margin of the measured values. Among the four parameters, $AUC_{0\text{-}tn}$, $AUC_{0\text{-}\infty}$, T_{max} and CL, all the predicted values fall within 0.5 to 2 times the measured values.

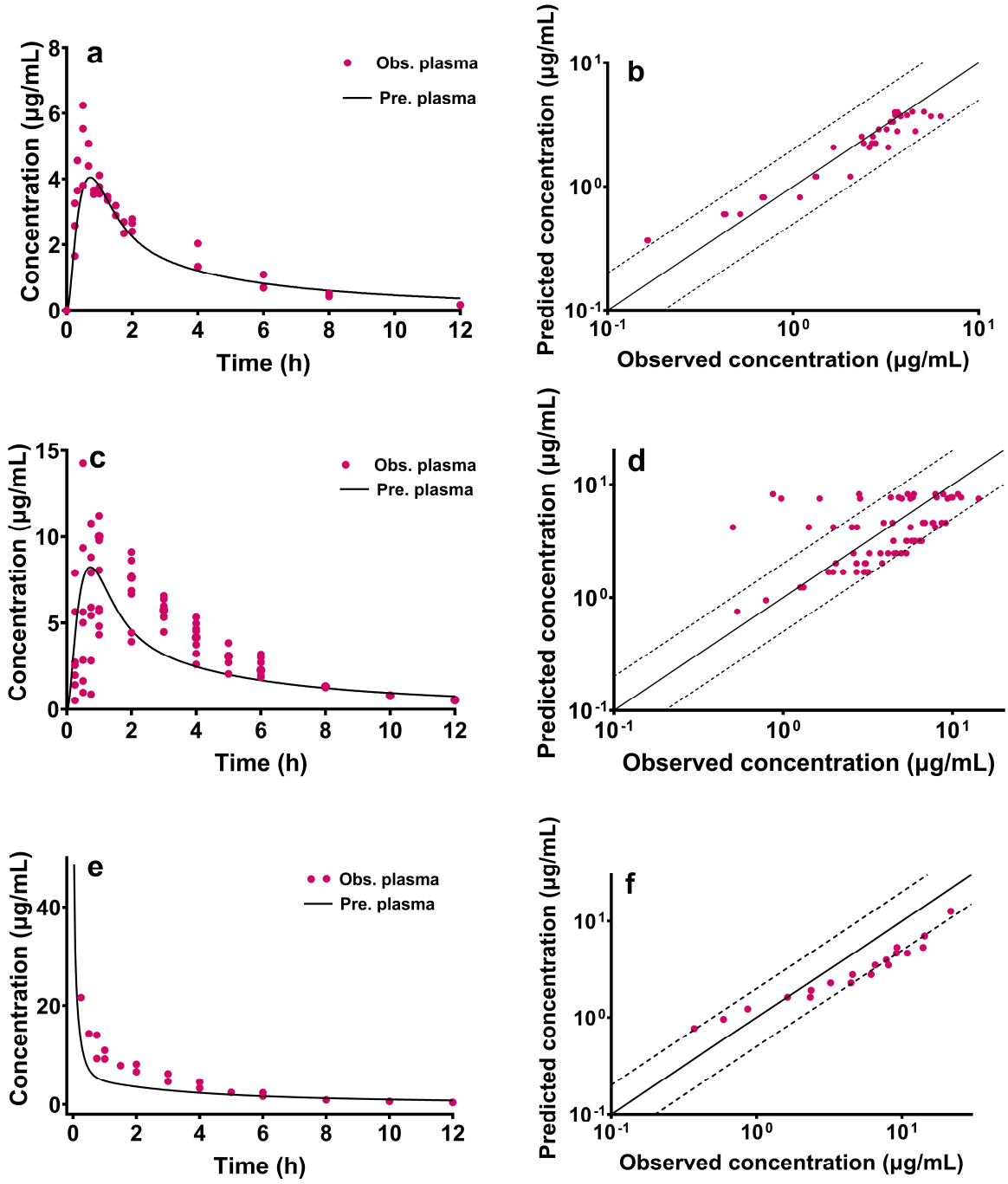

Fig. 1: The predicted (line) and observed (point) plasma concentration-time profiles in healthy volunteers. (a) APAP concentrations in healthy volunteers after a single oral dose of 500 mg. Observations were from the literature (Iqbal *et al*., 1995; Garcia Aguirre *et al*., 2019); (c) APAP concentrations in healthy volunteers after a single oral dose of 1000 mg. Observations were from the literature (Obodozie *et al*., 2004; Singla *et al*., 2012; Court *et al*., 2017; Achterbergh *et al*., 2019); (e) APAP concentrations in healthy volunteers after a single intravenous dose of 1000 mg. Observations were from the literature (Liukas *et al*., 2011; Singla *et al*., 2012); (b, d and f) The relationship between the observed and predicted plasma concentrations of APAP in healthy individuals. Solid and dashed lines respectively represent unity and 2-fold errors between observed and predicted data.

Table 1: Observed and predicted plasma pharmacokinetics parameters in healthy human following intravenous administration (iv.) and oral administration (oral).

Dose (mg)	$t_{1/2}$ (h)		$AUC_{0\text{-tn}}$ (h*μg/mL)		T_{max} (h)		C_{max} (μg/mL)	
	obs.	pre.	obs.	pre.	obs.	pre.	obs.	pre.
Oral 500 [a]	1.89±0.27	3.89	11.59±0.79	12.48	0.75±0.08	0.73	3.75±0.38	4.04
Oral 500 [b]	3.3±1.5	5.73	15.2±4.1	17.56	0.5(0.25,2.00)	0.73	7.2±2.8	4.04
Oral 500 [b]	3.6±2.0	5.73	14.7±4.5	17.56	0.5(0.25,2.00)	0.73	8.1±3.9	4.04
Oral 1000 [c]	2.4(2.2-2.7)	3.90	36.4(35.0-42.8)	32.41	0.41(0.25-0.53)	0.73	16.3(12.9-22.2)	8.23
Oral 1000 [d]	1.15±0.23	3.38	NR	22.62	1.2±0.32	0.73	8.011±0.895	8.23
Oral 1000 [e]	2.53±0.49	3.38	29.4±15.4	22.62	1(0.5-2)	0.73	12.3±5.6	8.23
	$t_{1/2}$ (h)		$AUC_{0\text{-}\infty}$ (h*μg/mL)		CL (mL/min/kg)		V_{ss} (L/kg)	
iv. 1000 [f]	2.7±0.6	7.15	44±13	40.06	4.6±1.1	5.94	1.04±0.22	2.47
iv. 1000 [g]	2.17±0.43	4.31	50.0±9.4	35.67	4.93±0.98	6.68	NR	1.89

NR (no reported), Obs. (observed), Pre. (Predicted), $t_{1/2}$ (half life), AUC (Area under the curve), T_{max} (time to peak), C_{max} (peak concentration). Most of the measured results are expressed as mean ± standard deviation.

Data of [a] were from (Iqbal *et al*., 1995). Data of [b] were from (Garcia Aguirre *et al*., 2019) and data of T_{max} were expressed by the median (minimum, maximum). Data of [c] were from (Achterbergh *et al*., 2019) and data were expressed by the median (25th–75th). Data of [d] were from (Obodozie *et al*., 2004). Data of [e] were from (Singla *et al*., 2012) and data of T_{max} were expressed by the median (minimum, maximum). Data of [f] were from (Liukas *et al*., 2011). The values of CL and V_{ss} are divided by 70 kg. Data of [g] were from (Singla *et al*., 2012). The values of CL and V_{ss} are divided by 70 kg.

Table 2: Observed and predicted plasma pharmacokinetics parameters in healthy human and pregnant women following oral administration (oral).

Dose (mg)	$t_{1/2}$ (h)		$AUC_{0\text{-tn}}$ (h*μg/mL)		T_{max} (h)		C_{max} (μg/mL)	
	obs.	pre.	obs.	pre.	obs.	pre.	obs.	pre.
Oral 650 (Con) [a]	2.02±0.08	3.01	33.3±2.53	18.78	0.77±0.11	0.73	11.6±1.57	5.29
Oral 650 (FT) [a]	1.62±0.06	2.86	27.65±3.05	17.46	0.8±0.1	0.73	11.16±1.02	5.15
Oral 1000 (Con) [b]	3.1±0.4	4.88	66.4±11.9	34.65	0.8±0.4	0.73	23.7±6.0	8.23
Oral 1000 (TT) [b]	3.7±0.4	4.55	48.15±12.6	24.66	0.8±0.4	0.73	20.8±6.9	7.61
Oral 1000 (TT) [c]	1.4	2.89	35	25.09	NR	0.73	12.3	7.61
Oral 1500 (Con) [d]	NR	1.45	NR	18.20	1.02±0.11	0.73	28.19±1.62	12.50
Oral 1500 (Con) [e]	NR	1.45	NR	18.20	0.75±0.10	0.73	34.4±4.3	12.50
Oral 1500 (FT) [d]	NR	1.40	NR	17.62	1.23±0.14	0.73	23.01±2.18	12.17
Oral 1500 (FT) [e]	NR	1.40	NR	17.62	0.77±0.14	0.73	26.8±2.7	12.17
Oral 1500 (ST) [d]	NR	1.34	NR	17.02	0.98±0.16	0.73	26.70±2.54	11.81
Oral 1500 (ST) [e]	NR	1.34	NR	17.02	1.20±0.15	0.73	21.4±2.2	11.81
Oral 1500 (TT) [d]	NR	1.30	NR	16.59	0.75±0.08	0.73	28.10±2.12	11.55

NR (no reported), Obs. (observed), Pre. (Predicted), Con (control), FT (first trimester), ST (Second trimester), TT (Third trimester). Most of the measured results are expressed as mean ± standard deviation. Data of [a] were from (Beaulac-Baillargeon and Rocheleau, 1994) and the area under the curve is expressed as $AUC_{0\text{-}\infty}$.

Data of [b] were from (Rayburn *et al*., 1986). Data of [c] were from (Nitsche *et al*., 2017) and the area under the curve is expressed as $AUC_{0\text{-}\infty}$. Data of [d] were from (Macfie *et al*., 1991). Data of [e] were from (Simpson *et al*., 1988).

Prediction and validation of pharmacokinetics in pregnant woman

As seen in figures 2a and 2b, after oral administration of 650 mg, the predicted pharmacokinetic concentration points in the body of most (76%) healthy people and pregnant women in the first trimester fell within 2 times the error of the measured value. Among them, the poorly predicted concentration points were concentrated in healthy people (6/12), but all predicted concentration points for pregnant women in the first trimester fell within 2 times the error of the measured value. After 1000 mg orally, only 44% of the predicted value in healthy people fell within twice the measured value (Figs. 2c and 2d). However, for pregnant women in the third trimester, although the measured values came from two literatures (Rayburn *et al*., 1986; Nitsche *et al*., 2017), most of the predicted values were less than 2 times the error of the measured values (Figs. 2c and 2d). After oral administration of 1.5 g APAP in healthy individuals, the predictive accuracy is limited, with only approximately 40% of the predicted values falling within a two-fold margin of error compared to the measured values (Figs. 2e and 2f). However, in the majority (27/38) of pregnant women who received 1.5 g APAP orally, the predicted values exhibited less than a two-fold deviation from the measured values (Figs. 2e and 2f). The results depicted in figures 2g and 2h demonstrate that following the loading intravenous dose of 2 g and subsequent maintenance doses of 1 g APAP

administered every 6 hours, the prediction yielded favorable outcomes, with approximately 91% of the predicted values falling within an acceptable range.

As for the pharmacokinetic parameters, most (23/33) of the predicted values of the pharmacokinetic parameters in table 2 were within 0.5-2 times of the observed values. Most (9/10) of the poorly predicted pharmacokinetic parameters are accounted for C_{max}. This may be related to factors such as experimental methods and individual differences in different studies. The predicted values of all parameters AUC and T_{max} are within a 2-fold error of the observed values. Notably, after 1000 mg of oral APAP, the area under the curve of APAP in the plasma of pregnant women in the third trimester decreased significantly compared with healthy people.

Effect of pregnancy on pharmacokinetic parameters

For oral administration, the $t_{1/2}$ remained unchanged after pregnancy in comparison to healthy subjects, while the parameter values of T_{max}, C_{max}, $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}\infty}$ gradually decreased as pregnancy progressed (Fig. 3a). The decrease in $AUC_{0\text{-}\infty}$ was most pronounced, with the $AUC_{0\text{-}\infty}$ of pregnant women in the third trimester decreasing to 81.5 % of that observed in healthy subjects (Fig. 3a). The parameters V_{ss}, $t_{1/2}$ and CL exhibited a gradual increase as pregnancy progressed for intravenous administration. Specifically, the levels of V_{ss}, $t_{1/2}$ and CL in the third trimester of pregnancy showed an increment of 22.6%, 20.2% and 16.2%, respectively. The third trimester saw a decrease of 15% and 14% in AUC0-12h and AUC0-∞, respectively, as compared to the healthy human group (Fig. 3b). The findings suggest that plasma metabolism may be enhanced post-pregnancy, leading to a reduction in the overall drug concentration in plasma. Theoretically, in order to achieve an $AUC_{0\text{-}\infty}$ similar to that of healthy individuals (1000 mg), pregnant women in the third trimester would need to increase their dosage to approximately 1230 mg and 1160 mg, respectively (Fig. 3c).

Sensitivity analysis

The T_{max} and C_{max}, which represent the rate and extent of absorption, are influenced by alterations in the gastrointestinal transport rate constant, k_i. Notably, a 3-fold increase in k_i significantly decreased the $AUC_{0\text{-}\infty}$ value to 85.5 % of the control (1-fold) (Figs. 4a-4e). The altered CYP450 activity ($V_{max,\ APAP}$) had minimal impact on the plasma pharmacokinetic profiles of APAP (Figs. 4b-4e). The alterations in sulfatase and glucuronidase activity significantly impacted the pharmacokinetic profiles. When the sulfatase ($V_{max,\ APAP\text{-}S}$) and glucuronidase ($V_{max,\ APAP\text{-}G}$) activity were reduced to one-third of their original levels, there was a respective increase in $AUC_{0\text{-}\infty}$ by 13.7 % and 6.7 %. Conversely, a three-fold elevation in sulfatase and glucuronidase activity led to a decrease in $AUC_{0\text{-}\infty}$ by 26.7 % and 16.0 %, respectively (Figs. 4c-4e). The above results indicate that the impact of each parameter change on the plasma pharmacokinetic behavior of APAP follows the order of $V_{max,APAP\text{-}S} > V_{max,APAP\text{-}G} > k_i > V_{max,APAP}$.

DISCUSSION

Implications of model building

APAP is a widely utilized medication in both the general and pregnant populations. Certainly, a limited body of literature has reported that pregnancy induces alterations in the pharmacokinetic behavior of acetaminophen in humans (Rayburn *et al*., 1986; Beaulac-Baillargeon and Rocheleau, 1994). However, there is a scarcity of comprehensive reports and the consistency among different studies remains inconclusive. Hence, efforts were made to forecast the pharmacokinetic profile in pregnant females with the PBPK model. Although researchers have developed a PBPK model to predict its metabolic behavior in pregnant women, the model was optimized using data from healthy individuals to obtain the most appropriate key parameters (such as K_m, V_{max}, intestinal permeability, etc.) (Mian *et al*., 2020). Thus, the parameters of the model established in this research are sourced from the literature to enhance the realism of the model establishment process. In addition, measured values were used for model validation.

Analysis and discussion of the results

After oral administration of 650 mg, the first trimester population exhibited a decrease of 19.8% in $t_{1/2}$, 17.0% in AUC and 3.8% in C_{max} compared to healthy subjects; however, there was no change observed in T_{max} (0.77 h vs 0.8 h) (Beaulac-Baillargeon and Rocheleau, 1994). The model prediction results (650 mg) showed a decrease of 5.0% in $t_{1/2}$, 7.0% in AUC and 2.6% in C_{max}, while T_{max} remained unchanged. In other literature, after an oral dose of 1000 mg, AUC and C_{max} in pregnant women during the third trimester decreased by 27.5% and 12.2%, respectively, while T_{max} remained unchanged and $t_{1/2}$ increased by 19.4% (Rayburn *et al*., 1986). These findings align with the maternal model wherein the AUC, C_{max} and $t_{1/2}$ in pregnant women during the third trimester decreased by 28.8%, 7.5% and 6.8%, respectively; however, T_{max} remained unaltered. As shown above, apart from $t_{1/2}$, the pharmacokinetic parameters predicted by the model were essentially consistent with the measured values. It is possible that the prediction was inaccurate due to the limited duration (2 hours) and variability of the study conducted in pregnant women following an oral dose of 1500 mg. Additionally, considering that 1500 mg is a high dosage, it is plausible that nonlinear elimination processes may occur within the body, leading to an elevated measured value. Overall trends reveal a progressive decline in C_{max}, AUC and $t_{1/2}$ values while T_{max} remains relatively stable.

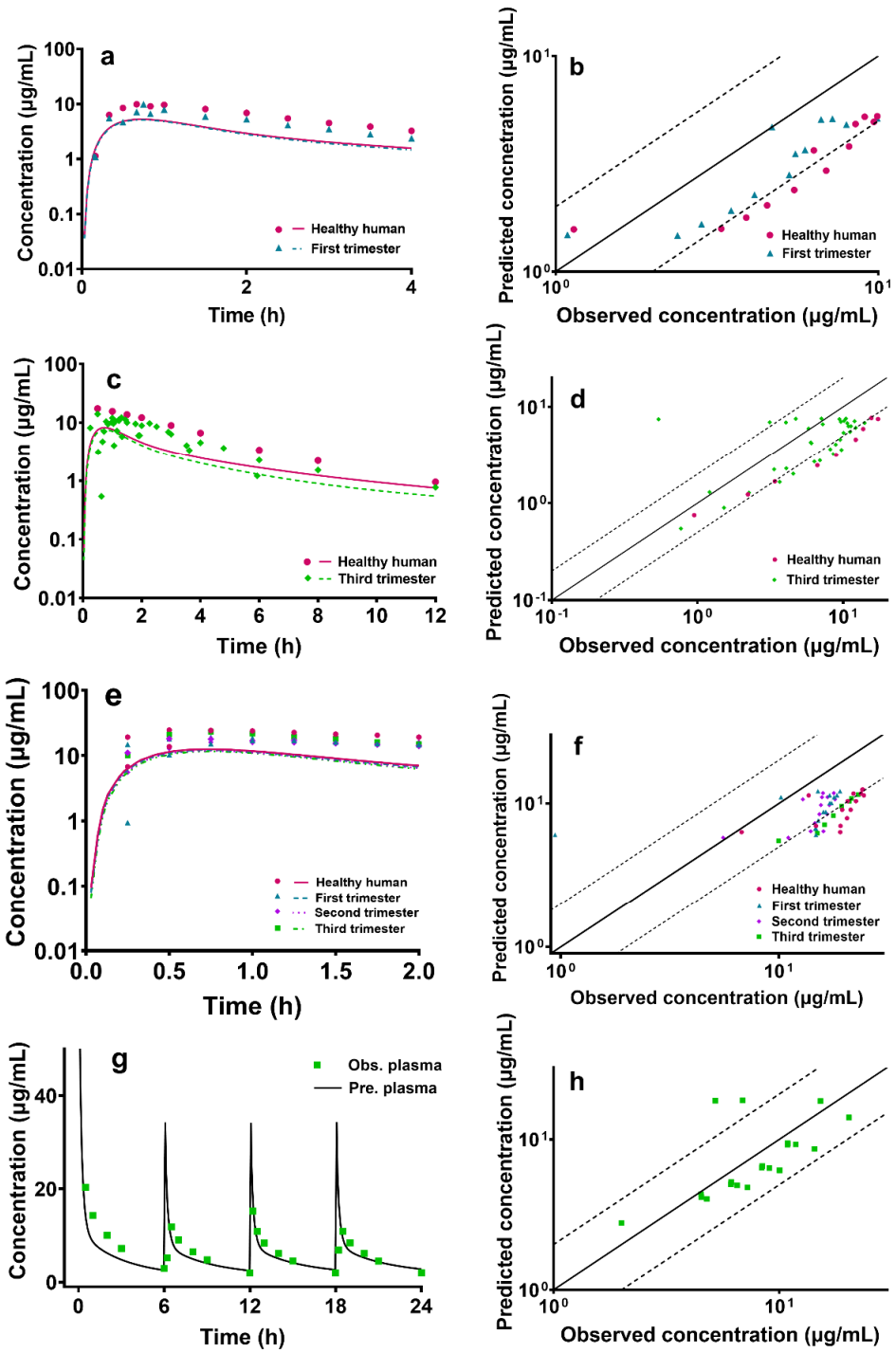

Fig. 2: The predicted (line) and observed (point) plasma concentration-time profiles in healthy human and pregnant women. (a) APAP concentrations in healthy volunteers and pregnant women in the first trimester after a single oral dose of 650 mg. The observations were obtained from Beaulac-Baillargeon (Beaulac-Baillargeon and Rocheleau, 1994); (c) APAP concentrations in healthy and pregnant women in the third trimester after a single oral dose of 1000 mg. Observations were from the literature (Rayburn *et al*., 1986; Nitsche *et al*., 2017); (e) APAP concentrations in healthy and pregnant women after a single oral dose of 1500 mg. Observations were from the literature (Simpson *et al*., 1988; Macfie *et al*., 1991); (g) APAP concentration after multi-dose intravenous administration (loading dose 2000 mg, maintenance dose 1000 mg every 6 hours). Observations were from the literature (Allegaert *et al*., 2015); (b, d, f and h) The relationship between the observed and predicted plasma concentrations of APAP in healthy individuals and pregnant women. Solid and dashed lines respectively represent unity and 2-fold errors between observed.

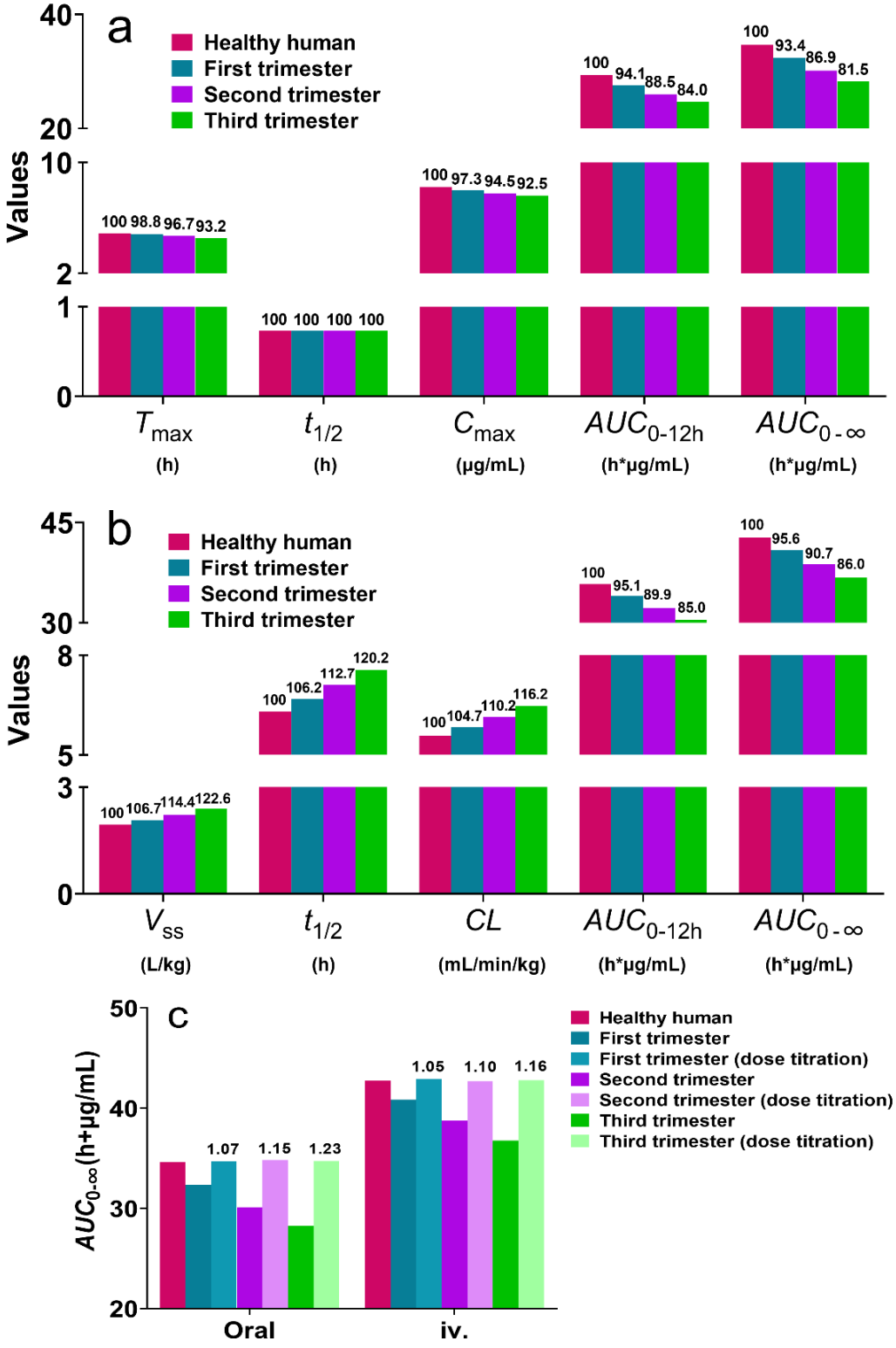

Fig. 3: Effect of pregnancy on pharmacokinetic parameters of APAP. (a-b) Changes of plasma pharmacokinetic parameters of APAP in healthy subjects, pregnant women in the first, second and third trimesters after (a) oral or (b) intravenous administration of 1000 mg APAP. The numbers on the bar graph are normalized to 100 percent of the healthy person parameters; (c) The $AUC_{0\text{-}\infty}$ values of APAP in plasma after adjustment of oral or intravenous dose in pregnant women (first, second, and third trimesters). The numbers on the bars are the fold change in the dose during pregnancy compared with the pre-adjustment dose (1000 mg)

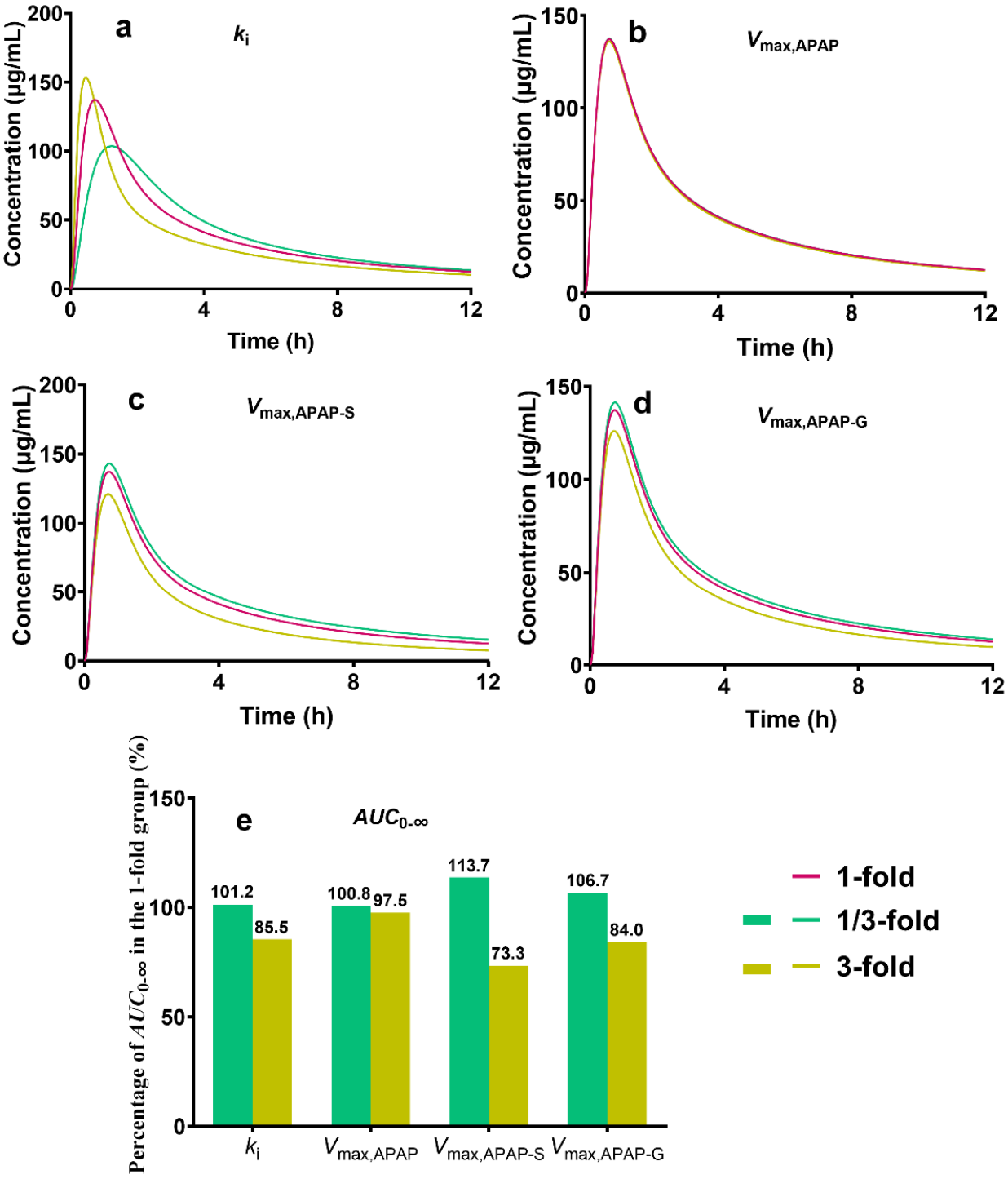

Fig. 4: Results of *in-vivo* sensitivity analysis of APAP in healthy individuals. The impact of variations in parameters on the pharmacokinetic profiles of APAP in plasma following oral administration of 1000 mg APAP in healthy subjects. (a) k_i (b) $V_{max,APAP}$; (c) $V_{max,APAP-S}$; (d) $V_{max,APAP-G}$; (e) Effect of changes in parameters k_i, $V_{max,APAP}$, $V_{max,APAP-S}$ and $V_{max,APAP-G}$ on $AUC_{0-\infty}$ of APAP in healthy human plasma. The $AUC_{0-\infty}$ value was normalized on the Y-axis by comparing it to the baseline $AUC_{0-\infty}$ in healthy subjects, serving as a reference of 100 %, after adjusting the parameters

The model's accurate predictions allowed for the investigation of the specific impact of pregnancy on its pharmacokinetic parameters in plasma. Currently, the commonly used tablet dosages in clinical practice are 500 mg and 1000 mg (Martinez-De la Torre *et al.*, 2020). Therefore, for the sake of the study, a dose of 1000 mg was used. After an oral dose of 1000 mg, it was observed that the T_{max} and C_{max} of pregnant women in the third trimester

decreased by 6.8% and 7.5%, respectively. These findings suggest a slight reduction in both the rate and extent of absorption following pregnancy. Due to reduced absorption and accelerated metabolism, the $AUC_{0-\infty}$ of pregnant women in the third trimester decreased to approximately 0.8 times that of healthy individuals. The presence or absence of pregnancy also influenced its pharmacokinetic behavior after intravenous administration. After pregnancy, there was a significant increase observed in the three parameters V_{ss}, $t_{1/2}$ and CL, while a notable decrease was noted in the AUC. The increased clearance ultimately led to a significant reduction in AUC. However, the prolonged half-life appears contradictory to the heightened clearance rate, necessitating further investigation into the specific reasons. Increasing its dosage in pregnant women, although it may elevate its AUC in maternal plasma, also poses a potential risk of increased formation of toxic metabolites. Therefore, careful consideration is necessary when contemplating dose escalation to achieve equivalent efficacy. Clinically, due to the potential risk of causing adverse fetal development (although this conclusion is subject to debate (Damkier *et al*., 2025)), it is generally recommended to use the lowest effective dose and to shorten the duration of medication as much as possible (Nilsen *et al*., 2023; Damkier *et al*., 2025). Since acetaminophen is an easily accessible over-the-counter drug, when its efficacy serves as the guideline for clinical use, there is no unified dosage standard and the incidence of adverse reactions becomes challenging to control. Moreover, when the plasma concentration of acetaminophen in pregnant women is lower than that in healthy individuals, in an effort to minimize the impact on fetal development, the dosage is deliberately regulated. Nevertheless, this approach may prove ineffective and instead increase the frequency of medication use, thus augmenting the risks. Therefore, a comprehensive understanding and prediction of the blood drug concentration and target tissue drug concentration in pregnant women can enhance the safety and efficacy of drug use among pregnant women.

Sensitivity analysis revealed that CYP450 activity had minimal impact on the pharmacokinetic profiles, whereas biphasic metabolism, involving slow sulfation and glucuronidation, significantly influenced the metabolic behavior. Subsequently, the rate of gastrointestinal transport also played a substantial role. While using APAP, physicians should carefully consider the effects of food, disease and concomitant medications on gastrointestinal transit.

Limitation

The model may introduce some error to the results due to certain assumptions. For instance, the healthy-person model uses gender-neutral data and parameters, disregarding the impact of gender on outcomes. Although previous studies have shown similarities in pharmacokinetic behavior between fetal and maternal (Nitsche *et al*., 2017), it is important to acknowledge that omitting direct consideration of fetal influence, particularly during the third trimester, could potentially affect the accuracy of the findings. The model is expected to improve through the incorporation of additional clinical data and research support in future endeavors.

CONCLUSION

In conclusion, this PBPK model was established successfully. The impact of pregnancy on the pharmacokinetics of APAP was in line with the observed trend documented in the literature. Pregnancy has the potential to accelerate *in-vivo* metabolism, leading to the down-regulation of certain metabolic parameters (e.g., $t_{1/2}$, C_{max} and AUC). Theoretically, by increasing the dose administered, the same AUC as in healthy people can be achieved; however, this may also elevate toxic metabolites and necessitate clinical monitoring. Sensitivity analysis showed that sulfatase and glucuronidase activity had the greatest impact, followed by gastrointestinal transport constant and CYP450s activity ($V_{max,APAP\text{-}S} > V_{max,APAP\text{-}G} > k_i > V_{max,APAP}$). Therefore, clinicians should consider the effects of food, disease and concurrent administration on gastrointestinal transport and enzyme activity. This study provides valuable insights for the clinical practice of dose adjustment for APAP in pregnant women.

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None.

Author's contributions

Weimin Kong and Tao Ma: Designed the experiments, analyzed the data and wrote the manuscript; Yiting Yang, Caixia Yan and Tao Ma: Conducted the experiments; Weimin Kong and Yiting Yang: Performed the data analysis; Xinru Guan and Yanting He: Drew the diagrams and reviewed the manuscript.

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Data availability statement

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethical approval

This study does not involve animals or humans.

Conflict of interest

The authors declare no conflict of interest.

Supplementary data
https://pjps.pk/uploads/2026/08/SUP1787725624.pdf

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