

Anatomical, Physiological and Metabolic Changes with Gestational Age during Normal Pregnancy

A Database for Parameters Required in Physiologically Based Pharmacokinetic Modelling

Khaled Abduljalil,¹ Penny Furness,² Trevor N. Johnson,¹ Amin Rostami-Hodjegan^{1,3} and Hora Soltani²

1 Simcyp Limited, Sheffield, UK

2 Health & Social Care Research Centre, Sheffield Hallam University, Sheffield, UK

3 School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK

Abstract

Background: Pregnancy is associated with considerable changes in the physiological, anatomical and biochemical attributes in women. These may alter the exposure to xenobiotics between pregnant and non-pregnant women who receive similar doses, with implications for different susceptibility to environmental pollutants or therapeutic agents. Physiologically based pharmacokinetic (PBPK) models together with *in vitro in vivo* extrapolation (IVIVE) of absorption, distribution, metabolism and excretion (ADME) characteristics may capture the likely changes. However, such models require comprehensive information on the longitudinal variations of PBPK parameter values; a set of data that are as yet not available from a singular source.

Aim: The aim of this article was to collect, integrate and analyse the available time-variant parameters that are needed for the PBPK modelling of xenobiotic kinetics in a healthy pregnant population.

Methods: A structured literature search was carried out on anatomical, physiological and biochemical parameters likely to change in pregnancy and alter the kinetics of xenobiotics. Collated data were carefully assessed, integrated and analysed for trends with gestational age. Algorithms were generated to describe the changes in parameter values with gestational age. These included changes in maternal weight, the individual organ volumes and blood flows, glomerular filtration rates, and some drug-metabolising enzyme activities.

Results: Articles were identified using relevant keywords, quality appraised and data were extracted by two investigators. Some parameters showed no change with gestational age and for others robust data were not available. However, for many parameters significant changes were reported during the course of pregnancy, e.g. cardiac output, protein binding and expression/activity of metabolizing enzymes. The trend for time-variant parameters was not consistent (with respect to direction and mono-tonicity). Hence, various mathematical algorithms were needed to describe individual parameter values.

Conclusion: Despite the limitations identified in the availability of some values, the collected data presented in this paper provide a potentially useful singular resource for key parameters needed for PBPK modelling in pregnancy. This facilitates the risk assessment of environmental chemicals and therapeutic drug dose adjustments in the pregnant population.

Introduction

Pregnancy is associated with a myriad of physiological, anatomical and biochemical changes that return to baseline at various rates in the postpartum period. The causative mechanism of these changes is poorly understood and most of them are believed to be regulated under hormonal control.

A number of these changes have a direct effect on the kinetics of xenobiotics. These include alterations on the level of cytochrome P450 (CYP) enzyme activity, volume of plasma, cardiac output and protein binding.^[1-4] Many of these changes begin early in pregnancy, reach their peak during the second trimester, and then remain relatively constant until delivery.^[5-8] The increase in total body volume is accompanied by retention

of 900–1000 mEq of sodium and 6–8 L of water which is distributed among the fetus, amniotic fluid, and maternal extracellular and intracellular spaces.^[9,10] The impact of these changes on kinetics depends on both the drug and the route of administration. These changes are not uniform for various parameters and their effects on each xenobiotic or drug may differ depending on absorption, distribution, metabolism and excretion (ADME) characteristics. Hence, extrapolation of dose-exposure relationship from pre-pregnant to pregnant women can lead to under- or over-estimation of exposure, with implications for risk assessment as well as therapeutic dose adjustment.

There is evidence that women continue to self-medicate during pregnancy with prescription, over-the-counter and herbal medications.^[11,12] Those with chronic conditions, such as depression, asthma and hypertension, continue to take their regular prescription drugs, and some may develop acute illnesses or complications that require medication.^[13–16] In such patients, care must be taken to select the safest drug from the necessary class of medication as continuous administration of these drugs at the pre-pregnant dose can adversely affect the fetus. Physiological alterations in pregnancy are considered likely to alter the ADME of drugs, and may have implications for medication dosage. The evidence base for these alterations and their implications for prescribed drugs is growing, with numerous published studies focusing on specific aspects of physiology during pregnancy or on certain groups of medication, as well as a number of review papers presenting composite results, evaluating and summarizing evidence.^[2,4,17,18]

With regards to therapeutic agents, the US FDA guidance has established a basic framework for designing and conducting pharmacokinetic/pharmacodynamic studies in pregnant women.^[19] It has advocated the development of pharmacokinetic models that account for likely changes in metabolism, blood flow and excretion with gestational age and considered optimized study design with respect to duration and statistical power.

Application of physiologically based pharmacokinetic (PBPK) models in drug development and toxicology has recently received much attention.^[20–22] Such models map the complex mechanistic drug movements in the body to a physiologically realistic compartmental structure, and allow the known physiological and biochemical changes to be incorporated into a meaningful model to predict ADME. The usefulness of this approach can be further enhanced by the incorporation of individual variability arising from the differences in physiology, biochemistry, genetics and pathophysiological conditions.^[22] Furthermore, incorporating the time vector of any physiological change that occurs during advancing pregnancy increases the applicability of the PBPK model.

There are a number of PBPK models that have investigated the effect of human pregnancy on drug kinetics.^[23–29] However, to the best of our knowledge, these models do not consider all the essential elements, most probably due to their narrow focus on specific compounds or a specific stage of pregnancy. For example, none of the models included the longitudinal changes in metabolizing enzymes during gestation. Neither do they consider the inter-individual variability of PBPK parameters. Hence, these models cannot account for within-individual variability with gestational age or between-individual variability in pharmacokinetics. In addition, many parameters related to certain organs are obtained from selected reports rather than a systematic review of all available data.

Recently, there has been an increasing interest in this population and much more data are becoming available on the changes of relevant parameters throughout pregnancy. Therefore, it seems timely to integrate all available data with the aim of facilitating the applicability of PBPK models in pregnancy and improving their performance.

The objectives of this study were to collate essential time-variant anatomical, physiological and biological parameter values needed for PBPK models defining pregnancy. These data were analysed in order to formulate algorithms which describe the average changes in parameter values and their variability with gestational age.

Methods

Data Sources

A structured literature search was carried out using MEDLINE on all anatomical, physiological and biological parameters likely to change during pregnancy. The search strategy was aimed to identify observational cohort studies in which the required parameters were longitudinally examined during pregnancy. Data from the control arm of case-control studies and randomized controlled trials were also considered for inclusion. For each parameter, a separate search was conducted, using the key word 'pregnant' plus the parameter of interest, for example 'blood flow', 'plasma volume', 'haematocrit', 'glomerular filtration', etc. No language or date restriction was applied but article titles and abstracts were screened to maintain the focus of the search on human, singleton, low-risk, normal pregnancies. Because parameters may change during birth, studies of women during delivery were excluded. A manual search of reference lists from selected articles and contact with experts in the field complemented the data collection process. Two researchers quality appraised each study,

extracted and entered the data into a Microsoft Excel® spreadsheet independently and this was subsequently double-checked by a third researcher prior to data modelling.

Inclusion Criteria

Data inclusion criteria were (i) singleton pregnancy; (ii) adult healthy women with no underlying conditions that are known to affect the parameters; and (iii) studies on dominantly Caucasian populations (in case of mixed population studies, the Caucasian population comprised at least 80% of the overall population).

Combining Data from Different Studies

When a tissue size was expressed by weight, the corresponding volume was calculated using tissue density. In the majority of cases only mean values (and variability) stratified for gestational age groups were available. The overall mean parameter value, \bar{X} , at a particular gestational age, from different studies was combined using equation 1:

$$\bar{X} = \frac{\sum_{j=1}^J n_j x_j}{\sum_{j=1}^J n_j} \quad (\text{Eq. 1})$$

where n_j is the number of subjects in the j^{th} study and x_j is the mean value from that study. The overall sum of squares was calculated according to equation 2:

$$\text{Overall sum of squares} = \sum_{j=1}^J \left[(SD_j)^2 + (x_j)^2 \right] \bullet n_j - N \bullet \bar{X}^2 \quad (\text{Eq. 2})$$

where SD_j is the standard deviation from the j^{th} study and N is the number of subjects in all studies ($N = \sum_{j=1}^J n_j$). Overall SD was calculated according to equation 3:

$$\text{Overall SD} = \sqrt{\frac{\text{Overall sum of squares}}{N}} \quad (\text{Eq. 3})$$

In turn, geometric mean or median values (assuming log-normal distributions) were calculated using equations 4–6, as follows:

To describe σ (sigma, which is analogous to the SD but in a log-scale), the following equation can be used:^[30]

$$\sigma = \sqrt{\ln(1 + CV^2)} \quad (\text{Eq. 4})$$

where the coefficient of variation (CV) is calculated by dividing reported SD by reported mean value, which are in normal scale.

A geometrical SD (GSD) can be defined as:

$$\text{GSD} = e^{\sqrt{\ln(1 + CV^2)}} \quad (\text{Eq. 5})$$

Once σ has been determined, the median can be calculated by determining the exponent of μ [mean of $\ln(x)$ values] after using the following equation:^[31]

$$\mu = \ln(x_j) - (0.5 \bullet \sigma^2) \quad (\text{Eq. 6})$$

where the mean value for samples is taken directly from the report. It should be noted that the exponent of μ also represents geometric mean (i.e. median = e^μ). The CV was used to add variability around the parameter mean and calculated as follows (equation 7):

$$CV = \frac{\sqrt{\text{Residual MS}}}{\bar{X}} \quad (\text{Eq. 7})$$

where residual MS is the mean residual sum of squares and \bar{X} is the weighted mean. In the absence of usable data from the literature, the CV values were assumed to be the same as those for a healthy pre-pregnant population.

Data Analysis

Before data analysis, when a parameter was reported in different units, these units were converted to a standard unit of measurement. Data analysis was performed using Microsoft Excel® 2007. In general, polynomial equations have been used to describe the longitudinal changes in parameters during pregnancy. Polynomial equations have been used to characterize age-related changes in body and organ weights from birth to adolescence in humans.^[32] Moreover, only polynomials were considered to develop the PBPK model for calculation of organ weights based on sex and total body weight, and to describe human postnatal growth from birth through to adulthood for normal^[27] and obese individuals of different ethnicities,^[33] and to relate fat-free mass (FFM) to fat mass that considers demographic covariates.^[34]

The choice of the polynomial degree to describe the physiological changes during pregnancy was dependant on the nature of the data to be interpolated. The data can be described better by fitting and taking into account the impact of covariates. Since the evaluated data are from population rather than from individual means and the covariates were not always available from all studies, the selection of polynomial equations is sufficient for the purpose of describing the trend. If a higher order of polynomial equation does not improve the fitting (R^2) and/or if it departed from the original data in comparison with a lower degree, then the lower one was chosen. Other options were considered where these were not adequately fitting using

polynomial equations. An example of this is for fetal volume during pregnancy where the Gompertz equation was used because negative values were generated using polynomials.

Results

The amount of information varied considerably depending on the type of parameters, so that while an abundance of information was available for gestational weight gain, information on compartmental blood flow, for instance, was very limited. Table I summarizes the results of the meta-analysis, along with regression equations and correlation coefficients.

Maternal Age Distribution at Conception

Data on the maternal age distribution of pregnancy were taken from the Office for National Statistics (ONS), Conception Statistics for a total of 887 900 singleton pregnancy in England and Wales for the year 2008^[187] and examined for frequencies at each age range. Age distribution, which should be used for Monte-Carlo sampling when population variability is considered in PBPK models, is given in figure 1.

Gestational Age Distribution at Birth

In this article, gestational age refers to the full-term gestational age, which ranges from 37 to 42 weeks of pregnancy counted from the first day of the last menstrual period, according to WHO classification.^[188,189] In a group of singleton pregnancies ($n = 12\,816$ Caucasian British women), the gestational age at delivery ranged between 23 and 43 weeks, with a median of 40 weeks.^[190] This is similar to the result obtained for a Swedish population ($n = 383\,484$ singleton, non-caesarean birth), giving a mean \pm SD of 40.14 ± 1.86 weeks and a median \pm SD of 40.29 ± 1.86 weeks.^[191] Data on gestational age distribution for a total of 4 710 209 live-born singleton births were obtained from the UK National Health Service Maternity Statistics.^[192] Figure 2 shows the data and distribution of full-length gestational age at delivery.

Gestational Weight Gain

The total amount of weight gained in normal-term pregnancies varies considerably among women. In its latest guidelines (2009), the Institute of Medicine gave a recommended pregnancy weight gain range for normal weight women as wide as from 10.0 to 16.7 kg for a singleton pregnancy.^[193] Generally, obtaining an appropriate baseline is a major confounding

factor in studies evaluating weight changes during pregnancy. Weight gain in multiple pregnancies,^[193] adolescent pregnancies,^[193] pre-eclampsia and hypertensive pregnant women^[194] were found to be higher than that in normal singleton pregnancy and, thus, such populations were excluded from this review. Underweight and obese pregnant data were excluded from this review as their weight gain pattern during pregnancy is also different from weight gain in normal pregnant women.^[195-197] During normal pregnancy, the gestational weight gain is generally higher in the second and third trimester and can vary depending on maternal ethnicity and age.^[193] Because women tend to retain weight at the postpartum period,^[35,48] it was not deemed appropriate to use postpartum values as a baseline for pre-pregnancy weight estimation. The gestational weight gain is therefore restricted to a normal weight, healthy adult Caucasian pregnant population with uncomplicated singleton pregnancies. The data are shown in table 1 of the Supplemental Digital Content (SDC), <http://links.adisonline.com/CPZ/A31>.

Meta-analysis of collected data indicated an increase in the mean total body weight (in kg) [mean \pm SD (CV)] from 61.1 ± 7.5 (15%) in pre-pregnancy state to 65.0 ± 11 (17%), 71 ± 10 (14%) and 75.2 ± 8.4 (11%) by the end of the first, second and third trimesters, respectively. The collated data show an addition of about 14 ± 5.1 kg (36%) weight by the end of pregnancy. These changes can be described using equation 8.

$$\text{Total body weight (kg)} = 61.1 + 0.2409 \text{ GA} + 0.0038 \text{ GA}^2 \\ \text{with } R^2 = 0.9263 \quad (\text{Eq. 8})$$

where GA is the gestational age in weeks. A figure of mean weight gain with the SD at different gestational weeks is given in the SDC.

Total Body Fat

Estimates of body fat mass gained during human pregnancy are necessary to assess the distribution of lipophilic compounds. Most of the total body fat mass was deposited during the second trimester, with little change taking place in the first and third trimesters.^[36] The mechanisms by which maternal fat mass is regulated during pregnancy is poorly understood; however, leptin has been suggested as an important regulator of body fat mass during pregnancy.^[198]

Fat gain accounts for about $55.5 \pm 20\%$ of total weight gain.^[199] It has been reported that postpartum mothers still retained an average of 2.2 kg fat mass over the mean pre-pregnancy value.^[36] Thus, studies using postpartum values as control were excluded from the analysis. To avoid the impact of other methodological variables, further refinement of the data was done by

Table 1. Anatomical, physiological and biological parameter values and regression equations needed for physiology-based pharmacokinetic models defining pregnancy, based on meta-analysis of the published data

Parameter (unit)	Value ^a [pregnancy status or GA]	Equation	R ²	References
TBW (kg)	61.1 ± 8.9, n = 4116 (15%) [pre-preg]	TBW = 61.1 + 0.2409 GA + 0.0038 GA ²	0.9263	8,35-47
	62.8 ± 10.1, n = 145 (16%) [9 wk]			
	65.0 ± 11, n = 707 (17%) [13 wk]			
	71 ± 10, n = 502 (14%) [26 wk]			
	74.0 ± 11.2, n = 734 (15%) [30 wk]			
	75.2 ± 8.45, n = 3484 (14%) [40 wk]			
TFM (kg)	17.14 ± 6.6, n = 117 (39%) [pre-preg]	TFM = 17.14 + 0.1305 GA + 0.0008 GA ²	0.8938	35-37,41,42,47-51
	19.09 ± 6.7, n = 205 (35%) [13 wk]			
	20.06 ± 6.84, n = 108 (34%) [18 wk]			
	19.80 ± 7.5, n = 184 (38%) [25 wk]			
	23.22 ± 10.7, n = 164 (46%) [32 wk]			
	22.6 ± 7.0, n = 323 (31%) [37 wk]			
TFFM (kg)	44.5 ± 5.5, n = 116 (12%) [pre-preg]	TFFM = 44.5 - 0.0474 GA + 0.0034 GA ²	0.9544	35,41,42,47-49,51
	44.8 ± 5.0, n = 134 (11%) [12 wk]			
	48.59 ± 6.2, n = 108 (13%) [25 wk]			
	50.68 ± 6.8, n = 174 (12%) [37 wk]			
Total body water (L)	31.67 ± 4.6, n = 241 (15%) [pre-preg]	Total body water = 31.67 + 0.275 GA + 0.0024 GA ²	0.9898	35,45,48,51-59
	35.22 ± 1.65, n = 204 (5%) [12 wk]			
	38.57 ± 6.01, n = 198 (16%) [20 wk]			
	40.14 ± 7.55, n = 90 (19%) [25 wk]			
	42.0 ± 8.73, n = 237 (21%) [32 wk]			
	46.0 ± 5.5, n = 149 (13%) [40 wk]			
ECW (L)	11.86 ± 2.0, n = 82 (17%) [pre-preg]	ECW = 11.86 + 0.0187 GA + 0.0016 GA ²	0.8687	45,51-54,58,60
	12.48 ± 2.44, n = 139 (20%) [12 wk]			
	13 ± 2.0, n = 142 (14%) [20 wk]			
	14.59 ± 3.5, n = 84 (24%) [35 wk]			
	14.81 ± 3.2, n = 32 (21%) [38 wk]			
ICW (L)	19.81 ± 2.1, n = 87 (11%) [pre-preg]	ICW = 19.81 + 0.5941 GA - 0.0007 GA ²	0.981	45,51-54,58,60
	23.3 ± 5.2, n = 129 (21%) [12 wk]			
	28.6 ± 4.7, n = 101 (16%) [22 wk]			
	27.63 ± 6.4, n = 66 (20%) [30 wk]			
	29.13 ± 3.6, n = 27 (11%) [38 wk]			
CO (L/h)	301 ± 65, n = 286 (22%) [pre-preg]	CO = 301 + 5.916 GA - 0.088 GA ²	0.9014	5,8,37,61-67
	354 ± 76, n = 143 (22%) [10 wk]			
	386 ± 75, n = 246 (20%) [20 wk]			
	423.7 ± 72.2, n = 173 (17%) [32 wk]			
	400 ± 79, n = 78 (20%) [36 wk]			
	391 ± 79, n = 69 (20%) [38 wk]			
Plasma volume (L)	2.50 ± 0.40, n = 285 (16%) [pre-preg]	Plasma volume = 2.50 - 0.0223 GA + 0.0042 GA ² - 0.00007 GA ³	0.9639	8,68-82
	2.67 ± 0.45, n = 136 (17%) [12 wk]			
	3.55 ± 0.61, n = 45 (17%) [24 wk]			
	3.74 ± 0.50, n = 130 (13%) [30 wk]			
	3.67 ± 0.64, n = 106 (17%) [36 wk]			
	3.74 ± 0.54, n = 205 (14%) [39 wk]			
RBC volume (L)	1.49 ± 0.15, n = 625 (10%) [pre-preg]	RBC volume = 1.49 + 0.0098 GA	0.9121	8,70,73,74,76,77,82
	1.55 ± 0.15, n = 539 (10%) [12 wk]			
	1.61 ± 0.11, n = 528 (6%) [20 wk]			

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Table I. Contd

Parameter (unit)	Value ^a [pregnancy status or GA]	Equation	R ²	References
Hct (%)	1.79±0.11, n=474 (6%) [24 wk]	Hct = 39.1 - 0.0544 GA - 0.0021 GA ²	0.9541	8,44,45,54,75-77,83-87
	1.82±0.10, n=489 (5%) [33 wk]			
	1.84±0.26, n=543 (15%) [36 wk]			
	1.90±0.16, n=530 (9%) [40 wk]			
	39.14±2.51, n=189 (6.4%) [pre-preg]			
	38.10±3.3, n=486 (8.7%) [10 wk]			
	37.30±3, n=937 (8%) [17 wk]			
	36.2±3.2, n=1059 (9.1%) [23 wk]			
	36.08±5.9, n=248 (16%) [27 wk]			
Plasma protein (g/L)	69.7±4.4, n=150 (6%) [>8 wk postpartum]	Plasma protein = 69.7 + 0.2085 GA - 0.0305 GA ² + 0.0006 GA ³	0.9974	43,84,87-89
	68.8±5.2, n=249 (8%) [12 wk]			
	65.1±4.4, n=540 (7%) [23 wk]			
	63.3±3.7, n=1425 (6%) [31 wk]			
	63.7±4.2, n=606 (7%) [34.8 wk]			
	64.1±3.1, n=43 (5%) [38.4 wk]			
Albumin (g/L)	45.8±3.5, n=465 (7.6%) [pre-preg]	Albumin = 45.8 - 0.1775 GA - 0.0033 GA ²	0.9403	54,71,75,84,86,89-92
	43.3±4.1, n=125 (9%) [10 wk]			
	41.4±3.0, n=250 (7%) [17 wk]			
	38.5±3.8, n=561 (10%) [30 wk]			
	37.56±3.6, n=193 (10%) [34 wk]			
	31.45±5.3, n=104 (17%) [40 wk]			
AAG (g/L)	0.74±0.17, n=32 (23%) [pre-preg]	AAG = 0.74 - 0.0088 GA + 0.0001 GA ²	0.7508	89,92-96
	0.73±1.6, n=41 (22%) [10 wk]			
	0.58±0.19, n=69 (33%) [20 wk]			
	0.60±0.18, n=69 (30%) [30 wk]			
	0.61±0.18, n=51 (30%) [35 wk]			
	0.60±0.16, n=67 (27%) [40 wk]			
Total lipids (g/L)	6.0±1.1, n=13 (18%) [>4 wk postpartum]	Total lipids = 6 + 0.1001 GA	0.9897	97
	6.0±1.0, n=15 (17%) [9 wk]			
	8.7±1.4, n=22 (15%) [25 wk]			
	9.5±1.2, n=20 (13%) [34 wk]			
	9.9±1.4, n=18 (14%) [40 wk]			
Total triglycerides (mg/dL)	78.54±39, n=56 (50%) [non-preg]	Total triglycerides = 79 + 0.6566 GA + 0.0925 GA ²	0.9558	98-101
	116±53, n=866 (46%) [12 wk]			
	132±65, n=45 (49%) [24 wk]			
	228±83, n=84 (36%) [36 wk]			
Total cholesterol (mg/dL)	178±38, n=56 (12%) [pre-preg]	Total cholesterol = 178 + 1.1045 GA + 0.0444 GA ²	0.977	98-101
	190±36, n=866 (19%) [12 wk]			
	238±46, n=45 (20%) [24 wk]			
	273±45, n=84 (17%) [36 wk]			
CYP1A2 activity (%)	100, n=25 [pre-preg]	CYP1A2 activity = 100 - 3.5814 GA + 0.0495 GA ²	0.9965	Calculated based on Tracy et al. ^[102]
	67±23, n=25 (37%) [16 wk]			

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Table I. Contd

Parameter (unit)	Value ^a [pregnancy status or GA]	Equation	R ²	References
CYP2D6 activity (%)	50 ± 27, n = 25 (56%) [26 wk]	CYP2D6 activity (%) = 100 + 2.2695 GA - 0.0348 GA ²	0.9948	Calculated based on Tracy et al. ^[102]
	35 ± 15, n = 25 (50%) [38 wk]			
	100, n = 25 [pre-preg]			
	129 ± 59, n = 25 (46%) [16 wk]			
	134 ± 42, n = 25 (31%) [26 wk]			
CYP3A4 activity (%)	136 ± 25, n = 25 (18%) [38 wk]	CYP3A4 activity (%) = 100 + 2.9826 GA - 0.0741 GA ²	0.7718	Calculated based on Tracy et al. ^[102]
	100, n = 25 [pre-preg]			
	137 ± 38, n = 25 (28%) [16 wk]			
	118 ± 38, n = 25 (32%) [26 wk]			
	109 ± 31, n = 25 (28%) [38 wk]			
GFR (mL/min)	114 ± 28, n = 67 (25%) [pre-preg]	GFR = 114 + 3.2367 GA - 0.0572 GA ²	0.9712	8,103-111
	136 ± 32, n = 25 (23%) [10 wk]			
	156 ± 26, n = 71 (16%) [16 wk]			
	160 ± 26, n = 65 (16%) [26 wk]			
	156 ± 42, n = 86 (27%) [36 wk]			
CL _{CR} (mL/min)	98.3 ± 14.4, n = 81 (15%) [pre-preg]	CL _{CR} = 98.3 + 3.9107 GA - 0.0789 GA ²	0.8193	54,112-114
	126 ± 20, n = 36 (16%) [12 wk]			
	155 ± 28, n = 31 (18%) [26 wk]			
	152 ± 39, n = 36 (25%) [33 wk]			
	124 ± 34, n = 45 (28%) [37 wk]			
Serum creatinine (mg/dL)	0.80 ± 0.11, n = 109 (13%) [pre-preg]	Serum creatinine = 0.8 - 0.0147 GA + 0.0003 GA ²	0.9543	8,113-115
	0.69 ± 0.09, n = 40 (13%) [18 wk]			
	0.64 ± 0.08, n = 27 (12%) [2 wk]			
	0.67 ± 0.08, n = 40 (12%) [34 wk]			
	0.66 ± 0.14, n = 53 (21%) [37 wk]			
Effective renal plasma flow (L/h)	32.3 ± 6.4, n = 59 (20%) [pre-preg]	Effective renal plasma flow = 32.3 + 1.6576 GA - 0.0389 GA ²	0.9469	103,104,106,109-111, 116
	44.5 ± 6.1, n = 27 (14%) [7 wk]			
	48.4 ± 8.8, n = 44 (18%) [16 wk]			
	47.8 ± 12.5, n = 61 (26%) [26 wk]			
	42.3 ± 11.2, n = 58 (27%) [36 wk]			
Effective renal blood flow (L/h)	53.1 ± 10.4, n = 59 (20%) [pre-preg]	Effective renal blood flow = 53 + 2.6616 GA - 0.0661 GA ²	0.9344	Calculated from effective renal plasma flow data ^[103,104,106,109-111,116]
	72.7 ± 9.9, n = 27 (14%) [7 wk]			
	77.9 ± 14.0, n = 44 (18%) [16 wk]			
	75.1 ± 19.7, n = 61 (26%) [26 wk]			
	64.4 ± 17.1, n = 58 (27%) [36 wk]			
Cerebral blood flow (L/h/100 g)	2.53 ± 0.38, n = 15 (15%) [pre-preg]	Cerebral blood flow = 2.53 + 0.0167 GA	0.9923	117
	2.66 ± 0.27, n = 31 (10%) [10 wk]			
	2.92 ± 0.28, n = 50 (10%) [22.5 wk]			
	3.11 ± 0.35, n = 129 (11%) [34.8 wk]			
Internal carotid artery blood flow (L/h)	17.64 ± 3.1, n = 15 (18%) [pre-preg]	Internal carotid artery blood flow = 17.64 + 0.1513 GA	0.9907	117
	18.78 ± 2.46, n = 31 (13%) [10 wk]			
	21.18 ± 2.44, n = 50 (12%) [22.5 wk]			
	22.93 ± 3.0, n = 129 (13%) [34.8 wk]			
Weight of the uterus (g)	80 ± 35, n = 36 (44%) [pre-preg]	Weight of the uterus = 80 + 8.2931 GA + 0.3546 GA ²	0.9956	118-120
	282 ± 82, n = 17 (29%) [13 wk]			
	314 ± 90, n = 6 (31%) [18 wk]			
	982 ± 237, n = 20 (24%) [40 wk]			

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Table I. Contd

Parameter (unit)	Value ^a [pregnancy status or GA]	Equation	R ²	References
Uterine blood flow (L/h)	1.71 ± 0.85, n = 82 (52%) [pre-preg] 17.5 ± 10, n = 161 (57%) [10 wk] 28.5 ± 11.5, n = 235 (40%) [22 wk] 44.4 ± 15, n = 269 (33%) [30 wk] 49.1 ± 14, n = 246 (29%) [38 wk]	Uterine blood flow = 1.71 + 0.2068 GA + 0.0841 GA ² - 0.0015 GA ³	0.9905	6,65,121-131
Breasts volume (mL)	985 ± 308, n = 89 (31%) [pre-preg] 1080 ± 469, n = 7 (43%) [10 wk] 1214 ± 396, n = 8 (33%) [21 wk] 1258 ± 356, n = 8 (28%) [31 wk] 1260 ± 381, n = 7 (30%) [37 wk]	Breasts volume = 985 + 14.244 GA - 0.1869 GA ²	0.9684	132-138
Estradiol (ng/mL)	0.062 ± 0.058, n = 355 (94%) [non-preg] 0.51 ± 0.45, n = 349 (90%) [8 wk] 1.91 ± 2.07, n = 982 (108%) [12 wk] 3.45 ± 1.81, n = 879 (51%) [16 wk] 5.86 ± 5.60, n = 642 (95%) [24 wk] 10.69 ± 5.70, n = 837 (52%) [27 wk] 13.35 ± 7.0, n = 836 (53%) [33 wk] 17.2 ± 6.3, n = 400 (54%) [36 wk] 15.65 ± 9.19, n = 525 (59%) [39 wk]	Estradiol = 0.06 + 0.0558 GA + 0.0103 GA ²	0.9634	39,43,68,99,110,139-146
Progesterone (ng/mL)	1.42 ± 3.34, n = 154 (235%) [non-preg] 24.63 ± 13.17, n = 112 (53%) [8 wk] 30.96 ± 16.6, n = 211 (54%) [12 wk] 39.66 ± 13.43, n = 433 (34%) [16 wk] 53.83 ± 17.41, n = 128 (32%) [20 wk] 84.72 ± 35.06, n = 117 (41%) [24 wk] 89.83 ± 29.0, n = 21 (32%) [30 wk] 142.7 ± 40, n = 189 (28%) [33 wk] 191 ± 47, n = 199 (22%) [38 wk]	Progesterone = 1.42 + 3.446 GA - 0.1334 GA ² + 0.0046 GA ³	0.9816	43,68,110,140,141,143,145-148
Intrauterine volume (mL)	Zero [pre-preg] 486 ± 170, n = 5 (35%) [14 wk] 990 ± 167, n = 103 (17%) [20 wk] 1834 ± 281, n = 103 (15%) [25 wk] 2689 ± 349, n = 110 (13%) [30 wk] 4157 ± 573, n = 76 (14%) [38 wk] 4524 ± 720, n = 38 (16%) [40 wk]	Intrauterine volume = 0.0 - 0.4758 • GA + 0.5174 GA ² + 0.1424 GA ³ - 0.0021 GA ⁴	0.9958	149,150
Gestational sac volume (mL)	Zero [pre-preg] 14 ± 13, n = 42 (90%) [6 wk] 38 ± 25, n = 48 (66%) [8 wk] 102 ± 43, n = 31 (42%) [10 wk] 144 ± 27, n = 417 (19%) [13.5 wk]	Gestational sac volume = 0.0 + 3.9351 GA - 2.373 GA ² + 0.4176 GA ³ - 0.0152 GA ⁴	0.927	151-154
Fetal volume (mL)	Zero [pre-preg] 0.5 ± 0.14, n = 7 (28%) [6 wk] 9.4 ± 2.9, n = 9 (31%) [10 wk] 76 ± 25, n = 264 (33%) [16 wk] 257.66 ± 33.3, n = 68 (13%) [19 wk] 292 ± 70, n = 10 (24%) [20 wk] 728 ± 176, n = 132 (24%) [25 wk]	Fetal volume = 0.01 exp { (0.955 / 0.0702) (1 - exp(-0.0702 GA)) }	Not applicable	37,155-170

Continued next page

Table I. Contd

Parameter (unit)	Value ^a [pregnancy status or GA]	Equation	R ²	References
Placenta volume (mL)	1513±291, n=1077 (19%) [30 wk]	Placenta volume = 0.0 - 0.716 GA + 0.9149 GA ² - 0.0122 GA ³	0.9952	121,149,156,158,162,165,166,169,171-179
	2547±439, n=1486 (17%) [35 wk]			
	3439±439, n=34 014 (13%) [40 wk]			
	Zero [pre-preg]			
	42±15, n=11 (34%) [9 wk]			
	134±58, n=28 (44%) [14 wk]			
	254±62, n=115 (24%) [20 wk]			
	460±173, n=158 (38%) [30 wk]			
	521±104, n=477 (20%) [34 wk]			
Amniotic fluid volume (mL)	593±90, n=1407 (15%) [36 wk]	Amniotic fluid volume = 0 + 1.9648 GA - 1.2056 GA ² + 0.2064 GA ³ - 0.0061 GA ⁴ + 0.00005 GA ⁵	0.9823	158,160,180-186
	659±103, n=11 901 (16%) [40 wk]			
	Zero [pre-preg]			
	41±15, n=19 (36%) [9 wk]			
	74.82±27.62, n=25 (37%) [12 wk]			
	200±64, n=17 (32%) [15 wk]			
	236.4±78.5, n=22 (33%) [17 wk]			
	359±106, n=8 (30%) [20 wk]			
	705.3±85.5, n=8 (12%) [26 wk]			
823±264, n=16 (32%) [34 wk]				
933.3±195.9, n=12 (21%) [38 wk]				
758±132, n=15 (18%) [40 wk]				

a Values are expressed as mean ± SD (coefficient of variation %).

AAG = α_1 -acid glycoprotein; **CL_{CR}** = creatinine clearance; **CO** = cardiac output; **CYP** = cytochrome P450; **ECW** = extracellular water; **GA** = gestational age; **GFR** = glomerular filtration rate; **Hct** = haematocrit; **ICW** = intracellular water; **n** = number of women; **pre-preg** = pre-pregnancy; **TBW** = total body weight; **TFFM** = total fat-free mass; **TFM** = total fat mass.

only selecting studies that used multi-compartment models to determine fat mass and FFM during gestation as these models are reported to be the gold standard for determining body composition during pregnancy.^[200] These data are given in SDC tables 2 and 3. Analysis of the available data shows that:

- The total fat mass in kg [mean ± SD (CV)] increases from 17.14 ± 6.6 (39%) pre-pregnancy value to 19.09 ± 6.7 (35%), 19.80 ± 7.5 (38%) and 22.6 ± 7.0 (31%) at the gestational weeks 13, 25 and 37 of pregnancy, respectively.
- The total FFM in kg [mean ± SD (CV)] shows no change from 44.5 ± 5.5 (12%) pre-pregnancy value to 44.8 ± 5.0 (11%), 48.59 ± 6.2 (13%) and 50.68 ± 6.8 (12%) at 12, 25 and 37 weeks of gestation. The following equations can be used to describe fat mass (equation 9) and FFM (equation 10) during pregnancy:

$$\text{Total fat mass (kg)} = 17.14 + 0.1305 \text{ GA} + 0.0008 \text{ GA}^2$$

with R² = 0.8938 (Eq. 9)

$$\text{Total FFM (kg)} = 44.5 - 0.0474 \text{ GA} + 0.0034 \text{ GA}^2$$

with R² = 0.9544 (Eq. 10)

The values 17.14 and 44.5 represent the baseline values of total fat mass and FFM (in kg), respectively, for pre-pregnant women.

The mean density of FFM was determined to be 1.099 g/cm³ at week 14 and 1.089 g/cm³ at week 37.^[201] At term, the mean FFM density was determined to range from 1.0895 to 1.0850 g/cm³ for non-oedematous pregnant women and 1.0830 to 1.0785 g/cm³ if the women developed generalized oedema.^[202] Such changes in density can affect the total FFM density of pregnant women, even if they have the same pre-pregnancy FFM; however, the accuracy of the method used is still uncertain.^[200] Plots of fat and FFM gain at different gestational weeks are given in the SDC.

Total Body Water

Total body water increases gradually with gestational age but with great inter-individual variability. This increase in total body water is important in expanding the plasma volume to fill the increased vascular bed that occurs during normal pregnancy.^[203] Studies that reported total body water during normal pregnancy are listed in tables 4 and 5 of the SDC. Data from pregnant women with generalized oedema were excluded from this evaluation.

Meta-analysis of the available data shows that the mean ± SD (CV) total body water (L) increases from 31.67 ± 4.6 (15%)

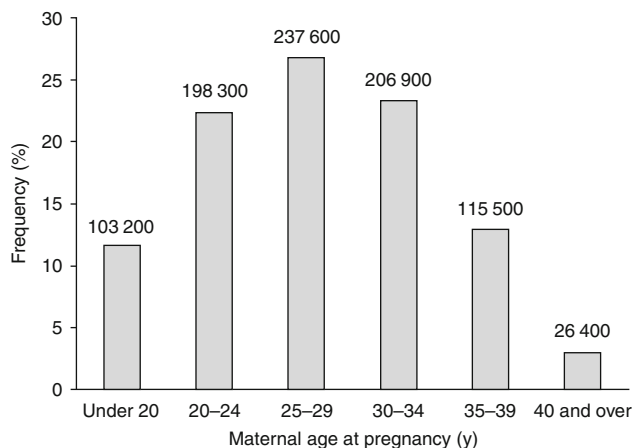


Fig. 1. Maternal age distribution.

before pregnancy to 35.22 ± 1.65 (5%), 40.14 ± 7.55 (19%) and 46.0 ± 5.5 (13%) at 12, 25 and 40 weeks of pregnancy, respectively.

Extracellular water (L) increases slightly from the pre-pregnancy value of 11.86 ± 2.0 (17%) to 12.48 ± 2.44 (20%), 13 ± 2.0 (14%), 14.59 ± 3.5 (24%) and 14.81 ± 3.2 (21%) at 12, 20, 35 and 38 weeks of pregnancy, respectively.

During pregnancy, intracellular water (L) increases from 19.81 ± 2.1 (11%) before pregnancy to 23.3 ± 5.2 (21%), 28.6 ± 4.7 (16%), 27.63 ± 6.4 (20%) and 29.13 ± 3.6 (11%) at 12, 22, 30 and 38 weeks of gestation, respectively. The following equations were derived to describe the change in total body water (equation 11), extracellular water (equation 12) and intracellular water (equation 13) during pregnancy:

$$\text{Total body water (L)} = 31.67 + 0.275 \text{ GA} + 0.0024 \text{ GA}^2$$

with $R^2 = 0.9898$ (Eq. 11)

$$\text{Extracellular water (L)} = 11.86 + 0.0187 \text{ GA} + 0.0016 \text{ GA}^2$$

with $R^2 = 0.8687$ (Eq. 12)

$$\text{Intracellular water (L)} = 19.81 + 0.5941 \text{ GA} - 0.007 \text{ GA}^2$$

with $R^2 = 0.981$ (Eq. 13)

Plots of water gain at different gestational weeks are given in the SDC.

Cardiovascular System

Several significant cardiovascular changes occur during the course of pregnancy, including an increase in cardiac output and plasma volume, and a reduction in vascular resistance in order to meet the increasing metabolic demands of the mother and fetus and to tolerate the acute blood loss that occurs with childbirth. These changes are believed to be under maternal hormonal control, including progesterone, aldosterone, estradiol

and renin.^[8,68,204] The interaction mechanisms of these changes are complex as these adaptations occur simultaneously, most of them begin during early pregnancy, and are critical at term. The unique feature associated with pregnancy is the increasing rise in cardiac output parallel to a continuous increase of blood volume and vasodilatation. The mean \pm SD systemic vascular resistance ($\text{dyne} \cdot \text{cm}/\text{sec}^5$) decreases from a pre-pregnancy value of 1461 ± 283 to 1124 ± 235 , 967 ± 222 , and 1012 ± 248 during the first, second and third trimesters, respectively.^[5,37,61,205] The stroke volume (in mL) increases from a pre-pregnancy value (mean \pm SD) of 80 ± 11 to 92 ± 16 , 92 ± 15 , 97 ± 16 and 96 ± 16 at 8, 15, 24 and 38 weeks of pregnancy, respectively.^[5,37] The heart rate increases by 10 to 20 beats/min starting at 5 weeks' gestation and continuing until 32 weeks.^[206,207] This change is mediated by estrogens via increasing myocardial α -receptors.^[206,208,209]

Cardiac Output

Cardiac output refers to the volume of blood ejected from each ventricle of the heart per unit of time. Generally, all studies reported an increase in cardiac output during normal pregnancy with increasing gestational age. The most significant increase in cardiac output occurs during the first half of pregnancy, mainly as the result of an increase in stroke volume.^[62] The increase of cardiac output in the second half of pregnancy was smaller and mostly attributable to an increased heart rate.^[121] Whether the cardiac output increases steadily until term or there is a decrease in late pregnancy remains controversial. Some studies report a steady increase until term,^[210-212] whereas others report a plateau or decrease in the third trimester.^[62,63,213] This discrepancy can be explained by differences in study design and methodology, including maternal position during the examination.^[64] Cardiac output is usually measured in a supine position; however, by positioning the mother in such a posi-

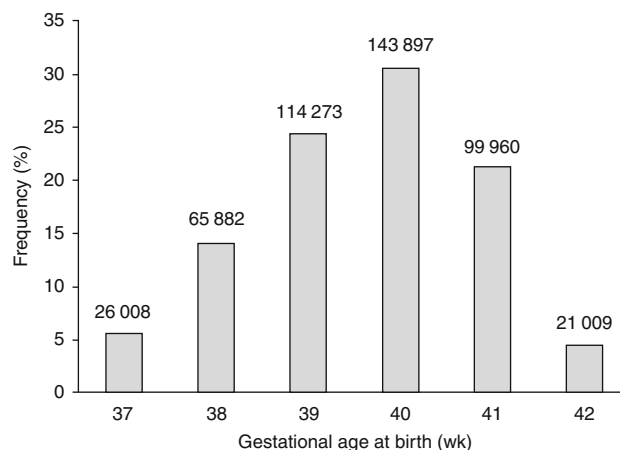


Fig. 2. Gestational age distribution.

tion in late pregnancy, the uterus seriously impedes venous return through the vena cava with a consequent fall in cardiac output.^[214,215] Thus, many studies measured cardiac output by having the subjects lay on their left side.^[37,206] Studies that did account for this phenomenon were included in this review. Information on cardiac output in pregnancy was gathered from a number of sources and only data measured by pulsed Doppler while subjects were lying on their left lateral decubitus position are included in this analysis (see table 6 in the SDC).

Data analysis shows that cardiac output (L/h) begins to rise gradually from early pregnancy [mean \pm SD (CV)], with increases from the pre-pregnancy value of 301 ± 65 (22%) to 354 ± 76 (22%), 386 ± 75 (20%), 400 ± 79 (20%) and 391 ± 79 (20%) at 10, 20, 36 and 38 weeks of gestation, respectively. Cardiac output reaches the peak of 400 L/h between 30 and 38 gestational weeks with the highest value of about 424 ± 72 L/h at 32 weeks of pregnancy. These changes can be described by equation 14:

$$\text{Cardiac output (L/h)} = 301 + 5.916 \text{ GA} - 0.088 \text{ GA}^2 \\ \text{with } R^2 = 0.9014 \quad (\text{Eq. 14})$$

A plot of cardiac output changes at different gestational weeks is given in the SDC.

Of note, cardiac output increases by 50% during labour and by 60–80% during the 15th to 20th minutes after delivery and remains elevated for 48 hours after delivery. It returns gradually to pre-pregnancy values over 2–12 weeks.^[216]

Plasma Volume

Expansion of the plasma volume begins as early as the fourth week of pregnancy, and increases 10–15% by 6–12 weeks of gestation with a continuous rises until parturition.^[7,69-71] Collected studies are given in table 7 of the SDC. Data analysis shows that the average plasma volume (in L) [mean \pm SD (CV)] increases from a pre-pregnancy value of 2.50 ± 0.40 (16%) to 2.67 ± 0.45 (17%), 3.55 ± 0.61 (17%), 3.74 ± 0.50 (13%), 3.67 ± 0.64 (17%) and 3.74 ± 0.54 (14%) at 12, 24, 30, 36 and 39 weeks of pregnancy, respectively. The total gain at term averages 1240 mL and results in a plasma volume range from 3200 to 4280 mL, which is 34–70% above that found in pre-pregnant women. Part of this variability can be teased out by accounting for many covariates such as parity^[72] and multiple births.^[73] A possible clinical consequence of this large variability is that it can result in different concentrations of biomarkers in plasma.^[217]

For modelling purposes, equation 15 can be used to describe the longitudinal change in plasma volume during pregnancy:

$$\text{Plasma volume (L)} = 2.50 - 0.0223 \text{ GA} + 0.0042 \text{ GA}^2 \\ - 0.00007 \text{ GA}^3 \quad \text{with } R^2 = 0.9639 \quad (\text{Eq. 15})$$

A plot of plasma volume expansion at different gestational weeks is given in the SDC.

Red Blood Cell Volume

Plasma volume expansion is accompanied by a lesser increase in red blood cell (RBC) volume^[218] to meet the needs of increased oxygen requirements for the mother and the fetus. The control of RBC production is complex and believed to be under the influence of erythropoietin hormone, which increases during pregnancy;^[219-221] however, other factors such as progesterone (which counters the inhibition effect of estrogens on erythropoietin), folic acid and iron are of great significance.^[222-225]

Collected data for RBC changes during pregnancy are listed in table 8 of the SDC. Data analysis shows that during pregnancy the volume of RBCs (in L) [mean \pm SD (CV)] rises from a pre-pregnancy value of 1.49 ± 0.15 (10%) to 1.55 ± 0.15 (10%), 1.61 ± 0.11 (6%), 1.79 ± 0.11 (6%), 1.82 ± 0.10 (5%), 1.84 ± 0.26 (15%) and 1.90 ± 0.16 (9%) at 12, 20, 24, 33, 36 and 40 weeks of gestation, respectively. Equation 16 can be used to describe the change in RBCs during pregnancy:

$$\text{RBC volume (L)} = 1.49 + 0.0098 \text{ GA} \quad \text{with } R^2 = 0.9121 \\ (\text{Eq. 16})$$

A plot of RBC volumes at different gestational weeks is given in the SDC.

Haematocrit

The haematocrit value is the percentage of RBCs relative to plasma volume. In pre-pregnant women haematocrit ranges from 38% to 45%. Pregnant women show a moderate decrease in the haematocrit value during gestation, most probably due to the increasing volume of plasma (haemodilution of pregnancy) and the fact that the proportion of increased RBC volume is less than the increase in plasma volume during normal pregnancy. Collected values of haematocrit during pregnancy are given in table 9 of the SDC. Studies that mentioned iron supplements were excluded.

Meta-analysis of the collected data shows that the haematocrit value (%) [mean \pm SD (CV)] falls from a pre-pregnancy value of 39.14 ± 2.51 (6.4%) to 38.10 ± 3.3 (8.7%), 37.30 ± 3 (8%), 36.2 ± 3.2 (9.1%), 36.08 ± 5.9 (16%), 35.4 ± 3.8 (11%), 34.98 ± 4.7 (13%) and 33.6 ± 3.0 (9%) at 10, 17, 23, 27, 30, 36 and 39 weeks of gestation, respectively. Equation 17 can be used to describe the change in haematocrit at any week during pregnancy:

$$\text{Haematocrit (\%)} = 39.1 - 0.0544 \text{ GA} - 0.0021 \text{ GA}^2 \\ \text{with } R^2 = 0.9541 \quad (\text{Eq. 17})$$

A plot of haematocrit at different gestational weeks is given in the SDC.

Plasma Protein

Plasma protein levels decrease during pregnancy, which may alter the unbound plasma concentrations of drugs that are highly protein bound. Collected data for the total plasma protein concentration in plasma during pregnancy are listed in table 10 of the SDC. Data analysis showed that the total plasma protein concentration (g/L), mean \pm SD (CV), decreases from 69.7 ± 4.4 (6%) pre-pregnancy to 68.8 ± 5.2 (8%), 65.1 ± 4.4 (7%), 63.3 ± 3.7 (6%), 63.7 ± 4.2 (7%) and 64.1 ± 3.1 g/L (5%) at 12, 23, 31, 34.8 and 38.4 weeks of gestation, respectively. Equation 18 can be used to describe the longitudinal decrease of plasma protein concentration during pregnancy:

$$\text{Plasma protein (g/L)} = 69.7 + 0.2085 \text{ GA} - 0.0305 \text{ GA}^2 + 0.0006 \text{ GA}^3 \quad \text{with } R^2 = 0.997 \quad (\text{Eq. 18})$$

A plot of total plasma protein at different gestational weeks is given in the SDC.

Albumin

Determination of the albumin level during pregnancy is of great importance. Most drugs are bound to different extents to this protein, affecting their disposition and effect. Reported changes in the maternal serum albumin concentration during pregnancy are given in table 11 of the SDC. Data analysis showed that the plasma albumin level (g/L), mean \pm SD (CV), decreased during pregnancy from the pre-pregnancy value of 45.8 ± 3.5 (7.6%) to 43.3 ± 4.1 (9%), 41.4 ± 3.0 (7%), 38.5 ± 3.8 (10%), 37.56 ± 3.6 (10%) and 31.45 ± 5.3 (17%) at 10, 17, 30, 34 and 40 weeks of gestation, respectively. Equation 19 can be used to describe the albumin concentration during pregnancy:

$$\text{Albumin (g/L)} = 45.8 - 0.1775 \text{ GA} - 0.0033 \text{ GA}^2 \quad \text{with } R^2 = 0.9403 \quad (\text{Eq. 19})$$

A plot of plasma albumin at different gestational weeks is given in the SDC.

α_1 -Acid Glycoprotein

The plasma α_1 -acid glycoprotein (AAG) level (g/L), mean \pm SD (CV), decreased during pregnancy from the pre-pregnancy value of 0.74 ± 0.17 (23%) to 0.73 ± 1.6 (22%), 0.58 ± 0.19 (33%), 0.60 ± 0.18 (30%), 0.61 ± 0.18 (30%) and 0.60 ± 0.16 (27%) at 10, 20, 30, 35 and 40 weeks of gestation, respectively. Equation 20 can be used to describe the change in AAG during pregnancy:

$$\text{AAG (g/L)} = 0.74 - 0.0088 \text{ GA} + 0.0001 \text{ GA}^2 \quad \text{with } R^2 = 0.7508 \quad (\text{Eq. 20})$$

Collected data are given in table 12 of the SDC. A plot of the AAG level at different gestational weeks is given in the SDC.

Plasma Lipids

During pregnancy serum lipids increase gradually until term. In addition, phospholipids increased from a pre-pregnancy average of 229 ± 47 mg/dL in 24 women to 323 ± 42 mg/dL at 38 weeks of pregnancy.^[98] Plasma total fatty acids are reported to increase during pregnancy; however, no clear trend was observed in erythrocyte fatty acids.^[226]

Total plasma lipids (g/L) increased during pregnancy from 6.0 ± 1.0 (mean \pm SD) at 9 gestational weeks to 8.7 ± 1.4 , 9.5 ± 1.2 and 9.9 ± 1.4 at 25, 34 and 40 weeks of gestation, respectively. The level of plasma lipids then decreased to 6.0 ± 1.1 g/L at 4 weeks postpartum. The total triglyceride concentration increased from a pre-pregnancy value of 78.54 ± 39 mg/dL to 116 ± 53 , 132 ± 65 and 228 ± 83 mg/dL during the first, second and third trimester, respectively. Total cholesterol has a similar trend; it increases from a pre-pregnancy value of 178 ± 38 mg/dL to 190 ± 36 , 238 ± 46 and 273 ± 45 mg/dL during the first, second and third trimester, respectively.

Collected data regarding total plasma lipids, triglycerides and cholesterol are given in table 13 of the SDC. The following equations can be used to describe the change in total plasma lipids (equation 21), triglycerides (equation 22) and cholesterol (equation 23) during pregnancy:

$$\text{Total lipids (g/L)} = 6 + 0.1001 \text{ GA} \quad \text{with } R^2 = 0.9897 \quad (\text{Eq. 21})$$

$$\text{Total triglycerides (mg/dL)} = 79 + 0.6566 \text{ GA} + 0.0925 \text{ GA}^2 \quad \text{with } R^2 = 0.9558 \quad (\text{Eq. 22})$$

$$\text{Total cholesterol (mg/dL)} = 178 + 1.1045 \text{ GA} + 0.0444 \text{ GA}^2 \quad \text{with } R^2 = 0.977 \quad (\text{Eq. 23})$$

Plots of plasma lipids, triglycerides and cholesterol levels at different gestational weeks are given in the SDC.

Gastrointestinal Tract

During pregnancy, the stomach is continuously displaced upward toward the left side of the diaphragm. In most pregnant women, this change leads to displacement of the intra-abdominal segment of the oesophagus into the thorax and can partly explain the gastric reflux that is experienced by many women during pregnancy.^[227]

Gastric pH

No differences in basal gastric pH or basal and peak acid outputs have been observed during pregnancy when compared with pre-pregnancy values.^[228,229] This is in contrast with a previous review, where an increase in gastric pH was reported.^[230]

Gastric Emptying and Gastrointestinal Transit Time

Gastric emptying is not altered in healthy women during pregnancy. Using water^[231] and disaccharide solution^[232] as test liquids, no difference in gastric emptying was observed during pregnancy. After oral administration of paracetamol (acetaminophen) tablets,^[231,233,234] no gastric emptying delay was observed in pregnant women in the first, second and third trimester compared with non-pregnant women. These results are supported by other techniques, where no change in gastric emptying could be demonstrated during pregnancy using serial gastric ultrasound examinations.^[231,232] This information is in contrast to a previous review, which reported a reduction in gastric emptying during pregnancy.^[230]

The oro-caecal transit time (OCTT) did not change during the first trimester of pregnancy; however, in the third trimester OCTT was longer (100 min vs 70 min).^[232] The observed prolongation in OCTT should be interpreted with caution as these women had mild dyspepsia during the first trimester and the observed range was 50.5–240 minutes during the third trimester and 40.5–240 minutes postpartum.

Bile

Using real-time ultrasonography, the fasting and residual volumes of the gallbladder were markedly increased during the second and third trimesters in 33 pregnant women compared with 11 pre-pregnant women. Gallbladder emptying has been reported to be incomplete and slower during pregnancy and the bile content tends to be more concentrated.^[235]

Limited information is available on gallbladder emptying times. In eight healthy women, the gallbladder emptying rate constant was decreased from $0.041 \pm 0.006 \text{ min}^{-1}$ in pre-pregnant women to $0.022 \pm 0.003 \text{ min}^{-1}$ during pregnancy.^[147] Fasting gallbladder volumes (mL) [mean \pm SD (CV)] determined by ultrasonography increased from a pre-pregnancy (n=223) value of 20.17 ± 8.35 (41%) to 30.75 ± 12.75 (41%) in 195 pregnant women at the second trimester and remained relatively constant, with a value 29 ± 12.9 (45%) in 115 pregnant women to the end of pregnancy.^[147,236-238] The gallbladder ejection fraction was lower in third trimester pregnant women (n=18) than in postpartum women after delivery (n=18) [$60.56 \pm 18.8\%$ vs $77.48 \pm 13.37\%$].^[238]

Liver

Despite the fact that there are marked changes in liver function during pregnancy,^[239-241] no evidence for significant change of liver morphology could be found. The liver receives about 70% of the blood from the portal veins and the other 30% is delivered at a greater velocity and higher pressure from the hepatic arteries.^[242]

Liver Blood Flow

Despite numerous literature reports of marked changes in the cardiovascular system during pregnancy, little is known about changes in hepatic blood flow and the existing data are contradictory. Munnell and Taylor^[243] did not find any difference between hepatic blood flows, measured using the Fick principle, with bromosulphthalein in 15 non-pregnant and 15 pregnant women: both were between 1400 and 1500 mL/min/1.73 m². In another study, Robson et al.^[83] calculated the apparent liver blood flow from indocyanine green clearance and found no significant changes during pregnancy. The apparent liver blood flow was found to account for 24% of cardiac output during pregnancy and increased to 37% after delivery. In contrast, Clapp et al.^[244] used ultrasonography to estimate portal vein blood flow and found that it rose significantly during early and mid pregnancy (n=6) at standing rest (580 ± 70 to 790 ± 120 mL/min) and was even higher at recumbent rest (from 660 ± 110 to 1090 ± 120 mL/min). The change in the portal vein blood flow during pregnancy reflects changes of similar magnitude in the overall splanchnic blood flow.^[244] This is because approximately two-thirds of splanchnic blood flow is returned to the liver via the portal vein.^[242]

Doppler velocimetry of the hepatic vein in healthy women showed a profound change in hepatic venous pulsatility during pregnancy and waveforms changed from their normal pulsatile nature to become flat with increasing gestation,^[245,246] most probably due to a reduction of liver compliance or by a rise in intra-abdominal pressure.^[246]

Based on the available information, and the knowledge that Doppler flow studies are subject to high variation between and within individuals,^[247,248] it is difficult, at this stage, to describe the magnitude and significant of changes in maternal hepatic blood flow. The increase of the portal venous return can explain the increase of hepatic perfusion observed after 26 weeks of gestation as the hepatic arterial blood flow remains unchanged.^[249] Collected values on hepatic blood flow are given in table 14 of the SDC.

Metabolic Enzyme Activity

Drug-metabolizing enzymes can be classified into two broad classes: cytochrome P450 (CYP) enzymes and non-CYP enzymes, including the uridine diphosphate glucuronosyl-

transferase (UGT) family. The activity of many of these enzymes has been shown to change during pregnancy and can affect drugs pharmacokinetics and therapy. For example, human pregnancy is associated with an increased metabolism of the CYP2D6 substrates metoprolol^[250-252] and dextromethorphan.^[102,253] CYP2D6 is a polymorphic gene and these polymorphisms can alter CYP2D6 activity regardless of pregnancy state.^[254] However, although there are no data to support that the activity of these variants changes in a variant-specific manner with pregnancy, maternal CYP2D6 polymorphisms have been shown to have the potential to alter fetal exposure to paroxetine.^[3]

While the causative mechanism of the observed changes of metabolizing enzymes has not been identified, accumulated data suggest that the protein expression of these enzymes are regulated by the higher level of hormones, mainly estradiol and progesterone, during pregnancy in a concentration-dependent manner.^[2,4,255,256] The known regulatory pathways involve the aryl hydrocarbon, constitutive androstane, pregnane X and estrogen receptors. At this time, for ethical and clinical reasons, it is not practical or possible to get hepatocytes from healthy pregnant women or to run a clinical study for drugs where their safety in pregnancy is not known. Available studies therefore reported any change in CYP activity as a percentage in relation to the pre-pregnant population. Examples of changes in these enzymes and the controlling hormones are given in table II.

Tracy et al.^[102] has reported maternal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 isoforms during pregnancy in 25 healthy women. The activity of CYP1A2 decreased from the pre-pregnancy level (100%) by $32.8 \pm 22.8\%$, $48.1 \pm 27\%$ and $65.2 \pm 15.3\%$ during the first, second and third trimester, respectively. The activity of CYP2D6 increased from the pre-pregnancy level (100%) by $25.6 \pm 58.3\%$, $34.8 \pm 41.4\%$ and $47.8 \pm 24.7\%$ during the first, second and third trimester, respectively. Similar to CYP2D6, the activity of CYP3A4 increased by 35%, 35% and 38% of the pre-pregnancy level during the first, second and third trimester, respectively. These changes were based on saliva clearance in case of caffeine and invariant urinary parent/metabolite ratios for dextromethorphan *O*- and *N*-demethylation, which are not pure markers of enzyme activity.^[278,279] Values of CYP2D6 (dextromethorphan/dextrorphan ratio) and CYP3A4 (dextromethorphan/3-hydroxymorphinan) at each trimester were corrected for the changes in renal function at the corresponding trimester by dividing by renal function relative to that at pre-pregnancy. The reciprocal of the quotients is then used as an index of CYP2D6- and CYP3A4-mediated formation of dextrorphan and 3-hydroxymorphinan, respectively, and, hence, of the change in relative enzyme activity.

For CYP1A2, no correction was applied since the half-life but not clearance can be detected from saliva. The percentage changes from the original uncorrected data are given in figure 3.

The change in the activity of these enzymes (%) during pregnancy over the pre-pregnancy level, after correction of data from Tracy et al.,^[102] can be described by using the following equations for CYP1A2 (equation 24), CYP2D6 (equation 25) and CYP3A4 (equation 26) isoforms:

$$\begin{aligned} \text{CYP1A2 activity (\%)} &= 100 - 3.5814 \text{ GA} + 0.0495 \text{ GA}^2 \\ &\text{with } R^2 = 0.9965 \quad (\text{Eq. 24}) \end{aligned}$$

$$\begin{aligned} \text{CYP2D6 activity (\%)} &= 100 + 2.2695 \text{ GA} - 0.0348 \text{ GA}^2 \\ &\text{with } R^2 = 0.9948 \quad (\text{Eq. 25}) \end{aligned}$$

$$\begin{aligned} \text{CYP3A4 activity (\%)} &= 100 + 2.9826 \text{ GA} - 0.0741 \text{ GA}^2 \\ &\text{with } R^2 = 0.7718 \quad (\text{Eq. 26}) \end{aligned}$$

These profiles are plotted in figure 4. The use of dextromethorphan *N*-demethylation as a marker of CYP3A4 activity leads to underestimate of the real increase in CYP3A4 activity during pregnancy. Use of a more sensitive probe such as midazolam indicated a higher increase in CYP3A4 at term.^[38] A wide range of the increase in CYP3A4 activity (50–100%) at term has been reported.^[280]

The activity of other enzymes such as CYP2A6, CYP2C9, UGT1A1, UGT1A4 and UGT2B7 have been reported to be higher during pregnancy than pre-pregnancy levels.^[4,17,281] Others such as CYP2C19 and *N*-acetyltransferase 2 (NAT2) have been reported to be lower during pregnancy.^[4,17,281] Although direction of the change (increase or decrease) in expression or activity is identified, little is known about the magnitude of these alterations.

Interestingly, levels of CYP2D6 and CYP1B1 expression in leukocytes were not significantly changed in 18 pregnant women between 35 and 37 weeks of gestation. A trend of increase was observed for CYP1B1 expression, but did not reach significance, most probably due to the observed very large variability between those individuals.^[282] Well designed *in vivo* and *in vitro* studies are required in this area to quantify the magnitude of induction or suppression of metabolizing enzymes during pregnancy as such changes are likely to have toxicological and therapeutic implications.

Kidney

During normal healthy pregnancy, kidney dimensions increase by approximately 1 cm, and kidney volume increases by as much as 30%.^[283,284] No information could be retrieved re-

Table II. Observed impact of maternal changes in metabolizing enzymes on drug pharmacokinetics

Metabolizing enzymes	Enzymatic changes during pregnancy [mediated by]	Controlling hormone	Observed pharmacokinetic consequences
CYPs	↓ mRNA expression level of CYP1A2 [AhR]	↑ Estradiol	↓ CL of CYP1A2 substrates: Caffeine ^[257-259] Theophylline ^[54,90,260]
	↑ mRNA expression level of CYP2A6 [ER (and PXR) activation]	↑ Estradiol	↑ CL of CYP2A6 substrates: Nicotine ^[261]
	↑ CYP2C9 expression [CAR and PXR]	Unknown	↑ CL of CYP2C9 substrates: Phenytoin ^[262,263] Glibenclamide (glyburide) ^[264]
	↓ CYP2C19 expression [CAR]	Unknown	↓ CL of CYP2C19 substrates: Proguanil ^[265,266]
	↑ CYP2D6 expression	Unknown	↑ CL of CYP2D6 substrates: Metoprolol ^[250-252] Dextromethorphan ^[102] Fluoxetine ^[267] Citalopram ^[268] Clonidine ^[269]
	↑ mRNA expression level of CYP3A4 [CAR (and PXR) activation]	↑ Estradiol	↑ CL of CYP3A4 substrates: Midazolam ^[38,270] Nifedipine ^[271] Methadone ^[272,273]
UGTs	↑ UGT1A1 expression [PXR activation]	↑ Progesterone	↑ CL of UGT1A1 substrates: Labetalol ^[274]
	↑ UGT1A4 expression [ER α activation]	↑ Estradiol	↑ CL of UGT1A4 substrates: Lamotrigine ^[275-277]

AhR = aryl hydrocarbon receptor (modified from^[2,4,17,256]); **CAR** = constitutive androstane receptor; **CL** = clearance; **CYP** = cytochrome P450; **ER** = estrogens receptor; **mRNA** = messenger RNA; **PXR** = pregnane X receptor; **TBW** = total body water; **UGT** = uridine diphosphate glucuronosyltransferase; ↓ indicates decreased; ↑ indicates increased.

garding any changes in kidney composition, enzyme and transporter expression during pregnancy in humans.

There are many physiological parameters that change during pregnancy in the urinary system such as the increasing renal

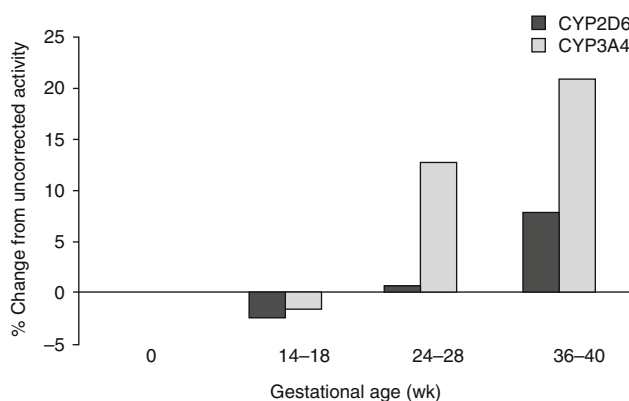


Fig. 3. Percentage changes in cytochrome P450 enzymes from the original uncorrected data published by Tracy et al.^[102] (no correction is needed for CYP1A2 activity). **CYP** = cytochrome P450.

blood supply, glomerular filtration rate (GFR) and creatinine clearance (CL_{CR}). Filtration fraction was significantly reduced during early pregnancy but rose to a value equivalent to the pre-pregnancy level during the third trimester.^[103] Systemic vasodilation occurs during early pregnancy, which is probably mediated by progesterone and relaxin.^[285,286] The renal collecting system becomes more dilated as early as the first trimester, leading to hydroureteronephrosis and reverts to normal by 6 weeks postpartum.^[287,288]

Glomerular Filtration Rate

The GFR, which describes the flow rate of filtered fluid through the nephrons, is one of the main physiological parameters of renal function. The GFR can be determined by injecting inulin into the plasma. Since inulin is neither reabsorbed nor secreted by the kidney after glomerular filtration, its rate of excretion is directly proportional to the rate of filtration of water and solutes across the glomerular filter. Available data show that GFR is raised throughout pregnancy and falls in late

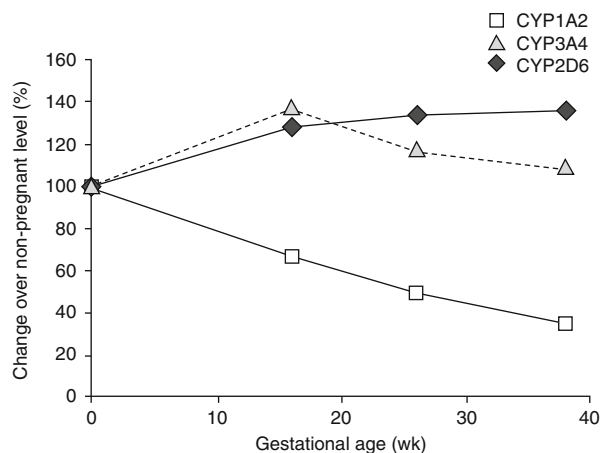


Fig. 4. Relative change in studied cytochrome P450 enzymes over gestational age to non-pregnant women. **CYP**=cytochrome P450.

pregnancy. This increase in GFR with plasma volume expansion can increase the clearance of renally excreted drugs during pregnancy as in the case of atenolol.^[289]

Available data for GFR measured by inulin clearance in healthy pregnant women are listed in table 15 of the SDC. A meta-analysis of the collected data showed an increase in the average level of GFR (mL/min) [mean ± SD (CV)], from 114 ± 28 (25%) in pre-pregnant women to 136 ± 32 (23%), 156 ± 26 (16%), 160 ± 26 (16%) and 156 ± 42 (27%) at 10, 16, 26 and 36 weeks of gestation, respectively. Equation 27 can be used to describe the changes in GFR during pregnancy:

$$\text{GFR (mL/min)} = 114 + 3.2367 \text{ GA} - 0.0572 \text{ GA}^2$$

with $R^2 = 0.9712$ (Eq. 27)

A plot of GFR at different gestational weeks is given in the SDC.

Creatinine Clearance

CL_{CR} is commonly used as a measure of GFR. However, because creatinine is also actively secreted by renal tubules to a small extent, CL_{CR} may overestimate actual GFR. Available data for CL_{CR} during pregnancy are listed in table 16 of the SDC. Data analysis showed an enhanced CL_{CR} during pregnancy in line with inulin clearance. CL_{CR} (mL/min) [mean ± SD (CV)], increases from a pre-pregnancy value of 98.3 ± 14.4 (15%) to 126 ± 20 (16%), 155 ± 28 (18%), 152 ± 39 (25%) and 124 ± 34 (28%) at 12, 26, 33 and 37 weeks of gestation, respectively. Equation 28 can be used to describe the change in CL_{CR} during normal pregnancy:

$$\text{CL}_{\text{CR}}(\text{mL/min}) = 98.3 + 3.9107 \text{ GA} - 0.0789 \text{ GA}^2$$

with $R^2 = 0.819$ (Eq. 28)

A plot of CL_{CR} at different gestational weeks is given in the SDC.

Serum Creatinine Level

The creatinine level in plasma is a balance between the kidney function and the production rate of creatinine from breakdown of creatine in muscle. As a consequence of increased CL_{CR} during the gestational period, plasma levels of creatinine are lower than pre-pregnancy levels as muscle mass does not change substantially. Collected data for serum creatinine during pregnancy are presented in table 17 of the SDC. Serum creatinine (mL/dL) [mean ± SD (CV)], decreases from the pre-pregnancy level of 0.80 ± 0.11 (13%) to 0.69 ± 0.09 (13%), 0.64 ± 0.08 (12%), 0.67 ± 0.08 (12%) and 0.66 ± 0.14 (21%) at 18, 15, 34 and 37 weeks of gestation, respectively. Equation 29 can be used to describe the changes in serum creatinine during normal pregnancy:

$$\text{Serum creatinine (mg/dL)} = 0.8 - 0.0147 \text{ GA} + 0.0003 \text{ GA}^2$$

with $R^2 = 0.9543$ (Eq. 29)

A plot of the serum creatinine level at different gestational weeks is given in the SDC.

Effective Renal Plasma Flow

Effective renal plasma flow (ERPF) is measured via para-aminohippuric acid clearance. ERPF is an indirect measurement of effective renal blood flow (ERBF). Collected data for ERPF are given in table 18 of the SDC. Data analysis showed that the ERPF increased during early pregnancy but fell towards term. ERPF increased from a mean ± SD [L/h (CV)] pre-pregnancy value of 32.3 ± 6.4 (20%) to 44.5 ± 6.1 (14%), 48.4 ± 8.8 (18%), 47.8 ± 12.5 (26%) and 42.3 ± 11.2 (27%) at 7, 16, 26 and 36 weeks of gestation, respectively. It peaks during the second trimester around 20–25 weeks of gestation with a value of 50 L/h. Equation 30 can be used to describe the change in ERPF during pregnancy:

$$\text{ERPF (L/h)} = 32.3 + 1.6576 \text{ GA} - 0.0389 \text{ GA}^2$$

with $R^2 = 0.947$ (Eq. 30)

A plot of ERPF at different gestational weeks is given in the SDC.

Effective Renal Blood Flow

Limited data have been found on the change of the ERBF during pregnancy and in 1991 de Swiet^[6] published a graph of average values showing an increase of the renal blood flow from about 47 L/h pre-pregnancy to 65, 77, 73, 69 and 54 L/h at 10, 15, 20, 30 and 40 weeks of gestation, respectively.

Here, in this analysis, the ERBF data for each gestational stage of pregnancy were calculated from ERPF assuming the same distribution as for ERPF and by correcting the data for mean haematocrit values at the respective gestational week using equation 31:

$$\text{ERBF} = \text{ERPF}/(1 - \text{Hct}) \quad (\text{Eq. 31})$$

where Hct is haematocrit. Calculation of ERBF resulted in a trend similar to that observed for the ERPF, showing that ERBF (L/h) increases from a pre-pregnancy value, mean \pm SD (CV), of 53.1 ± 10.4 (20%) to 72.7 ± 9.9 (14%), 77.9 ± 14.0 (18%), 75.1 ± 19.7 (26%) and 64.4 ± 17.1 (27%) at 7, 16, 26 and 36 weeks of gestation, respectively.

Although the ERBF can be calculated for modelling purposes by using ERPF and applying the corresponding haematocrit value to the gestational week, the following equation (equation 32) can also be used to describe the change in ERPF as a function of gestational age during pregnancy:

$$\text{ERBF (L/h)} = 53 + 2.6616 \text{ GA} - 0.0661 \text{ GA}^2 \\ \text{with } R^2 = 0.9344 \quad (\text{Eq. 32})$$

A plot of ERBF at different gestational weeks is given in the SDC.

Brain

Brain Mass

In a recent study, brain size was measured in nine healthy women using three-dimensional (3D) magnetic resonance imaging (MRI)^[290] before and after delivery. Interestingly, the study found that brain size is reduced during pregnancy, with a maximal reduction at term, with the brain returning to its original size by 6 months after delivery (see table 19 of the SDC). The ventricular system measured included both lateral ventricles and the third ventricle but not the aqueduct or the fourth ventricle. The ventricular size showed a corresponding increase in size during pregnancy and a decrease in size after delivery. It is difficult at present to draw conclusions regarding these parameters based on this study, and more data are required to support this evidence.

Cerebral Blood Flow

During pregnancy, maternal cerebral blood flow (CBF), measured by the Fick principle with nitrous oxide,^[291] was reported to be similar to that found in non-pregnant women. However, recently, Nevo et al.^[117] assessed CBF by measuring blood flow volume in the internal carotid artery by dual-beam angle-independent digital Doppler ultrasound.^[117] They found that CBF gradually increased during normal pregnancy (see

table 20 of the SDC). The following equations can be used to describe the increase in cerebral (equation 33) and internal carotid artery (ICA) [equation 34] blood flow to the brain during pregnancy:

$$\text{CBF (L/h/100 g)} = 2.53 + 0.0167 \text{ GA} \\ \text{with } R^2 = 0.9923 \quad (\text{Eq. 33})$$

$$\text{ICA blood flow (L/h)} = 17.64 + 0.1513 \text{ GA} \\ \text{with } R^2 = 0.9907 \quad (\text{Eq. 34})$$

Plots of cerebral and ICA blood flow at different gestational weeks are given in the SDC.

Uterus

During pregnancy, the uterus undergoes substantial morphological and physiological changes to accommodate and protect the developing fetus. The weight of the uterus increases by 10–20 times during pregnancy. With no difference attributable to the stage of gestation, water and blood constitute 82.3% and 8% of the uterus weight.^[118] More recently, following analysis of data obtained on 3D volume using uterine ultrasonography, it has been shown that the normal uterine volume varies with gravidity and parity.^[292] Uterine volume (cm³) increased from 55.3 ± 25.7 (n=91) to 66.5 ± 29.3 (n=38) and 103.2 ± 33 (n=81) in nulli-, primi- and multi-gravid women, respectively. On the other hand, uterine volume increased from 56.5 ± 26.3 (n=112) to 81.7 ± 36 (n=29) and 104.5 ± 32 (n=69) cm³ in nulli-, primi- and multi-parous women, respectively. Unfortunately, these results were not given in terms of how the uterine volume changed along the pregnancy period, as reliable information could not be found about the menstrual cycle from most of the women in this study.

Uterine Mass

Pregnancy results in a 10-fold increase in uterine wet weight and this value increases with the number of previous pregnancies.^[119,120] The mean wet mass of the non-pregnant uterus varies from about 44 g in the nullipara to over 110 g at parity 5 or over.^[119] Hence, each successive pregnancy alters the baseline value for the pre-pregnancy or 'normal' state, leading to an increase in the baseline variability. A value of 80 g was reported for a reference adult female.^[293] Blood constitutes about 8% of the weight of the uterus.^[118] The available data are given in table 21 of the SDC, which shows a gap of information for uterine weight, particularly between 20 and 35 weeks of pregnancy; however, a weight gain are assumed during this period.

Equation 35 best fits the available data:

$$\text{Weight of the uterus (g)} = 80 + 8.2931 \text{ GA} + 0.3546 \text{ GA}^2$$

$$\text{with } R^2 = 0.9956 \quad (\text{Eq. 35})$$

A plot of uterine mass at different gestational weeks is given in the SDC.

Uterine Blood Flow

Previous studies have shown that the uterus receives about 0.5%^[65] of cardiac output in pre-pregnant women. This increases during pregnancy to 3.5% at early pregnancy,^[122] 4.2% at 13 weeks of gestation,^[65] 5.6% at 22 weeks of pregnancy^[121] and 12% at late pregnancy.^[121,122] Collected data about uterine blood flow during pregnancy are presented in table 22 of the SDC. The observed variability between studies is due to differences in the methodology, mainly positioning and time, site of sampling, the techniques and analytical algorithm used, and the differences between individual characteristics. For the purpose of the current data analysis, when a study measured uterine blood flow at one side of the common trunk, the other side is assumed to be the same.

Data analysis showed that the mean \pm SD (CV) uterine blood flow (L/h) increases from a pre-pregnancy value of 1.71 ± 0.85 (52%) to 17.5 ± 10 (57%), 28.5 ± 11.5 (40%), 44.4 ± 15 (33%) and 49.1 ± 14 (29%) at 10, 22, 30 and 38 weeks of gestation, respectively. Equation 36 can be used to describe the longitudinal increase of uterine blood flow during pregnancy:

$$\text{UBF (L/h)} = 1.71 + 0.2068 \text{ GA} + 0.0841 \text{ GA}^2 - 0.0015 \text{ GA}^3$$

$$\text{with } R^2 = 0.9905 \quad (\text{Eq. 36})$$

A plot of uterine blood flow at different gestational weeks is given in the SDC.

Mammary Glands

Mass

As for many other parameters, the mass of mammary glands in non-pregnant women is very variable.^[132,294-296] Variations in breast volume of up to 36% were found with weekly ultrasonic measurements during the course of seven normal menstrual cycles.^[297] Such variability in the baseline makes it difficult to derive a common picture about the increase due to pregnancy from the cross-section studied. Using a computerized breast measurement technique, a wide range of 600–1840 mL has been reported for both breasts in eight women before conception.^[132] The absolute increase (mean \pm SD) was approximately 145 ± 69 mL of the breast volume ($n = 13$ breasts) at the end of pregnancy.^[132] In another study, 10 of 11 left breasts measured for their volumes during pregnancy using a

water displacement technique exhibited volume increases of between 60 and 480 mL, while the volume of one breast decreased by 20 mL.^[133] It should be pointed out that this indirect measurement is not precise and is influenced by the individual's position.^[133] Data obtained using a water displacement technique were excluded in our analysis. Advanced techniques such as 3D scan and MRI are now available by which breast volume can be measured more accurately and precisely to guarantee objective and exact recording.^[134,135] However, although these methods have been used to describe breast volume in non-pregnant women, no study could be found using these techniques in pregnancy. Collected data are given in table 23 of the SDC. Equation 37 can be used to describe the longitudinal increase of total volume of both breasts during pregnancy:

$$\text{Breasts volume (mL)} = 985 + 14.244 \text{ GA} - 0.1869 \text{ GA}^2$$

$$\text{with } R^2 = 0.9684 \quad (\text{Eq. 37})$$

A plot of the volume of mammary glands at different gestational weeks is given in the SDC.

Blood Flow

Early studies measured mammary blood flow indirectly during pregnancy by means of skin temperature increase, as a measure of blood flow increases to the gland.^[298] Burd et al.^[299] found that breast skin temperature rose by 1°C from week 0 to 20 and was then stable until day 1 postpartum when it rose further. No estimate of changes in relative blood flow was made with this method.

Thoresen and Wesche^[136] used a pulsed Doppler ultrasound velocity meter to measure blood velocities in the mammary branch of the right lateral thoracic artery in one subject throughout pregnancy and postpartum. They found that the blood velocity in the breast artery was 0.01 m/s before pregnancy and increased 2.5-fold from about 0.07 to 0.16 m/s at the 12th and 25th week of pregnancy and then remained steady until partus. The study also reported a dilation of breast arteries of up to 40% during pregnancy. Another study^[300] demonstrated a continuous increase in the mean blood flow velocity in the breast with gestational age from a pre-pregnancy value of about 0.9 kHz to about 1.4 kHz at the 11th week and 2.5 kHz at the 28th week of gestation. Most of the increase was reported to be before the end of the second trimester of pregnancy, after which it tended towards a plateau until the pregnancy was almost full term. Unfortunately, the data were from one woman only but both breasts were studied. It should be noted that in both studies, only figures were given and the numbers given above were extracted (see the Methods section).

Although there is some evidence that mammary gland blood flow increases during pregnancy, no reliable data could be

recovered that could conclude that the increase is a function of the gestational time. Consequently, most of our knowledge is based upon very limited data from case studies.

Other Changes

There are many changes in other maternal tissues during pregnancy and these are described below; most have little data describing them and many have no place in the current PBPK models.

Respiration

Pregnancy is associated with major mechanical and biochemical changes in the respiratory system.^[301] The gradual enlargement of the uterus leads to changes in the abdominal size and shape, shifting the diaphragm up to 4 cm above its usual position.^[302,303] The thoracic cage circumference increases by 5–7 cm during pregnancy. These changes begin at the end of the first trimester and continue throughout the rest of gestation, reaching a peak at week 37.^[302,304] The most pronounced changes in the pregnant respiratory system include the increase in tidal volume from 450 to 700 mL, progressive decrease in respiratory reserve volume from 700 to 550 mL and decrease in the residual volume from 1000 to 800 mL. The inspiration capacity increases from 2500 mL in non-pregnant women to 2750 mL during pregnancy.^[305,306] Inspiratory reserve volume, vital capacity and total lung capacity remain relatively unchanged.^[302,306] Ventilation increased from a median of 9.4 L/min in the pre-pregnancy state to 10.5 L/min by 8–11 weeks and then slowly increased to 12.6 L/min in late pregnancy.^[307] The hyperventilation of pregnancy has been attributed primarily to a progesterone effect.^[303,308]

Oxygen consumption at rest varies between 249 and 331 mL/min in pregnant women and between 191 and 254 mL/min in non-pregnant women; it increases during pregnancy by 37 (range 30–40) mL/min^[307,309–312] to meet the increasing metabolic demands during pregnancy. This increase in consumption is accounted for by (i) the needs of the fetus (12 mL/min); (ii) the placenta (4 mL/min); (iii) increased maternal cardiac output (7 mL/min); (iv) ventilation (2 mL/min); (v) the kidneys (7 mL/min); and (vi) extra breast and uterine tissue (5 mL/min).^[313] The mean \pm SD basal metabolic rate increases from pregravid value of 5430 \pm 660 kJ/24 h to 5570 \pm 640, 5740 \pm 680, 6860 \pm 680 and 7180 \pm 1180 kJ/24 h at 14, 20, 32 and 35 weeks of gestation, respectively.^[37,314]

Pulmonary vascular resistance significantly decreases (by about 34%) from 119 \pm 47 dyne \cdot cm/sec⁵ in pre-pregnant women to 78 \pm 22 dyne \cdot cm/sec⁵ during the 36th–38th week of

pregnancy.^[61] Mean pulmonary artery pressure is unchanged during pregnancy.^[61]

Sex Hormones

In non-pregnant women, the ovary is the main source of sex hormones, progesterone and estrogens. Pregnancy is characterized by about 100-fold elevated levels of circulating estrogens and progesterone, which increase with advancing gestational age. By the end of the first trimester, the feto-placental unit becomes the major site of steroid hormone production and secretion during pregnancy. Progesterone protects the embryo by preventing hypoxia and by aiding the delivery of both oxygen and glucose. Between the 7th and 9th gestational week, progesterone production shifts from the corpus luteum to the placenta.^[315,316] Estrogens levels also increase during pregnancy, including estradiol, estrone, estriol and estetrol.^[315] Among these, only estradiol is reported here. The levels of pregnancy estradiol are significantly and strongly correlated in successive pregnancies of the same woman.^[39,317] The increasing estradiol level during pregnancy has been linked to the many changes that occur throughout gestational time, such as in water and sodium retention resulting in an expanded plasma volume and up- and down-regulation of metabolizing enzymes. In addition to the effect of previous conception on sex hormone concentration, plasma levels of both progesterone and estradiol vary within each healthy woman, with the lowest level during the follicular phase and the highest level during the luteal phase.^[315,318,319] For these reasons, it is difficult to justify which concentration should be used as a basal value; therefore, reported values from the three phases regardless of parity were pooled and the mean was selected as a baseline for the gestational time-dependent profile. Collected studies for estradiol (table 24) and progesterone (table 25) are given in the SDC.

The average estradiol level (ng/mL) [mean \pm SD (CV)] increases during pregnancy from the pre-pregnancy value of 0.062 \pm 0.058 (94%) to 0.51 \pm 0.45 (90%), 3.45 \pm 1.75 (52%), 6.60 \pm 3.86 (59%), 5.86 \pm 5.59 (95%), 11.0 \pm 5.51 (50%), 17.2 \pm 9.3 (54) and 15.7 \pm 9.2 at 8, 16, 21, 24, 27, 36 and 39 gestational weeks, respectively.

Average progesterone level (ng/mL) [mean \pm SD (CV)] increases during pregnancy from the pre-pregnancy value of 1.42 \pm 3.34 (234%) to 24.63 \pm 13.7 (53%), 39.66 \pm 13.43 (34%), 84.72 \pm 35.06 (41%), 89.83 \pm 29.0 (32%), 142.7 \pm 40 (28%) and 190.8 \pm 47.3 (22%) at 8, 16, 24, 30, 33 and 38 gestational weeks, respectively.

The following equations can be used to describe the longitudinal increase of female estradiol (equation 38) and proges-

terone (equation 39) during pregnancy:

$$\text{Estradiol (ng/mL)} = 0.06 + 0.0558 \text{ GA} + 0.0103 \text{ GA}^2 \\ \text{with } R^2 = 0.9634 \quad (\text{Eq. 38})$$

$$\text{Progesterone (ng/mL)} = 1.42 + 3.446 \text{ GA} - 0.1334 \text{ GA}^2 \\ + 0.0046 \text{ GA}^3 \quad \text{with } R^2 = 0.9816 \quad (\text{Eq. 39})$$

Plots of plasma estradiol and progesterone levels at different gestational weeks are given in the SDC.

Thyroid

Thyroid volume did not change during the follicular (8.8 ± 3.2 mL) and luteal (9.7 ± 3.1 mL) phase in 11 healthy non-pregnant women.^[320] A clinically detectable up to 3-fold increase in thyroid size has been found in iodine-deficient areas, causing what is called 'goiter of pregnancy'.^[321,322]

In iodine-replete areas, thyroid volume, measured by ultrasonography, did not change in ten healthy women during pregnancy. The volume readings (mean \pm SD) were 10.3 ± 5.1 , 10.6 ± 4.4 , 9.6 ± 3.8 and 9.4 ± 3.0 mL before pregnancy and during the first, second and third trimesters, respectively.^[320] Thyroid volume did not change in pregnant women living in marginally iodine-deficient areas when they administered iodine supplementation for the prevention of goiter.^[323] No information could be found regarding thyroid blood flow during normal pregnancy. Serum concentrations of free triiodothyronine and free tetraiodothyronine decline slightly during pregnancy.^[37,320]

Peripheral Blood Flow

Skin changes are common during pregnancy, including vascular and haematological changes, blood flow, temperature, thickness, pigmentation, alterations in glandular activity, and mucous membrane changes.^[324-326] There is abundant clinical evidence that blood flow in the skin is increased during pregnancy, particularly in the extremities. Increased blood flow to maternal skin allows dissipation of the heat generated by the fetus.^[327] This can explain the common phenomena that pregnant women complain of the heat and feel warm with clammy hands, most probably due to the increased metabolic rate during gestation.^[319,328] Most blood flow measurements in the extremities have been made non-invasively using different techniques including plethysmographic,^[327,329] photoelectric flow recorder^[330] and Doppler flowmetry.^[331] Available studies that gave the blood flow reading in terms of volume/time are given in table 26 of the SDC. Regardless of high variability in the obtained measurements, it is obvious from these data that the blood flow to the hand is 3- to 7-fold higher at term than the

pre-pregnancy value. A small increase in the calf, arm and forearm blood flow during pregnancy can be visualized from the collected data.

Products of Pregnancy

The products of conception (placenta, fetus, amniotic fluid) comprise approximately 35% of the total gestational weight gain^[332] and their longitudinal changes are considered below as part of PBPK information to model kinetics of xenobiotics during various stages of pregnancy.

Intrauterine Volume

During the first 20 weeks of pregnancy, the volume of the amniotic fluid is the major component of intrauterine volume.^[319] All intrauterine components grow rapidly during the second trimester to reach about 2100 ± 500 mL by the end of the second trimester.^[149] From the beginning of the third trimester to term, fetal growth is the major contributor to increased intrauterine volume. Collected information about total intrauterine volume is given in table 27 of the SDC. There is clearly a gap in these data sets during the first trimester. Due to lack of certainty, an interpolation was done between time zero and the time of the first observation at 13 gestational weeks. A lower growth rate during this early time was assumed. Decomposition of the intrauterine volume profile to its sub-components is covered later in this article. The change in intrauterine (IU) volume can be described by equation 40:

$$\text{IU volume (mL)} = 0.0 - 0.4758 \text{ GA} + 0.5174 \text{ GA}^2 + \\ 0.1424 \text{ GA}^3 - 0.0021 \text{ GA}^4 \\ \text{with } R^2 = 0.9958 \quad (\text{Eq. 40})$$

A plot of intrauterine volumes at different gestational weeks is given in the SDC.

Fetus

Accurate predictions of fetal size and age have an important place in clinical management during antenatal care. The fetus in humans is called an embryo until about 8 weeks after fertilization, after which it is called a fetus. Before the embryo is identified, the gestational sac is the only available intrauterine structure that can be used to determine if an intrauterine pregnancy exists.^[318,333] Using ultrasonography, the gestational sac can be visualized as early as 4.5 weeks. The growth of the gestational sac during embryonic life is given in table 28 of the SDC. The volume growth during the first month of pregnancy is very slow and becomes faster during the third month of

gestation. During 8–12 gestational weeks, water constitutes 92% of the wet weight.^[155]

The mean \pm SD (CV) gestational sac volume (GSV) [mL] is about 14 ± 13 (90%), 38 ± 25 (66%), 102 ± 43 (%) and 144 ± 27 (19%) at 6, 8, 10 and 13.5 weeks of pregnancy, respectively. The variability is higher at lower sac volumes, most probably due to the limitations of the methodology. Based on these data, the GSV can be described by equation 41:

$$\text{GSV (mL)} = 0.0 + 3.9351 \text{ GA} - 2.373 \text{ GA}^2 + 0.4176 \text{ GA}^3 - 0.0152 \text{ GA}^4 \quad \text{with } R^2 = 0.927 \quad (\text{Eq. 41})$$

A plot of GSV at different gestational weeks is given in the SDC.

At term the mean fetal density, determined by air displacement, is about 1.030 ± 0.030 g/mL.^[334] The fetal density is not a static measurement and varies during the gestational age as the body composition changes with factors such as fetal fat, water, muscles and bone contents.^[335] Since these covariates were not reported in each study, and because no single number can be used throughout the gestational time, a value of 1 g/mL was assumed here to get the volume from the weight in this paper.

Collected data for fetal growth are given in table 29 of the SDC. Meta-analysis of these data sets showed that the fetus grows significantly during the second and third trimester. The mean \pm SD (CV) fetal volume (mL) increases from 0.5 ± 0.14 (28%) to 9.4 ± 2.9 (31%), 76 ± 25 (33%), 292 ± 70 (24%), 728 ± 176 (24%), 1513 ± 291 (19%), 2547 ± 439 (17%) and 3439 ± 439 (13%) at 6, 10, 16, 20, 25, 30, 35 and 40 weeks of conception, respectively.

The use of polynomial equations did not describe the data well. The sixth-order polynomial equation performed well from the 7th to 25th week of gestation, but not on both ends. The fifth-order polynomial equation predicted quite well from the 26th week to term, but its prediction during the early growth was worse (2-fold overprediction at the 12th week and more than 20-fold underprediction in the negative field). The fourth-order polynomial equation massively overpredicted fetal volume during the first trimester.

Gompertz and logistic functions were checked for their appropriateness as they have been widely cited and used to describe fetal growth.^[25,336,337] Gompertz function was reported to be superior to both polynomial and logistic functions to describe human fetal growth data.^[337] These functions were considered here and their parameters were solved using the Microsoft Excel® Solver 2007 to solve its parameters. The Gompertz function gave the best fit among these functions (figure 5); while the logistic function showed good description of the data from 18th week of gestation to term, it failed to describe the early growth during the first trimester. Actually,

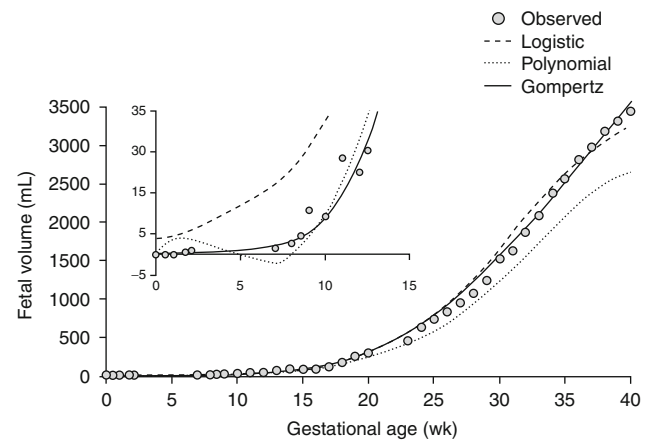


Fig 5. Fetal volume growth during pregnancy: performance of different functions vs actual data. The inset graph represents the expanded view of the first trimester values.

more accurate description and interpretation of this data requires fitting a model that takes into account variables such as fetal sex, maternal parity, height, weight, gestational age and other sources of variability, mainly intra-individual and inter-studies variability terms. The impacts of such covariates on fetal weight have been reported during pregnancy.^[156,157,338-340]

For the current description, the Gompertz equation (equation 42) can be used to describe the longitudinal increase of fetal volume during pregnancy.

$$\text{Fetal volume (mL)} = 0.01 \exp \left\{ \left(\frac{0.955}{0.0702} \right) (1 - \exp(-0.0702 \text{ GA})) \right\} \quad (\text{Eq. 42})$$

A plot of mean fetal volumes with SDs at different gestational weeks is given in the SDC.

Placenta

A major role of the placenta is to transmit nutrient substances to the fetus, thereby providing essential regulation of fetal metabolism and growth. In addition to its nutritional function, it has an endocrine function as it becomes the main source of progesterone during the second and third trimesters^[316] and regulates fetal exposure to maternal intake of xenobiotics via an anatomical and physiological barrier, the ‘blood-placenta barrier’. This barrier consists of a single layer of syncytiotrophoblasts and fetal capillary endothelium,^[341-343] both of which express a wide range of proteins, mainly transporters and metabolizing enzymes, that determine the level of fetal exposure to maternal intake.^[344-349]

Typically, the placenta has a discoid shape. It can be identified as early as 6 weeks gestation by transvaginal evaluation and by 10 weeks gestation by transabdominal evaluation as

a rim around the gestational sac.^[350] The average placenta volume/weight ratio is 1.048 ± 0.006 mL/g determined by the water displacement method in 30 normal placentas.^[171] Of its total wet weight, a human placenta at term contains about $84.6 \pm 1.3\%$ water ($n = 54$), $12 \pm 0.88\%$ protein ($n = 54$), $1.3 \pm 0.32\%$ collagen ($n = 16$), $1.0 \pm 0.4\%$ ash ($n = 16$) and $0.4 \pm 0.07\%$ lipid ($n = 12$).^[351] In 46 normal term placentas, the specific gravity was found to be 0.995.^[352] Decomposition of a typical wet placenta of 658 g at term is 200 g cord, membranes and drainable blood, 320 g water, 100 g trapped blood, 13 g inert protein, 22 g metabolic protein and 3 g non-protein solids.^[353]

The volume of the placenta is continuously increasing during pregnancy, with considerable variability.^[171,172] At birth the cord and both the cord and membrane constitute about 5% and 16.3% of the total untrimmed placental weight, respectively^[354] and receive about 33% of the total fetoplacental blood circuit.^[355] Reported placenta size for intrauterine growth-restricted, large and small for gestational age fetuses were excluded here. Therefore, placental weight reported for normal and appropriate for gestational age fetuses was included in this study. These data are shown in table 30 of the SDC.

Data analysis showed that the volume of the placenta (mL) increases during pregnancy with a mean value \pm SD (CV) of 134 ± 58 (44%), 254 ± 62 (24%), 460 ± 173 (38%), 593 ± 90 (15%) and 659 ± 103 (16%) at 14, 20, 30, 36 and 40 weeks of conception, respectively. Equation 43 can be used to describe the longitudinal increase of placenta volume during pregnancy:

$$\text{Placenta volume (mL)} = 0.0 - 0.716 \text{ GA} + 0.9149 \text{ GA}^2 - 0.0122 \text{ GA}^3 \quad \text{with } R^2 = 0.9952 \quad (\text{Eq. 43})$$

A plot of placenta volume at different gestational weeks is given in the SDC.

Amniotic Fluid Volume

Amniotic fluid volume during pregnancy is a dynamic process. In early gestation, the amniotic fluid is likely formed by active transport by the amnion into the amniotic space and water is allowed to flow passively.^[356] Fetal urine contributes to the volume of amniotic fluid from 11 weeks of gestation^[158,159,357] and becomes the major source of amniotic fluid production in the second half of the pregnancy. The fetal urine production rates were found to be about 7.5, 22.2, 56.1 and 125.1 mL/h at 25, 30, 35 and 40 gestational weeks, respectively.^[358] Fetal secretion from the lungs and from the oral-nasal cavity contributes to the overall amniotic fluid volume.^[356] On the other hand, fetal swallowing plays a part in the elimination of amnii as early as 11 weeks gestation and becomes the major source of elimination at the second half of gestation^[356,359] as it is prob-

ably not transferred across the skin in a significant amount in the third trimester.^[159]

The specific gravity of amniotic fluid removed at 14 weeks' gestation was determined to be 1.007.^[160] The composition of amniotic fluid is similar to that of the fetal extracellular fluid before 20 weeks of gestation and its volume is closely related to the fetal weight. After 20–22 weeks of gestation fetal skin becomes keratinized and offers no impediment to the movement of fluid.^[159]

Earlier studies that measured amniotic fluid volume in the first half of gestation have been made directly on the contents of the amniotic sac after therapeutic hysterotomy or hysterectomy.^[180,181] During the second half of gestation or in pregnancies intended to be continued, a dye dilution method was used instead of a direct method.^[360] More recently the volume of amniotic fluid has been measured by ultrasonography. Ultrasound evaluation of amniotic fluid volume can never represent a true 'quantitative' method and its actual reliability has not consistently been proved by scientific evidence.^[361]

Collected studies reporting amniotic fluid volumes from normal outcomes are summarized in table 31 of the SDC. Unfortunately, only limited data could be found between 21 and 33 weeks of gestation. Analysis of the collected data showed that the mean \pm SD (CV) amniotic fluid volume (mL) increases from 41 ± 15 (36%) to 200 ± 64 (32%), 359 ± 106 (30%), 823 ± 264 (32%) and 758 ± 132 (18%) at 9, 15, 20, 34 and 40 weeks of gestation, respectively. Equation 44 can be used to describe the longitudinal increase of amniotic fluid (AF) volume during pregnancy:

$$\text{AF volume (mL)} = 0 + 1.9648 \text{ GA} - 1.2056 \text{ GA}^2 + 0.2064 \text{ GA}^3 - 0.0061 \text{ GA}^4 + 0.00005 \text{ GA}^5 \quad \text{with } R^2 = 0.9823 \quad (\text{Eq. 44})$$

A plot of amniotic fluid volume at different gestational weeks is given in the SDC.

Discussion

The PBPK models offer a systematic approach to assessing the exposure of pregnant women to various xenobiotics in the different stages of pregnancy and to discern potential differences compared with non-pregnant women. However, such models require substantial data gathering related to the system (human body) to be combined with compound-related information on the drug or xenobiotic prior to PBPK modeling being conducted. To our knowledge, no unique source is currently available to offer the data required for PBPK models during pregnancy and this shortcoming may lead to unnecessary repetition of the data gathering exercise.

Moreover, research reports describing the longitudinal changes of relevant parameters are limited.

This report summarizes available data in peer-reviewed literature for many physiological changes in healthy, predominantly Caucasian, pregnant populations in terms of how they change from preconception or early pregnancy to the end of pregnancy. This database can be analysed to derive many parameters (point estimates and distributions), which are required to develop deterministic or probabilistic PBPK models for this population. The developed PBPK models can then be used for pharmacological and toxicological studies, including the dose (exposure)-response relationship, dose adjustment and risk assessment. Moreover, a robust PBPK model based on correlated Monte Carlo simulation can be built when appropriate relationships between the various parameters are established using relevant statistical tools.

The starting point for gathering systems data for PBPK would be the body size and its composition. Measurement of changes in body composition during pregnancy is confounding mainly due to the lack of appropriate baseline data and methodology. Body composition can change as early as in the first trimester^[35,37,52,319] and 'baseline' measurements obtained at the postpartum period or early in pregnancy may not represent the pre-pregnancy composition.^[35,36,48] Most commonly, methods used to quantify the changes in pregnant body composition are based on different assumptions. For example, the two-component model in body composition methods^[202,362] assumes that the densities of fat mass and FFM are constant during pregnancy and known (i.e. FFM is composed of 73% water, 20% protein and 7% bone mineral).^[363] This model was modified by van Raaij et al.,^[202] based on the average changes in density and composition of the FFM during pregnancy. Studies that compared two-, three- and four-component models of estimating body fat mass during pregnancy^[48,364] found that two-component models varied from underestimating fat mass by 9% to overestimating fat mass by 22% compared with the four-component model. Three-component models provided much more accurate fat mass values, within 1% of the four-component model. The accuracy of these methods is still questionable and more valid methods of quantifying fat mass in individual women during pregnancy are needed.

An additional hurdle to gathering data observed during the study was the fact that many studies performed their analysis after pooling the data into three trimesters, at monthly or 10-weekly intervals. Selection of such intervals can introduce much distortion of the results. For instance, it can mask a peak, if any, of a parameter within the studied intervals that occurs at a given gestational point in another publication. In many pa-

pers, authors reported only the mean value of the parameter of interest without mentioning the variability around it. On the other hand, many studies reported the results in terms of graphical figures and extracting the data from these may lead to technical errors.

Despite all the difficulties described above, the current level of data collection seems sufficient as a starting point for building pregnancy PBPK models encompassing longitudinal changes of physiological and biological values with gestational age. These applications surely require verification for their performance against field data (clinical observation on pharmaceutical drugs or opportunistic data on environmental chemicals). Such models have to be viewed as live models that are built on a flexible framework that allows new data to be incorporated as it becomes available. Based on the current study, there are a number of areas where data are lacking; in most cases due to clinical or ethical reasons and lack of appropriate methodology. This is particularly marked in parameters, which are related to early fetal growth, regional distribution of maternal cardiac output to different tissues and tissue composition (neutral lipid, phospholipids and protein levels), and are necessary for estimating volume of distribution and xenobiotic partition coefficients. In addition, less is known about regional distribution of blood flow to both maternal and fetal organs during gestation. Although there is some information regarding the direction of change in the activity of many metabolizing enzymes during pregnancy, the magnitude of these changes is not well described. For those enzymes whose activities were described, most of these data were uncorrected for the impact of other factors such as the change in protein binding and renal function.

We also identified sets of sparse data that come from cross-sectional studies and at a particular gestational age, where the cross-validation of methodology between different approaches is questionable. Application of non-linear mixed effect analysis to such a set by accounting for different sources of variability is warranted. In addition to previous limitations, extrapolation of experimental methods from a pre-pregnant to a pregnant population needs to be re-assessed.

It is clear that for many parameters there are limited existing data, such as activity of metabolizing enzymes, uterine mass, and blood flow to the mammary glands and liver during pregnancy. The current evaluation of these data was carried out based on the collected data presented in the SDC tables. Thus, the provided mean and variability values for poorly described parameters may not represent the actual mean or variability in the real situation. Collected data determined the sort/order of the derived equations and their coefficients. However, the current

paper provides up-to-date data and reveals gaps in existing knowledge, identifying areas where further research is required.

At the moment, pregnant women are excluded during clinical studies and most published results stem from retrospective reports. Unfortunately, longitudinal studies, where the same subject acts as a control and a test subject, are very limited in their purpose and sample size. We aimed to provide a comprehensive database for a Caucasian pregnant population. The equations derived were descriptive in terms of how their parameters change during pregnancy. In order to develop a mechanistic model, multivariate analysis of pregnant covariates, means and distribution should be carried out and the results integrated with the model parameters. Such analysis is required to achieve biological plausibility of the relationship between physiological parameters, which is not the scope of the current paper.

This paper also shows the need to understand the molecular mechanisms that underlie the temporal, physiological, and anatomical and biochemical adaptations occurring during pregnancy. In addition to the divergent methodologies that have been used, the nature of the underlying signalling molecules, how these molecular mechanisms and signals interact, in what ways these changes are influenced by individual and population factors, and whether the adaptations observed during first pregnancy are memorized and affect subsequent pregnancies can be identified as a hot topics for further investigation. When we understand how these molecular changes can affect drug pharmacokinetics more clearly, we will be able to build more mechanistic pregnancy PBPK models and improve their predictive capabilities.

Conclusion

The changes in kinetics of xenobiotics or drugs during pregnancy might stem from a highly complex myriad of factors that influence various compounds in different ways. However, capturing variations in the system parameters, which include alterations in body composition, organ functions and biological processes, are a common element in any PBPK model. We have provided a repository of such information and have shown that various elements of system parameters relevant to PBPK in pregnancy follow different temporal trajectories of change with gestational age. The interaction between these temporal changes during gestation and specific properties of the exogenous compounds results in time-dependent differences in kinetics and, consequently, dynamics of effects that these compounds may exert; with implications for the susceptibility of pregnant women to the effects of these compounds.

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Correspondence: Dr *Khaled Abduljalil*, Simcyp Limited, Blades Enterprise Centre, John Street, Sheffield, S2 4SU, UK.
E-mail: k.abduljalil@simcyp.com