Session 2: Modeling Pregnancy Pharmacokinetics

Industry perspective on role of PBPK modeling in pregnancy

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Healthy Mum, Healthy Baby, Healthy Future

The Case for UK Leadership in the Development of Safe, Effective and Accessible Medicines for Use in Pregnancy

May 2022

6. Increasing investment in pregnancy research

Reproduction and childbirth is a ‘blindspot’ area of research. It receives neither the funding, attention, nor status that other areas of science and health research garner. Though the area directly affects up to 51% of the population – it is the entire population, since we are a product of reproduction – only 2.1% of health research funding in the UK is spent on reproductive health and childbirth.

The UK spends about £21 million a year on pregnancy research, a small fraction of which is relevant to medicines use in pregnancy. For every £1 spent on pregnancy care in the NHS, only 10p is spent on research. For comparison, pregnancy-related litigation costs to the NHS in 2018-20 was £2.7 billion, making up approximately 49% of the total cost of clinical negligence claims.

Pregnancy-related litigation costs to the NHS in 2018-20: £2.7 billion

This paucity of investment – and subsequent paucity of pregnancy R&D – has witnessed a ‘ticking time bomb’. One estimate stated that the UK remains a 19th century leadership in the field, where other areas of health sciences have flourished. This is cut through every stage from basic biology in preclinical medicine screening, and translation into novel therapies and other medicines which could save lives and relieve suffering for many mothers and babies.

Despite remarkable scientific advances in our understanding of human health and disease in other areas, we know little in comparison about basic human reproductive biology – the early embryos. How medicines affect the workings of the placenta; how medicines cross the placenta from mother to child; the function of medicines by the fetus, and much of the basic physiology of pregnancy is still poorly understood. Improved understanding of this science is reproductive health and epidemiology is vital. Many of the issues in pregnancy are laid down at the earliest stages – in the first 10 weeks of gestation – so learning the science of the early stage may be particularly crucial.

Understanding these basics better would help us as an earlier stage in the process of designing and developing medicines for use in pregnancy. For example, it could show us that a new medicine does not cross the placenta at all, this would provide some reassurance for testing that specific drug is a clinical trial with pregnant women.

Better pre-clinical trials would lead to a more secure and more certain knowledge base before medicines go into clinical trials with pregnant women. This would mean potentially that medicines likely to be harmful in pregnancy would be screened out earlier. Good in vitro, in vivo and in silico models are needed to screen drug candidates and test the potential effectiveness of medicines given to pregnant, the human clinical challenge.

However, our lack of basic research knowledge and the unique nature of human pregnancy have been barriers.

There are no good animal models to test medicines candidates in pregnancy. These candidate is used and have different physiological systems from humans, and do not naturally develop the pregnancy complications preclinical models, for example.

Recent advances bring some hope in the field. A human placental cell line has successfully developed by Japanese researchers in 2016 and 2018. And technological improvements in areas such as virtual clinical studies, tissue engineering, metabolomics and organoids (miniature versions of the fetus) means that we may see effective placenta-on-a-chip models in the next three to five years. The UK could pioneer these technologies, and it must accelerate pregnancy medicines research faster – provided research investment was prioritised.

The Commission also heard from different sectors that the low scale and funding of reproductive science creates difficulties in attracting and retaining researchers. This work, young scientists are best in higher profile and better-resourced areas such as cancer. This is also a challenge on the clinical side of research and care – there are too many to obstetric physicians in the entire UK, highly resourced in London and Greater.

Together, the Commission was convinced of the need for stronger national research in pregnancy research; to address funding issues across the field; to secure long-term solutions to clinical trials and evaluate studies and to make the sector more attractive to recruits and retain selected researchers. There was also a compelling rationale to develop better and more efficient pre-clinical screening tools and processes that protect medicines. Providing clear local policies or public and patient involvement as factor for a safer UK clinical research, well treated and wider global benefit and innovation, will be crucial in accelerating progress.

RECOMMENDATIONS

1. Deliver effective advocacy for medicines in pregnancy through a coalition of pregnancy and baby charities, working together with the public, researchers from academia and industry as well as Government to create a shared vision for safe medicines evaluation and development in pregnancy. This will allow for clear and consistent messages to the public and clinicians.

2. Pregnant women should be offered the opportunity to take part in all clinical trials of medicines that could be used in pregnancy, unless there is specific safety concern.

3. Prioritise updates for existing medicines with the potential to be used in pregnancy, with regulations and industry working towards pregnancy-specific information on safety, dosing and effectiveness. Resources should be put in place to maintain the activity, particularly for generic medicines.

4. De-risk insurance processes for early and late phase clinical trials of new and existing medicines for use in pregnancy, using carriers and insurers from other challenges.

5. Incentivise industry to develop pregnancy-specific medicines, utilising cross-sectoral working to ensure that the UK is in a globally-competitive – and globally-competitive – position to drive drug development for pregnancy-specific conditions.

6. Establish a UK-wide national network of research centres encouraging major public and private investment and collaboration in pregnancy research expertise and infrastructure. This will ensure sustainable drug development from discovery science through to pre-clinical screening tools and clinical evaluation.

7. Improve use of routine clinical care maternity data to help assess the safety and effectiveness of new existing medicines used in pregnancy. Establish a dedicated maternity health data Research Data Hub through Health Data Research UK with a focus on medicines evaluation in pregnancy.

8. Assist a UK Steering Committee aligned to the Government’s Women’s Health Strategy to deliver the above recommendations, with oversight of implementation, ensuring milestones are set and monitored.

We basically do not understand enough about the physiology of normal pregnancy and certainly about pregnancy complications, in order to know what we should be targeting.

Professor Graham Burton, University of Cambridge
Gestational stage and terms of pregnancy (consider both pregnant and unborn)

The gestational stage as defined per U.S. Department of Health and Human Services (HHS) recommendations:

- 1-12 weeks for the 1st trimester,
- 13-28 weeks for the 2nd trimester
- 29-40 weeks for the 3rd trimester

What Does It Mean to Have a Full-Term Pregnancy? (verywellfamily.com)
Physiologically Based Pharmacokinetic Modelling (PBPK)

- Integrate physiological, biochemical and physical chemical information
- Estimate kinetics in a target tissue or organ (effect compartment)
- Evaluate the effect of various intrinsic (age, race, gender, disease, etc.) and extrinsic (DDI, environment, smoking, etc.) factors on drug exposure and response
- Model variability and uncertainty

User friendly software,
- SimCYP
- PK-Sim
- SimulationPlus

Learn, Confirm, Predict Approach!
Precision dosing of methadone during pregnancy: A pharmacokinetics virtual clinical trials study

Raj K S Badhan 1, Rosalind Gittings 2

Affiliations + expand

PMID: 34118985 DOI: 10.1016/j.jsat.2021.108521

Found 1 result for pkbk pregnancy

Pharmacometrics in pregnancy: An unmet need.
Ke AB, Rostami-Hodjegan A, Zhao P, Unadkat JD.
PMID: 24392692 Review.

Model-Informed Dose Optimization in Pregnancy.
Chaphekar N, Canitis S, Venkataramanan R.
PMID: 33205432 Review.

Physiologically Based Pharmacokinetics Model in Pregnancy: A Regulatory Perspective on Model Evaluation.
Coppola P, Kerwash E, Cole S.
Infection, pregnancy related etc, n=35 for ongoing, recruiting and completed
Integrating knowledge in PBPK to EXTRAPOLATE!

Intrinsic Factors
- Hepatic Impairment
- Renal Impairment
- Pregnancy
- Pediatrics
- Bariatric Surgery & Obesity
- Ethnicity & Genetics
- Cancer
- Chinese

Extrinsic Factors
- Smoking
- Alcohol
- Diet
- Drug-drug Interactions
- Generic
- Adipose
- Bone
- Brain
- Heart
- Kidney
- Muscle
- Skin
- Liver
- Spleen
- Pancreas
- Gut
- Portal Vein
- EHC
- IV Dose
- PO Dose

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Pharmacotherapy during pregnancy/Lactation - status

• Total avoidance of pharmacological treatments is often not feasible during pregnancy.
  o Pregnancy-related conditions (hypertension, gestational diabetes)
  o breastfeeding-related conditions (mastitis, cracks, lesions)
  o Chronic conditions (e.g., asthma, allergy, epilepsy, depression, HIV/infections)

• Fixed non-pregnant dose does not provide the required efficacy.

• Knowledge of proper dosing is required to prevent poor disease control, fetal/neonatal outcomes and teratogenic effects, ..., etc.

• Many drug labels advise not to take many drugs during pregnancy due to the absence of reliable safety data (~ 25% prescribed drugs use during pregnancy are off label and based on safety data from non-pregnant subjects).

• Pregnancy/Lactation studies have been performed in the post-marketing settings
  \[ \rightarrow \] delays in drugs availability to pregnant/breastfeeding women
Regulatory considerations

Guidance for Industry
Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling

Postapproval
Pregnancy Safety
Studies
Guidance for Industry

Clinical Lactation
Studies: Considerations
for Study Design
Guidance for Industry

Pregnant Women:
Scientific and Ethical
Considerations for
Inclusion in Clinical Trials
Guidance for Industry

Regulatory Considerations for the
Mother, Fetus and Neonate in Fetal
Pharmacology Modeling

Physiologically Based
Pharmacokinetics Model in
Pregnancy: A Regulatory Perspective
on Model Evaluation

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Challenges in Pregnancy PK/PD Clinical Trial Design

**Physiological Variability**
- Change in enzyme/transporters with gestational age
- Return to baseline
- Growth of the feto-placental unit
- Body size metrics

**Enrolment Difficulties**
- Usually enrolling ill (target population) pregnancy (HV is unethical unless for vaccine trial)
- Rare disorders: getting enough patients enrolled to satisfy statistical requirements

**Choice of Pharmacodynamic Endpoints**
- Sensitive, robust, and clinically relevant biomarkers validated in non-pregnant male adult male subjects can be different in women during perinatal period
- Non-invasive biomarkers only

**Challenges in Determining Dosing Regimen**
- Traditional extrapolation from adult? Use WT, BSA or ...?

**Sparse Sampling vs. Intensive Sampling**
- Often sparse sampling in pregnancy clinical studies

**Safety monitoring**
Only in the duration of the pregnancy
Table 1 shows the average gestation length, number of fetuses, maternal weight, neonate weight and the placental barrier type in human and relevant species.

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Gestation length (days)</th>
<th>Number of fetuses</th>
<th>Maternal pre-pregnancy weight (kg)</th>
<th>Neonate weight (g)</th>
<th>Placenta barrier type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>266</td>
<td>1</td>
<td>5900</td>
<td>3183</td>
<td>Hemimonochorial villous</td>
</tr>
<tr>
<td><em>Homo sapiens</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>20</td>
<td>5-6</td>
<td>19</td>
<td>1</td>
<td>Hemochorial</td>
</tr>
<tr>
<td><em>Mus musculus</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>22</td>
<td>9</td>
<td>283</td>
<td>6</td>
<td>Hemochorial</td>
</tr>
<tr>
<td><em>Rattus norvegicus</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea pig</td>
<td>67</td>
<td>3-4</td>
<td>728</td>
<td>80</td>
<td>Hemimonochorial labyrinth</td>
</tr>
<tr>
<td>Cavia porcellus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinchilla</td>
<td>113</td>
<td>1-2</td>
<td>480</td>
<td>40</td>
<td>Hemimonochorial labyrinth</td>
</tr>
<tr>
<td><em>Chinchilla lanigera</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>30</td>
<td>5</td>
<td>1591</td>
<td>39</td>
<td>Hemidochorial labyrinth</td>
</tr>
<tr>
<td>Oryctolagus cuniculus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>153</td>
<td>1-2</td>
<td>39.100</td>
<td>2376</td>
<td>Epitheliochorial</td>
</tr>
<tr>
<td><em>Ovis aries</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>115</td>
<td>5-14</td>
<td>84.000</td>
<td>400-1900</td>
<td>Epitheliochorial</td>
</tr>
</tbody>
</table>

Data are acquired from the PanTheria database [22].

*Dependent of the breed of pig (domestic pig or mini-pig) [22].
The role of physiologically-based pharmacokinetic (PBPK) models

- PBPK models combined drug-related data with pregnancy-related physiological changes.
- Impact of inter-individual variability (genotypes, demographics, enzyme activity) of subjects can be addressed.
- PBPK model have been applied recently to*
  - predict maternal and umbilical drug levels
  - evaluate the requirement of dose adjustment or proposing new dosing regimen during pregnancy

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Pregnancy PBPK application</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>proposing a dosing regimens for prevention of Zika Virus disease</td>
<td>Olafuyi &amp; Badhan 2019</td>
</tr>
<tr>
<td>Darunavir (+ ritonavir)</td>
<td>Dosing optimisation strategy based on predicted umbilical vein concentration</td>
<td>Schalkwijk et al., 2018</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>CYP2D6 Genotype-based dose optimization</td>
<td>Almurjan et al., 2020</td>
</tr>
<tr>
<td>Piperaquine</td>
<td>Assess the impact of efavirenz or ritonavir on piperaquine in distinct customised HIV infected population (Thailand, Sudan &amp; Papua New Guinea)</td>
<td>Olafuyi et al., 2017</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Dosing optimisation strategy</td>
<td>Badhan &amp; Macfarlane 2020</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>CYP2B6 Genotype-based dose optimization</td>
<td>Chetty et al., 2020</td>
</tr>
</tbody>
</table>

Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 enzymes during pregnancy

Khaled Abduljalil1 · Amita Pansari1 · Masoud Jamei1

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✓ Caffeine
✓ Theophylline
✓ Metoprolol,
✓ Propranolol
✓ Paroxetine
✓ Midazolam
✓ Nifedipine
✓ Rilpivirine
Metoprolol PK during Pregnancy (CYP2D6)

Non-pregnant women

Intravenous and oral

Pregnant women

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Metformin is a substrate for several transporters – OCT1, OCT2, MATEs.

Pregnancy ontogeny for OCT2 considered in model
Maternal-Placental-Fetal drug transfer

Maternal circulation

Maternal drug metabolism

Placental transport

Placental metabolism

Umbilical cord/Fetal circulation

Fetal metabolism, renal excretion

Amniotic fluid

Metabolic differences??: For example, thalidomide is a severe teratogen in humans causing phocomelia, but not in rats.


Richardson et al. (2020) Front. Physiol. 11:715.
PBPK model framework

Animal Toxicity
- Dose
- IC\textsubscript{50}
- Cultured animal embryonic cells
- Stem cells, midbrain cells,
- Mesenchyme cells, etc
- Whole embryos culture

Animal fetal tissue exposure

Animal feto-maternal systemic exposure

Toxicodynamic Model
- % Effect

Predicting Human Fetal toxicity

Human fetal tissue exposure

Human feto-maternal systemic exposure

Human embryonic stem cell

Model application to assess fetal exposure: vital for safety assessment

Application of a Physiologically Based Pharmacokinetic Approach to Predict Theophylline Pharmacokinetics Using Virtual Non-Pregnant, Pregnant, Fetal, Breast-Feeding, and Neonatal Populations

Khaled Abdulkarim, Iain Gardner, and Masoud Zeinali

FIGURE 1 | Workflow of the implemented perinatal theophylline physiological-based pharmacokinetic (PBPK) model. The neonatal model includes caffeine PBPK as a formed metabolite.

https://www.frontiersin.org/articles/10.3389/fped.2022.840710/full?utm_source=Email_to_authors&utm_medium=Email&utm_content=T1.115e1_author&utm_campaign=Email_publication&field=journalName=Frontiers_in_Pediatrics&id=840710
Non-pregnancy calibration

FIGURE 2 | Plasma concentration profiles after intravenous infusion and oral administration in the non-pregnant population. Solid lines, predicted means; Dashed lines, 5th and 95th centiles. Circles, observed means. (A) Trial design NPI (31), (B) Trial design NPI (10), (C) Trial design NPI (21), (D) Trial design NPI (33), (E) Trial design NPI (31), (F) Trial design NPI (31), (G) Trial design NPI (33), (H) Trial design NPI (10), and (I-L) Trial design NPI (33). See the Methods section for trial settings.
Simulation

**FIGURE 5.** Theophylline concentration profiles after multiple oral administration in pregnant population during pregnancy and at delivery. Solid lines, predicted means; dashed lines, 5th and 95th percentiles; circles, individual observations (open, maternal; black, artificial cord). This representation is for illustrating trials: (A) Trial design 1 ([41],[43]), (B) Trial design 2 ([41],[43]), (C) Trial design 3 ([41],[43]). Note: additional points are used for comparison (two-bolus randomization). (C1, C2) Trial design 1 ([41],[43]). (C3) Trial design 1 ([41],[43]). (C4) Trial design 1 ([41],[43]). See the Method section for trial settings.
Design evaluations

FIGURE 1: Theophylline (left) and caffeine (right) concentration profiles in various studies with scrambled (A-C) and clear (D-F) administration of theophylline. Solid lines, predicted means; dashed lines. On each graph, closed circles, individual observations; closed circles, mean; lines, computer-simulated observations in (B) normal computer user; and mean, (C) 135% computer user; (D) open computer user (H); (F) design NT (1); (E) design NT (7); (G) design NT (17); (H) design NT (21); (I) design NT (25); (J) design NT (26); (K) design NT (27); (L) design NT (28). See the Method section for the settings.

FIGURE 2: Predicted mean (95%–90% percentile) theophylline (left) and caffeine (right) concentration profiles during the first 2 weeks of life with different gastrointestinal weeks. Top, left: mean; middle: observed; bottom: simulated. The first three plots show, respectively, theophylline exposure in neonates with a dosage of 20 mg/m² of 3 mg/kg as a leading dose followed by 1.5 mg/kg per day. The second three plots show, respectively, theophylline exposure in neonates with a dosage of 20 mg/m² of 3 mg/kg as a leading dose followed by 1.5 mg/kg per day. The third three plots show, respectively, theophylline exposure in neonates with a dosage of 20 mg/m² of 3 mg/kg as a leading dose followed by 1.5 mg/kg per day.
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