MHRA perspective on pregnancy PBPK models

Paola Coppola, Pharmacokinetics Assessor
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Disclaimer

The views expressed in this presentation are those of the speaker and are not necessarily those of MHRA.
Overview

Use of medicines during pregnancy

Regulatory case study

Pregnancy PBPK MHRA/BMGF project
Use of medicines in pregnant women

Self-reported medicine use in Europe, the Americas, and Australia

- >80% women used at least one medicinal product during pregnancy
- 67% of women used non-prescription or OTC medicinal products
- 17% of women used medicine for chronic conditions

5 prescription medicines licensed in the UK for non-obstetric use in pregnancy

(amoxicillin, labetalol, diazoxidine injection, doxylamine succinate/pyridoxine hydrochloride, sodium feredetate)

Pregnancy PK knowledge

- Effect of medicine on pregnancy outcome?
- Newer medicines not prescribed in pregnancy
- Does the dose need changes?
- Why should pregnant women be enrolled?

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

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

DRAFT GUIDANCE

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY:
NEED FOR POST-AUTHORISATION DATA
PBPK in pregnancy: Regulatory case study

Active substance X

<table>
<thead>
<tr>
<th>Regulatory Application</th>
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<tbody>
<tr>
<td>• Support SmPC changes (sections 4.6, 5.2)</td>
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<td>•</td>
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<table>
<thead>
<tr>
<th>PK</th>
</tr>
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<tbody>
<tr>
<td>• Cytochrome P450 substrate</td>
</tr>
<tr>
<td>• No pregnancy PK data</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Pregnancy</th>
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<tbody>
<tr>
<td>• Expected increase in systemic exposure</td>
</tr>
<tr>
<td>• Pregnancy PBPK to predict exposure</td>
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- Increased exposure predicted in pregnancy
- Model validated in nonpregnant subjects only
- Clinical data needed to validate and qualify the pregnancy model
PBPK Project: Evaluating PBPK modelling and simulation to inform drug dosing in pregnant women

Aim
To improve the knowledge of medicines used during pregnancy, based on changes in systemic exposure, and to evaluate existing PBPK models for their potential to support dosing in pregnant women

- Data collection
- Pregnancy PBPK evaluation
- Training
Collection of pregnancy PK data

Main list
- ~ 200 medicines
- 16 therapeutic areas

Priority list
- 20 medicines
- e.g. Epilepsy, Antiemetics, Pain, Antidepressants, Antibiotics, Antivirals, Antimalarials, Antipsychotics

Based on MHRA Medical Assessors’ experience

Endorsed by the CHM, EAGs and UK experts
Collection of pregnancy PK data

- Pregnancy PK data available < 50% of identified medicines
- Data in all trimesters only for 19 medicines
- Nonpregnant/postpartum not always available
- Unbound exposure not investigated
- Often limited number of subjects
- Only sparse data in some cases
- PopPK and PBPK used in several cases

Data will be published on MHRA website and peer reviewed journals
## Pregnancy PBPK model qualification

<table>
<thead>
<tr>
<th>Main clearance pathway</th>
<th>Number of medicines</th>
</tr>
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<tbody>
<tr>
<td>CYP3A4</td>
<td>3</td>
</tr>
<tr>
<td>CYP3A4 + UGT</td>
<td>1</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>2 (+1 priority)</td>
</tr>
<tr>
<td>Multiple CYPs</td>
<td>2</td>
</tr>
<tr>
<td>Multiple CYPs + UGTs</td>
<td>2</td>
</tr>
<tr>
<td>Renal (passive transport)</td>
<td>1</td>
</tr>
<tr>
<td>Renal (active transport e.g. OCTs, OATs)</td>
<td>4</td>
</tr>
<tr>
<td>Biliary</td>
<td>1</td>
</tr>
</tbody>
</table>
Pregnancy PBPK model

PBPK development/evaluation in nonpregnant subjects (in vitro + clinical PK data)

Model verification (data in nonpregnant subjects)

Does the model adequately account for drug ADME properties?

Evaluation of pregnancy PBPK model - Does the model account for pregnancy changes which may impact ADME?

PBPK may be used to predict PK exposure in pregnancy

NO: Can the pregnancy system model be improved?

The model was then applied to some of the priority medicines.
General considerations

PBPK model evaluation

• Very few compounds with rich literature sets across all trimesters and nonpregnant/postpartum controls (some contradictory)

• Knowledge on the impact of pregnancy on PK needs to be improved

• Available data are insufficient for qualification of high impact regulatory decision

• Promising simulation results for medicines renally excreted (passive transport)
General considerations

PBPK model evaluation

• It may be difficult to build model from scratch

• Model of compounds with complex elimination pathways and/or distribution might be challenging

• Modelling for prodrug may be complex

• CYP2D6 substrates showed biggest changes in exposure during pregnancy, but data are limited

• Data are not available for all relevant pregnancy-related physiological changes, but PBPK providers are working on this
PBPK – Regulatory impact

- High-impact application requiring robust model evaluation
- Dosing based on exposure only is an extrapolation
- Framework could be useful to bridge knowledge gaps to support exposure/E–R investigation - could be informed by PBPK

Requirement for regulatory high impact application

- Use of several compounds with ADME similar to investigational drug (e.g. similar clearance pathway)
- PK data of drugs used to inform PBPK model for all gestational trimesters (age-related pregnancy changes)
- Distribution and elimination should be captured
- If multiple enzymes or transporters are involved, larger qualification data set may be required
MHRA/BMGF Trainings

• Training held on January 2020:
  o Importance to collect PK data in pregnancy and postpartum
  o Introduction on the use of modelling to support PK evaluation in pregnancy
  o Introduction on the MHRA/BMGF project

• Next training planned on 2022
MHRA/BMGF - Project results publication

• Publication on the MHRA perspective on the use of pregnancy PBPK model:

• Results of data collection and PBPK modelling will be published on MHRA website and peer reviewed journals

• Trainings and events will be advertised on MHRA MedRegs
  https://medregs.blog.gov.uk/category/medicines-in-pregnancy/
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