MHRA perspective on pregnancy PBPK models

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Fetal Pharmacology and Therapeutics Workshop, 22nd October 2021

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

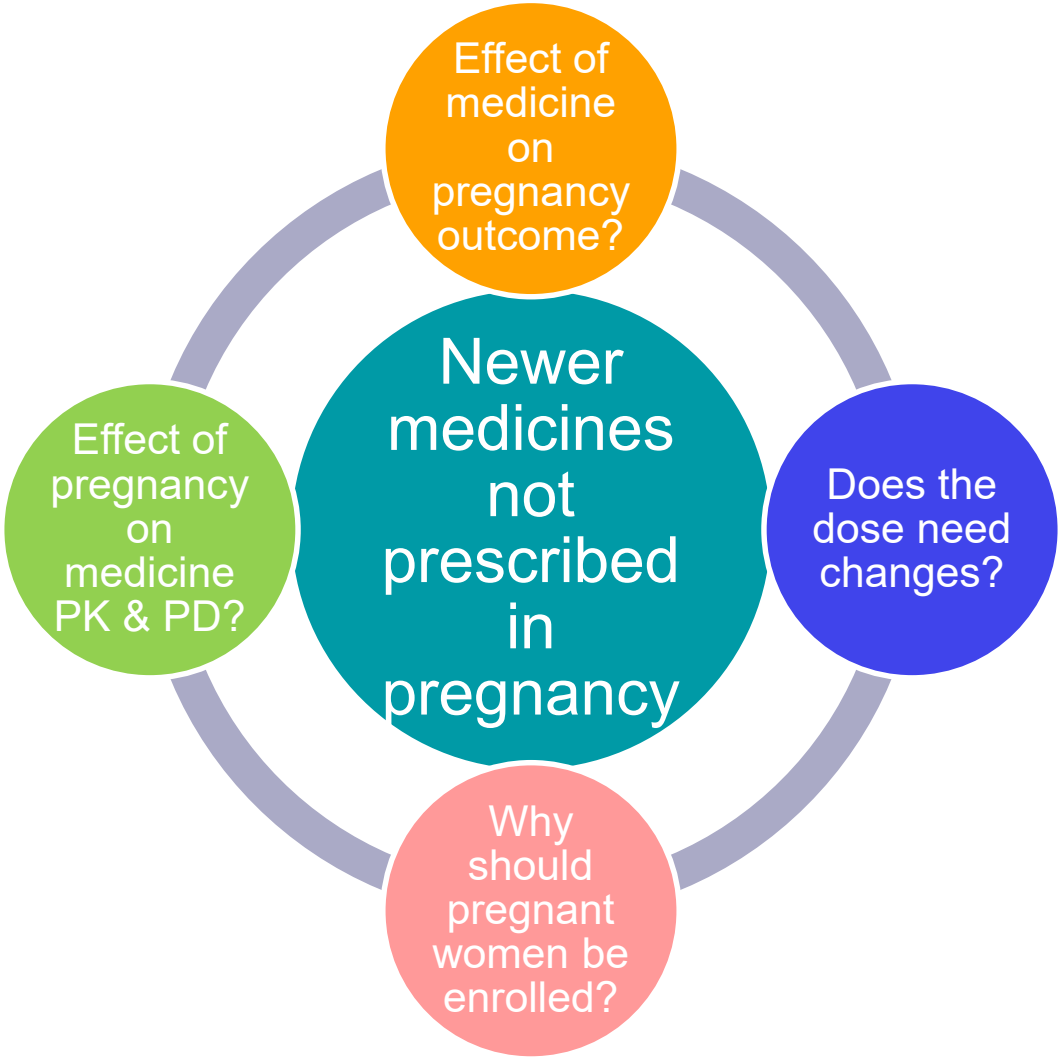
5 prescription medicines licensed in the UK for non-obstetric use in pregnancy

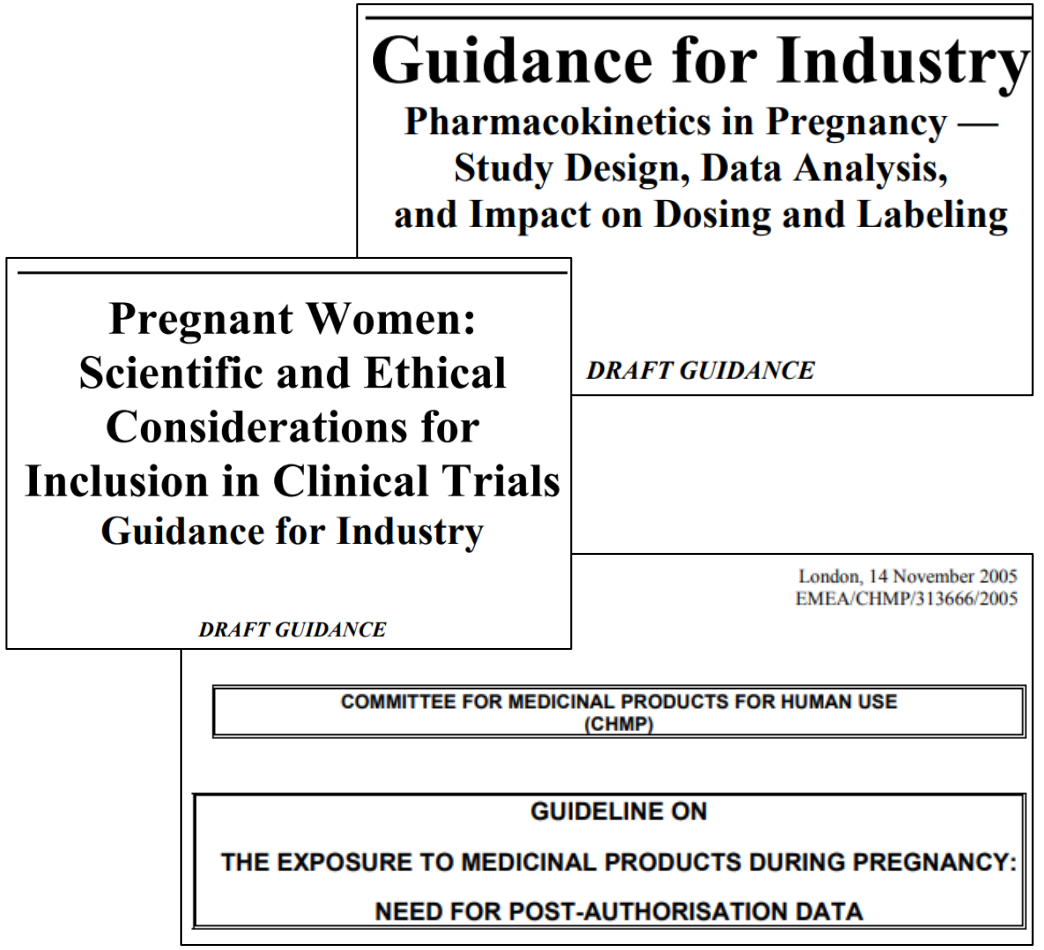
(amoxicillin, labetalol, diazoxidine injection, doxylamine succinate/pyridoxine hydrochloride, sodium feredetate)

Lupattelli et al. BMJ Open. 2014 Feb 17;4(2):e004365. doi: 10.1136/bmjopen-2013-004365

Cole S et al. CPT Pharmacometrics Syst. Pharmacol. 2020. 9: 547-549. doi.org/10.1002/psp4.12551

Pregnancy PK knowledge





Guidance for Industry

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

DRAFT GUIDANCE

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

Guidance for Industry

DRAFT GUIDANCE

London, 14 November 2005
EMEA/CHMP/313666/2005

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

Regulatory Application	PK	Pregnancy
•Support SmPC changes (sections 4.6, 5.2) •	•Cytochrome P450 substrate •No pregnancy PK data	•Expected increase in systemic exposure •Pregnancy PBPK to predict exposure

- Increased exposure predicted in pregnancy
- Model validated in nonpregnant subjects only
- Clinical data needed to validate and qualify the pregnancy model

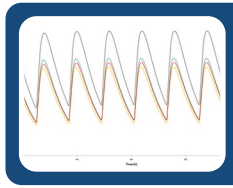
MHRA/BMGF

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

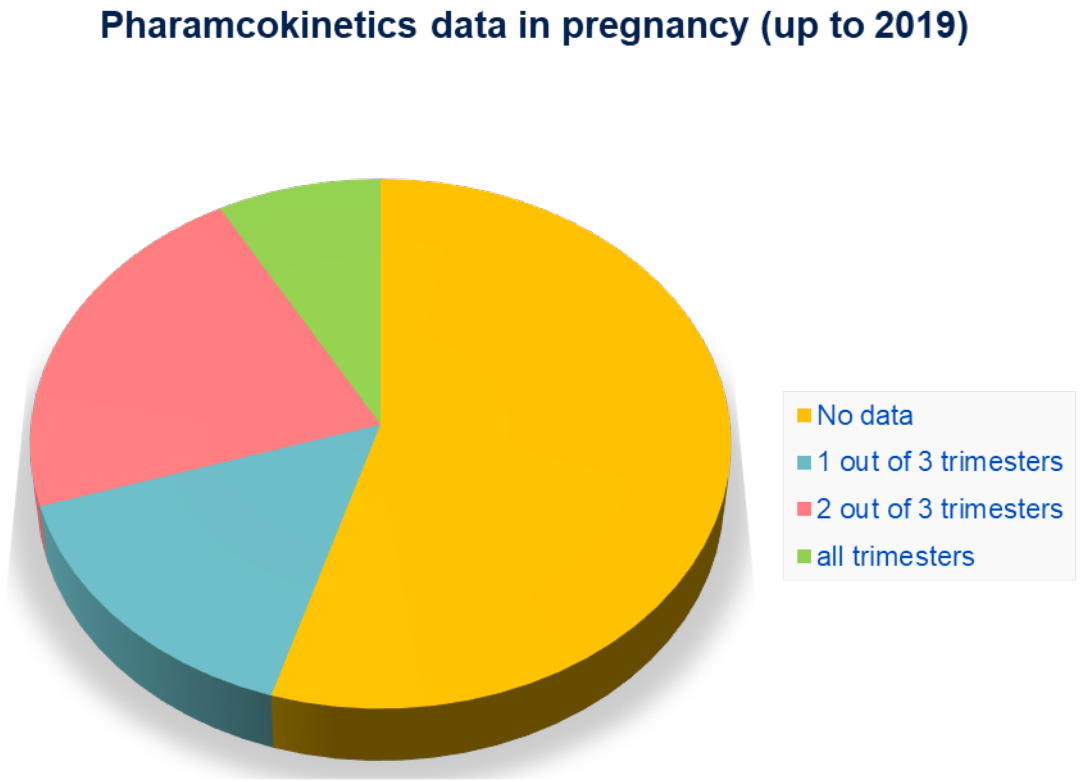
Priority list

- 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

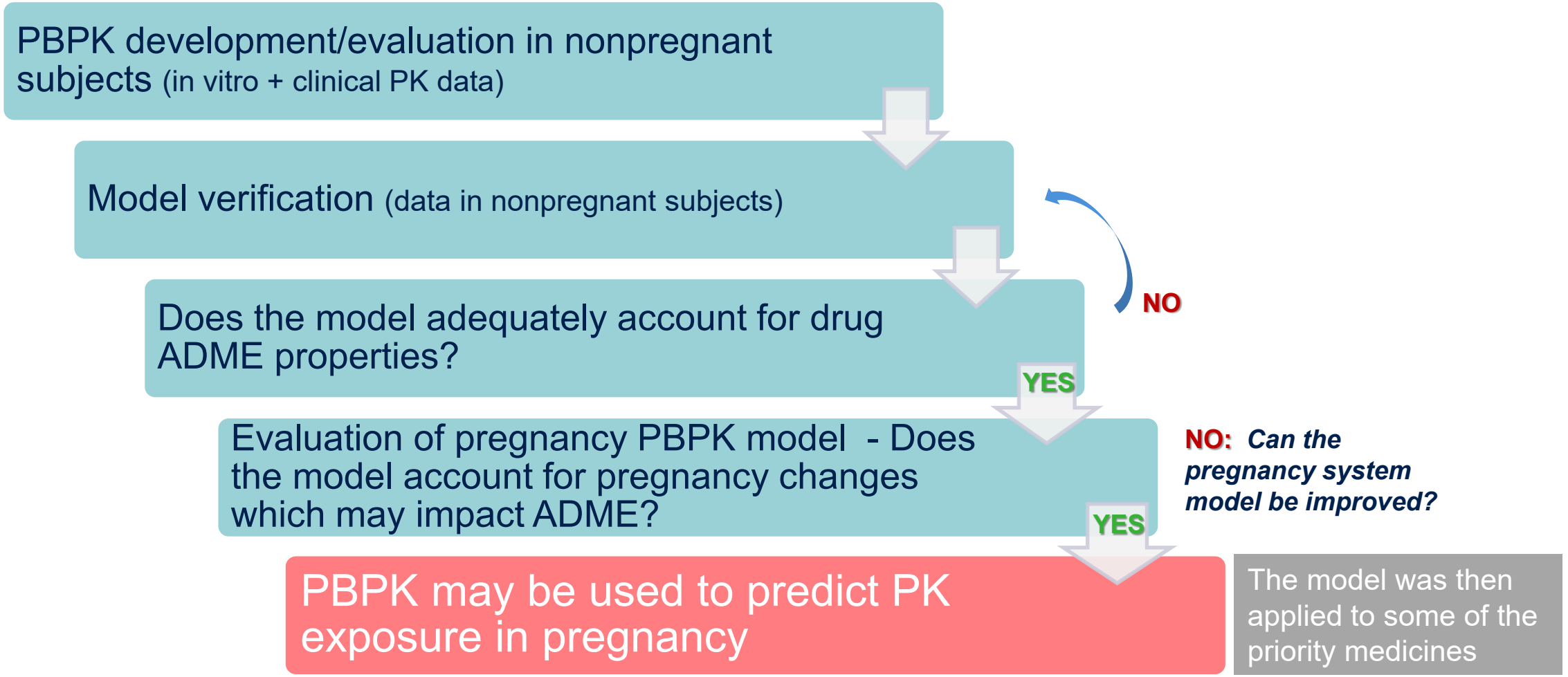


Data will be published on MHRA website and peer reviewed journals

Pregnancy PBPK model qualification

Medicines used for model qualification	
Main clearance pathway	**Number of medicines**
CYP3A4	3
CYP3A4 + UGT	1
CYP2D6	2 (+1 priority)
Multiple CYPs	2
Multiple CYPs + UGTs	2
Renal (passive transport)	1
Renal (active transport e.g. OCTs, OATs)	4
Biliary	1

Pregnancy PBPK model



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:
  - Importance to collect PK data in pregnancy and postpartum
  - Introduction on the use of modelling to support PK evaluation in pregnancy
  - 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:
  - Cole S, Coppola P, Kerwash E et al. Pharmacokinetic Characterization to Enable Medicine Use in Pregnancy, the Potential Role of Physiologically-Based Pharmacokinetic Modeling: A Regulatory Perspective. CPT: PSP. 2020, 1–3; doi:10.1002/psp4.12551
  - Coppola P, Kerwash E, Cole S. Physiologically based pharmacokinetics model in pregnancy. Application to clinical practice, a regulatory perspective. Front. Pediatr. 9:687978. doi: 10.3389/fped.2021.687978
- 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/

Acknowledgments

Susan Cole, Pharmacokinetics Group Lead, MHRA

Essam Kerwash, Senior Pharmacokinetics Assessor, MHRA

Janet Nooney, Expert Scientific Assessor, MHRA

Swati Bhat, Senior Medical Assessor, MHRA

Medical Assessors at MHRA

Ping Zhao, Bill & Melinda Gates Foundation

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Thank You

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