## 1 PLACENTAL PHARMACOLOGY STUDIES TO CHARACTERIZE THE EFFECTS AND DISPOSITION OF PHARMACEUTICALS: LESSONS FROM HUMAN TISSUES AND CELLS FOR IMPROVING DRUG SAFETY IN PREGNANCY

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The placenta plays a key role in maintaining a healthy pregnancy. In order to improve drug safety during pregnancy, it is therefore relevant to understand to which extent and at which rate drugs are transferred across the placenta and how pharmaceuticals may affect placental function. Translational and predictive pharmacology studies based on human tissues and cells are becoming increasingly important in characterizing the effects and disposition of pharmaceuticals. With regard to the placenta, such approaches may for example be readily combined with physiology-based pharmacokinetic (PBPK) modeling to predict fetal exposure of drugs, as well as placental tissue exposure in the clinic. In addition, placental tissue and cells can be used to study potential effects of drugs, as well. The current presentation, will highlight several studies that investigated the placental disposition and effects of both small and large molecule pharmaceuticals, as well as how such data can help to better understand the clinical pharmacology of therapeutics.

## 2 PITFALLS AND OPPORTUNITIES FOR CENTRALIZED TDM SERVICES: A BELGIAN SINGE-CENTRE EXPERIENCE

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Therapeutic drug monitoring (TDM) requires a multidisciplinary approach with different stakeholders (nurse, bio-analyst, pharmacist, pharmacologist, pharmacometrician, physician). In recent years, a pharmacist-guided TDM dosing advice service, mainly for anti-infective therapy, has been installed at the Ghent University Hospital, a tertiary hospital in Flanders, Belgium. From this experience, advantages, pitfalls and opportunities for centralized TDM services are being summarized. Together with the previous talk, this talk will serve as a basis for discussion with the audience.

# General abstracts

## 3 THE EXPOSURE TO AND EFFICACY OF DORAVIRINE IN PREGNANT WOMEN AS ASSESSED BY PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELLING

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**Introduction** Doravirine is currently not recommended for pregnant women living with HIV due to the lack of efficacy and safety data. Physiological changes during pregnancy can significantly decrease drug exposure, and, thereby, lower the efficacy. Awaiting clinical data, this study aimed to predict maternal and fetal doravirine exposure by integrating human placenta perfusion experiments with pregnancy physiologically-based pharmacokinetic (PBPK) modelling.

**Methods** An existing and validated three-compartment PBPK model of doravirine for a healthy, non-pregnant population was modified to a 18-compartment PBPK model using Simcyp Simulator V20. The permeability-limited placenta model was included in the extended PBPK model to study placental transfer to the fetus. To parameterize the placenta model, ex vivo human cotyledon perfusion experiments were performed, and a mechanistic model was developed to derive placental transfer constants. The final pregnancy PBPK model was used to predict the maternal and fetal geometric mean (GM) concentration at 24h after dosing (C24h) at 26, 32 and 40 weeks of pregnancy. The GM C24h was compared to the target derived from in vivo exposure-response analysis of 0.23 mg/L.

**Results** Perfusion experiments showed that doravirine extensively crosses the placenta. In comparison to non-pregnant women, the final pregnancy PBPK model estimated a maternal decrease in GM C24h of 55% for 40 weeks pregnancy. All predicted maternal GM C24h were <0.23 mg/L.

**Conclusions** Substantially reduced maternal doravirine exposure was predicted during pregnancy, possibly resulting in impaired efficacy. Therapeutic drug and viral load monitoring are advised for pregnant women treated with doravirine, and the use should preferentially be restricted to clinical trials.

## 4 RISKS ASSOCIATED WITH ANTIDEPRESSANTS IN PATIENTS WITH HYPERTENSION DURING PREGNANCY: A RETROSPECTIVE COHORT STUDY

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**Introduction** Given the proportion of pregnant women with gestational hypertension or pre-eclampsia using an antidepressant we aimed to gain insight into the effects concerning for both mother and neonate especially on birth weight, APGAR score, and pregnancy duration.

**Study design** Retrospective cohort study of women with hypertension disorders, whether or not using antidepressants.

Main outcome measures: Birth weight, APGAR score, admittance to Obstetrical High Care unit (OHC) and or Neonatal Intensive Care Unit and pregnancy duration

**Results** The use of antidepressants was associated with lower APGAR scores at 10 minutes, p= 0.008, OR = 2.298; 95% CI 1.255–4.273, compared to neonates from mothers without antidepressants. Women using antidepressants were more often admitted to the OHC (crude OR= 1.95; p=0.049; 95% CI 0.99–3.77). Multivariable logistic regression analysis revealed that thyroid disease and preterm ending of pregnancy contributed to the model, where use of antidepressants remained significant (OR=6.28; 95% CI 2.32–18.31).

**Conclusions** Women with hypertension disorders during pregnancy and using antidepressants might have an increased risk for complications leading to OHC admission.