NIfedipine levels in Mothers with and without PreEclampsia and their Newborns.

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Primary Objective: To compare the fetal/maternal ratio of nifedipine blood concentrations between pregnancies with and without hypertensive disorders, including preeclampsia.Secondary Objective: To compare predicted fetal/maternal drug ratios with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Maternal complications of pregnancy
Study type	Observational invasive

Summary

ID

NL-OMON46737

Source
ToetsingOnline

Brief title
NIMPEN

Condition

- Maternal complications of pregnancy
- Vascular hypertensive disorders

Synonym
for instance preeclampsia, hypertensive pregnancy disorders

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting De Merel

Intervention

Keyword: Hypertensive pregnancy disorder, Pharmacokinetics, Placental transfer

Outcome measures

Primary outcome

Concordance between the fetal/maternal ratio (both predicted and calculated) between pregnancies without and with hypertension or PE. Since variation is expected to be high, values <0.1 (limited transfer), 0.1-1 (transfer) and >1 (fetal accumulation) will be considered as similar between both groups.

Secondary outcome

Concordance between the fetal/maternal ratio between the placental perfusion model and the in vivo data. Since variation is expected to be high, values <0.1 (limited transfer), 0.1-1 (transfer) and >1 (fetal accumulation) will be considered as similar between both groups.

Study description

Background summary

The placenta is the most crucial organ in the development of the fetus(1). Via the placenta, the fetus receives oxygen and nutrients, while fetal waste is removed via diffusion and active transport. To fulfill this task, the placenta has a strict separation of the fetal and the maternal circulation.
Suboptimal development of the placenta may lead to severe complications of pregnancy, most importantly pre-eclampsia (PE), characterized by elevated blood pressure and proteinuria in the mother, potentially leading to maternal and fetal morbidity and mortality (2, 3). Examination of placentas from PE pregnancies shows structural changes in the placental blood vessels, such as arterial vessel wall thickening and obstruction by atherosclerotic plaques, resulting in increased placental vascular resistance and a reduction in placental blood flow (4-6). The precise aetiology of the clinical symptoms of PE is still largely unknown. However, we and others have demonstrated that changes in the ratio of pro-angiogenic factors produced by the placenta,

probably in response to hypoperfusion, lead to a decrease in vascular endothelial growth factor (VEGF) and an increase in endothelin-1 (ET-1), a strong vasoconstrictor (7). ET-1 is thought to be responsible for the hypertension and nephropathy in PE. ET-1 receptor blockers (ERAs), currently used by patients with pulmonary hypertension, may therefore represent a novel treatment option for PE. However, due to teratogenicity in animal models, ERAs are currently contraindicated during pregnancy. Although suggested from the vascular changes described above, it is currently unknown whether placental drug transfer in general is different in hypertensive pregnancy disorders compared to healthy placentas. To consider ERAs or other treatment options for a clinical study in PE we first need to increase our knowledge about placental drug transfer in general and in PE, which has not been studied before. For this aim we will use a placental perfusion model (METC EMC-prg 1 2016-418). Since direct comparisons between in vivo measurements and data obtained using the model are scarce, we want to compare in vivo data (i.e. the drug concentration in maternal and umbilical blood levels) with predicted data using the ex vivo model.(8) For this purpose, we will use nifedipine as a model drug, since it is used both in patients with gestational hypertension, in patients with PE and in patients without hypertension who are at risk for premature birth.(9-11) Nifedipine is (together with labetalol) used in pregnancy for decades as second line option after methyldopa.(12) Limited PK data suggest that metabolism of nifedipine is faster during pregnancy probably due to induction of CYP3A4/5.(13, 14) Although placental transfer takes place this does not lead to accumulation, however patients with or without hypertensive pregnancy disorders have not been compared previously.(8) (14)

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Study objective

Primary Objective:
To compare the fetal/maternal ratio of nifedipine blood concentrations between pregnancies with and without hypertensive disorders, including preeclampsia.

Secondary Objective:
To compare predicted fetal/maternal drug ratios with observed fetal/maternal drug ratios in pregnancies with and without a hypertensive pregnancy disorder including preeclampsia.

Study design

The study will be a case-control study including both patients with hypertension and suspicion of pre-eclampsia and patients at risk for preterm birth (< 34 weeks of gestation). The study duration will be estimated one year, the time needed to include eight women for each group for placental analysis. Since patients with hypertension are at high risk of development of PE, we will include these patients at the outpatient clinic. The maximum number of extra venepunctures for this study will be two: one trough level in steady state, one just before and one just after delivery. In addition, during regular vein sampling an extra tube will be collected for pharmacokinetic modelling.

Study burden and risks

The procedure involves between three to five additional blood samples taken from the mother dependent on the time between inclusion and delivery. The risk is trivial. There is no direct benefit for the patient.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- pregnant
- prescription of nifedipine
- delivery planned in Sophia Children*s hospital
- understanding of Dutch / English in speaking and reading
- written informed consent

Exclusion criteria

- not unwilling or unable to give written informed consent
- multiple pregnancy
- infectious diseases (e.g. HIV, hepatitis B, ZIKA) for laboratory safety
- fetal congenital abnormalities
- manual placenta removal

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-03-2019
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO Date:	28-09-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL65425.078.18