Difference in pharmacokinetics of antibiotics during pregnancy in normal, overweight and obese women.

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PrimaryTo examine the pharmacokinetics of standard antibiotic regimen used at the department of Obstetrics at the Erasmus MC for postsurgical prophylaxis after caesarean section.Secondary- To examine the relation between the weight category (1. BMI

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Pregnancy, labour, delivery and postpartum conditions
Study type	Observational invasive

Summary

ID

NL-OMON52470

Source
ToetsingOnline

Brief title
DinAbO - study

Condition

- Pregnancy, labour, delivery and postpartum conditions

Synonym
BMI-related, Postsurgical prophylaxis after caesarean section; antibiotic treatment

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Antibiotic regimen, Pharmacokinetics, Post surgical prophylaxe, Pregnant women

Outcome measures

Primary outcome

To examine the maternal pharmacokinetics of standard antibiotic regimen admitted at the Department of Obstetrics at the Erasmus MC - Sophia for antibiotic treatment for postsurgical prophylaxis after caesarean section. Farmacokinetic parameters, which will be determined are: distribution (VD), clearance (Cl), elimination-rate constant (kel), steady-state concentration (Css), half-life (t1/2), bioavailability (F).

Secondary outcome

1. To examine the relation between the weight category (1. BMI <25, 2. BMI 25-<30, 3. BMI 30-40, 4. BMI >40) before conception and the pharmacokinetics of the antibiotic regimen (primary objective).

2. To examine the relation between the gestational age (weeks) and the pharmacokinetics of the antibiotic regimen (primary objective).

3. To examine the relation between maternal age (years) and the pharmacokinetics of the antibiotic regimen (primary objective).

4. To examine the relation between fetal sex and the pharmacokinetics of the antibiotic regimen (primary objective).

5. To examine the relation between maternal SNPs in cytochrome P450 isoenzyme genes and the pharmacokinetics of the antibiotic regimen (primary objective).

Study description

Background summary

Antibiotic use in the general population has increased over the last decades, {Adriaenssens, 2011 #6} which has also resulted in an increased antibiotic use during pregnancy.{Broe, 2014 #7} Nowadays 21% of pregnancies are complicated by an infection for which antibiotics are required, such as urinary tract infection, upper respiratory infection but also wound infections.{de Jonge, 2014 #8} Pregnant women with overweight (BMI>25-30) and obesity (BMI >30) are at increased risk for infection due to the effects obesity has on the immune responses {Bearden, 2000 #15} and thus antibiotic use.{Broe, 2014 #7} In the Netherlands, 30-50% of all pregnant women have a BMI > 25, which accounts for 25.000-35.000 pregnancies per year.{Gaillard, 2013 #9}{Gaillard, 2013 #9}
Health care-associated infections contribute to the increasing cost of health care as well as patient morbidity and mortality. Pregnant women with an increased BMI, defined as BMI> 25, are also more likely to have maternal complications, such as a caesarean section and an increased risk for operative morbidity such as wound complications.{Marchi, 2015 #10} Of all hospital-based surgeries performed in the United States, cesarean deliveries were the most frequently performed surgery.{Valent, 2017 #11} Approximately, 3% to 12% of all caesarean sections are complicated by surgical site infection (SSI) and with increasing maternal weight, the risk of SSI increases. {Alanis, 2010 #12;Leth, 2011 #13;Wloch, 2012 #14}
Obese, non-pregnant patients have higher percentage of adipose tissue, lower percentage of total body water and lean body mass. {Tucker, 2014 #16} In addition, during pregnancy, most maternal organ systems are affected by both anatomical and physiological changes, which include increased total body water and plasma volume, decreased concentrations of drug-binding proteins and altered activity of drug-metabolizing enzymes in the liver. Enzymes affected by pregnancy include the cytochrome P450 isoenzymes CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2C19. (reviewed in {Pariente, 2016 #17}) Obesity and pregnancy combined cause several alterations in cardiac output, blood volume, volume of distribution (Vd), renal function, and hepatic function.{Pai, 2007 #18;Pai, 2000 #19}
Pharmacokinetic changes caused by aforementioned variations must be taken into account when prescribing antibiotics, as they will undoubtedly influence clinical outcomes and the potential for antimicrobial resistance and drug toxicity.{Pai, 2007 #18} Despite weight differences in pregnant women, there are no differences in the dosing regimens of most antibiotics. Neither has been investigated, re-evaluated or refined to determine the optimal doses or treatment interval for different BMI-classes. With the current health care approach of personalized medicine in mind, the same universal approach for everybody, independent of gestational age, maternal weight or comorbidity one dose does not fit all since it often has not the desired effect. Due to the lack of optimization of the above mentioned antibiotic drug regimens,

significant gaps in knowledge exist. An important aspect to set up, investigate and understand dosing and also dosing interval experiments, is knowledge of the maternal individual pharmacokinetics and pharmacogenetics of the drug of interest during pregnancy. As an example, most antibiotics are eliminated by the liver by action of the above mentioned cytochrome P450 isoenzymes and variations of Single Nucleotide Polymorphisms (SNPs) in these genes will result in different drug effects and even potential adverse effects.

Study objective

Primary
To examine the pharmacokinetics of standard antibiotic regimen used at the department of Obstetrics at the Erasmus MC for postsurgical prophylaxis after caesarean section.

Secondary
- To examine the relation between the weight category (1. BMI <25, 2. BMI 25-<30, 3. BMI 30-40, 4. BMI >40) before conception and the pharmacokinetics of the antibiotic regimen (primary objective).
- To examine the relation between the gestational age (weeks) and the pharmacokinetics of the antibiotic regimen (primary objective).
- To examine the relation between maternal age (years) and the pharmacokinetics of the antibiotic regimen (primary objective).
- To examine the relation between fetal sex and the pharmacokinetics of the antibiotic regimen (primary objective).
- To examine the relation between maternal SNPs in cytochrome P450 isoenzyme genes and the pharmacokinetics of the antibiotic regimen (primary objective).

Study design

A clinical observational pilot study.

Study burden and risks

For all participants the burden will be the insertion of an intravenous canule that will solely be used for blood sample collection. After the administration of antibiotics, blood samples (approximately 5 ml, 1 EDTA tube) will be collected in sampling time windows according to the following schedule: t0 (administration), t0-30 min, t1-3 hrs, t5-8 hrs, t10-12hrs. Insight into individual pharmacodynamics of antibiotics and its association with SNPs of the cytochrome P450 isoenzymes as well as patient characteristics will allow for future trials with individualized regimens to maximize benefits and minimize side effects which could lead to personalized and patient-tailored medicine for infection or postsurgical prophylaxis.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1) Older than 18 years of age
2) Admitted at the Department of Obstetrics at Erasmus MC - Sophia for caesarean section.
3) Understanding of Dutch in speaking and reading.
4) Written informed consent.

Exclusion criteria

1) Women unable or unwilling to agree with the procedures.
2) Women unable or unwilling to give written informed consent.
3) Women with acute obstetric complications requiring immediate delivery at time of admission.

4) Women with interacting drugs, this can influence PK.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-08-2020
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO

Date:	02-07-2020
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	NL71977.078.19