Non invasive prenatal testing (NIPT) of fetal genetic disorders in maternal blood

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Developing targeted non-invasive prenatal analysis for single-gene disorders and chromosomal disorders using cff DNA and RNA in maternal plasma. We will investigate when and how the aberrant cells disappear during prenatal development.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON50448

Source
ToetsingOnline

Brief title
NIPT genetic disorders

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
genetic disorders

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: chromosomal anomalies, fetal anomalies, monogenic disorders, prenatal diagnosis

Outcome measures

Primary outcome

- Develop a non-invasive prenatal test for chromosomal and monogenic

abnormalities in the pregnant woman's blood.

Doest targeted/genome-wide molecular analysis of cell-free DNA or RNA indicate:

- the presence or absence of fetal mutation (s) in maternal plasma

- the presence of sufficient concentration of fetal DNA / RNA in maternal

plasma to enable reliable diagnosis of monogenic disorders.

- the presence of aneuploidies, structural abnormalities, and monogenic

disorders

- when and how the aberrant cells disappear during prenatal development

Secondary outcome

NA

Study description

Background summary

Conventional prenatal diagnosis (PND) for single-gene disorders and chromosomal anomalies requires invasive procedures, either chorionic villus sampling between 11 and 14 weeks gestation or amniocentesis after 15 weeks. Although these approaches to obtain foetal DNA currently provide the golden standard for PND, the invasive procedures carry a risk of miscarriage of 0.5-1%. A reliable non-invasive alternative has long been sought. Circulating cell-free foetal (cff) nucleic acids (DNA and RNA), which are present in maternal blood during pregnancy, can be used for non-invasive prenatal testing (NIPT). Although NIPT

of monogenic and chromosomal disorders is technically challenging, due to the predominance of maternal DNA sequences, several genetic disorders have been currently diagnosed in maternal blood. In this study, we aim to develop non-invasive targeted molecular and genome wide analysis using cffDNA and cffRNA for single-gene disorders and chromosomal anomalies, in pregnant women referred to the departments of Clinical Genetics of Maastricht University Medical Centre (MUMC+) and Radboud University Medical Centre (RUMC) for conventional PND.

Genetic aberrations are highly prevalent in early- stage human embryos, resulting in mosaic embryos which consist of normal and abnormal cells. The degree of mosaicism reduces during gestation, resulting in ongoing pregnancies and healthy live births. It is speculated, that cell lineages containing these genetic aberrations survive in the trophectoderm, and therefore having no or little influence on fetal development. Furthermore, euploid blastomeres may outgrow blastomeres with chromosomal aberrations, resulting in normal development of the embryo. However, the exact correction mechanisms of vanishing aberrant cells later in development remains elusive. In this study, we will try to investigate the etiology of the mechanism of vanishing embryonic mosaic cells.

Study objective

Developing targeted non-invasive prenatal analysis for single-gene disorders and chromosomal disorders using cff DNA and RNA in maternal plasma. We will investigate when and how the aberrant cells disappear during prenatal development.

Study design

This is a "proof of concept" study. We want to show that molecular genome-wide analysis can show the presence or absence of a fetal disease in maternal plasma. Pregnant women who have an increased risk of having a child with a monogenic disorder or chromosomal abnormality and their partners are asked to donate blood at 1 to 4 times during pregnancy. Depending on the moment of entry and willingness of the participants. After birth, we collect placenta and umbilical cord blood to create genetic profiles of the child and the placenta. Here, we also look at mosaicism and confirm whether it is present in the child or the placenta. In addition, we will relate the outcome of the mosaic examination to the clinical outcome of the pregnancy. Finally, we try to isolate fetal cells from maternal blood and perform genetic testing of those cells.

Study burden and risks

Minimal burden: one to max four moments of blood sampling for the pregnant

woman and her partner. In most cases, blood sampling will be combined with regular blood sampling. Benefit: no benefit for this pregnancy as in the study phase the result of the invasive prenatal test is leading.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

P. Debyelaan 25
Maastricht 6202 AZ
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

P. Debyelaan 25
Maastricht 6202 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Pregnant women and their partners (18+) of which:
Group 1: the woman is pregnant after PGD for a chromosomal anomaly or monogenic disorder
Group 2: the fetus is at risk for a chromosomal anomaly because of an adverse result of regular NIPT testing (Dutch TRIDENT-1 or -2 study) for aneuploidy with or without additional findings.
Group 3: the foetus is at high risk of having a de novo disorder on the basis

of ultrasonography findings and couple will undergo PND
Group 4: the fetus is at high risk of having inherited a dominant or recessive disorder of his/her affected parent(s) and couple ask for conventional PND

General:
- the pregnant woman and partner are 18 years or older
- the pregnant woman has sufficient understanding of Dutch language and is able to give informed consent.

Exclusion criteria

- in the opinion of the treating physician psychological distress is so severe that asking for participation is not safe.
- the pregnant woman is treated for a malignancy
- patients in group 1 (testing performed with only PCR or OnePGT for monogenic disorders), group 3 and 4 will be excluded from this study if they do not opt for NIPT (with/without additional findings) or PND (with at least a QF PCR of chromosomes 13, 18, 21)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-06-2014
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO Date:	07-05-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-08-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-06-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-11-2020
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT02339402
CCMO	NL48304.068.14