Non-invasive prenatal diagnosis using cell-free fetal DNA in maternal plasma.

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

Summary

ID

NL-OMON37584

Source
ToetsingOnline

Brief title
Non-invasive prenatal diagnosis (NIPD)

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Neonatal and perinatal conditions

Synonym
fetal genetic abnormalities, including aneuploidies and recessive genetic disorders

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Fetal, Genetic abnormality, Maternal plasma, Non-invasive diagnosis

Outcome measures

Primary outcome

Technical performance: technical failures, throughput, turnaround time, cost

Clinical performance: sensitivity, specificity and predictive values

Secondary outcome

Not applicable.

Study description

Background summary

Currently, prenatal diagnosis of fetal genetic abnormalities, including aneuploidies and recessive genetic disorders, requires an invasive diagnostic procedure, specifically chorionic villus sampling or amniocentesis, to obtain fetal material for genetic testing. Although the safety of these invasive procedures has improved since their introduction, these tests carry a risk of iatrogenic fetal loss of about 1%, and are therefore reserved for pregnancies considered to be at high risk for a fetal genetic abnormality (Tabor 1986, Odibo 2008a, Odibo 2008b, Tabor 2010).

The risk of aneuploidy is assessed by prenatal screening, nowadays offered to all pregnant women. Risk calculation is based on maternal age, nuchal translucency measurement by sonography and the serum markers pregnancy-associated plasma protein-A (PAPP-A) and free beta hCG (free β-hCG). This first trimester combination test can identify 85-90% of affected fetuses. Of all women participating, 5-6% is screen-positive (also referred to as false-positive, because the vast majority of fetuses in this group are normal) and therefore offered an invasive diagnostic procedure. Since the screening test only detects epiphenomena rather than the core pathology of chromosomal abnormalities, it lacks diagnostic power (Snijders 1998, Wald 1999, Wald 2003, Malone 2005, Kagan 2008).

The discovery of the presence of cell-free fetal DNA (cff DNA) in the plasma of pregnant women has opened up possibilities for non-invasive prenatal diagnosis (NIPD) (Lo 1997). DNA of fetal origin is detectable early in pregnancy in

amounts of approximately 10% of the total DNA circulating in maternal plasma (Lo 1998, Lun 2008). The cff DNA is cleared from the maternal bloodstream within hours after birth; thus, misdiagnosis resulting from remaining DNA from a previous pregnancy is unlikely (Lo 1999). Detection of fetal-specific DNA sequences is already used successfully for non-invasive determination of fetal sex in women carrying a sex-linked recessive genetic disorder (Zhong 2000, Rijnders 2001, Scheffer 2010) and of fetal Rhesus D genotype in Rhesus D negative women (Faas 1998, Lo 1998, Bianchi 2005, Finning 2008, Scheffer 2011).

Unfortunately, detection of fetal genetic abnormalities, including aneuploidies and recessive genetic disorders, from cff DNA is far more complicated. Fetal DNA represents only a minor fraction of total DNA in maternal plasma, and is therefore substantially diluted by the maternal DNA contribution. However, using massively parallel shotgun sequencing (MPSS), it is possible to sequence the first bases of millions of DNA fragments in maternal plasma to determine their specific chromosomal origin (Chiu 2008, Fan 2008). Using this technique, even relatively small changes in the representation of chromosomes, from a fetus carrying three rather than two copies of a chromosome, can be detected with statistically significant power. The results of recently published studies using MPSS to detect fetal trisomy 21 in high-risk populations showed a combined sensitivity and specificity of 99.1% (334/337) and 99.7% (2020/2027), respectively (Chiu 2011, Ehrich 2011, Palomaki 2011).

Furthermore, research has shown the presence of cff RNA in maternal plasma as well. In due time, it could be possible to monitor the unborn child and the course of pregnancy through observation of fetal expression of certain genes through the analysis of cff RNA in maternal plasma.

Previously, as described in phase 1 of the approved CMO protocol 2008/349 *Niet-invasieve prenatale diagnostiek naar Down syndroom met gebruik van DNA en/of RNA in het maternale plasma*, blood samples from pregnant women scheduled for an invasive procedure have been collected, processed and stored in our center, starting from March 2010. Whenever possible, a blood sample from their (male) partners was collected, processed and stored as well. As described in phase 2 of the approved protocol, 52 of the stored maternal plasma samples have been used for a pilot study of NIPD through MPSS of cff DNA in maternal plasma. Results are very promising: all fetal aneuploidies for chromosomes 13, 18 and 21 and sex chromosomal aberrations could be reliably detected, with 100% sensitivity and specificity (Faas 2012, in press).

Study objective

The ultimate goal of this research is the clinical implementation of a non-invasive test for prenatal fetal genotyping, including fetal sex determination, using cff DNA in maternal plasma, to replace the current standard practice of invasive tests, specifically chorionic villus sampling or amniocentesis.

Available data from literature and in-house testing show that the application of MPSS of cff DNA in maternal plasma for NIPD of fetal aneuploidies is robust and sensitive, with diagnostic accuracy of this method even approaching that of invasive tests. However, before clinical implementation of NIPD of fetal aneuploidies and other fetal genetic abnormalities is feasible, extended studies are needed to further improve and validate this new technique in our own laboratory, and to study its performance in clinical practice.

This study aims to address the following primary objectives:
*- developing a standardized protocol, including quality control parameters, for the use of NIPD by MPSS of cff DNA;
*- determine the sensitivity and specificity of NIPD by MPSS of cff DNA;
*- optimize throughput, turnaround time and costs;
*- determine the predictive values of NIPD by MPSS of cff DNA when used in a clinical setting.

To be able to address the goal and objectives stated above, plasma and DNA fractions of both pregnant women and their (male) partners are required. This study therefore aims to collect, process and store maternal and paternal plasma and DNA fractions, to be used for the further development and validation of a non-invasive test for prenatal fetal genotyping, including fetal sex determination.

Study design

The study will be a prospective, multicenter cohort study, consisting of multiple phases.

Phase 1: technical and logistic optimization
The first phase of this study is aimed to develop a standardized protocol for NIPD by MPSS of cff DNA in maternal plasma. Methods to demonstrate the presence of cff DNA and measure the amount and fraction of cff DNA present will be further developed and validated. Quality control parameters will be established. Parts of laboratory and data analysis will be automated. Furthermore, the logistics necessary to collect and analyze plasma samples, and to document and distribute test results on a large scale, throughout the region will be set up.

Phase 2: prospective validation
The second phase of this study is aimed to assess the performance of NIPD of fetal aneuploidies using cff DNA in maternal plasma in a clinical setting, applying the standardized protocol developed in phase 1 of this study.

Study burden and risks

In some female participants, and the vast majority of male participants, the

drawing of a study blood sample will not be able to be combined with an already scheduled venipuncture as part of standard prenatal care. These participants will have an additional venipuncture. The risks associated with this procedure are negligible.

Participants will not benefit from their partaking in this study in any way.

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

All pregnant women planning to have prenatal screening or prenatal diagnosis as part of standard prenatal care are eligible to participate in this study (='patients').
Inclusion criteria: maternal age 18 years or older, vital pregnancy, able to understand the information and give informed consent.;Additionally male partners of participating pregnant

women will be asked to participate in this study as well (='healthy volunteers').
Inclusion criteria: paternal age 18 years or older, partner of a pregnant woman participating in this study, able to understand the information and give informed consent.

Exclusion criteria

Exclusion criterion: participant is unable to understand the information, e.g. due to a language barrier.

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):	15-05-2012
Enrollment:	6000
Type:	Actual

Ethics review

Approved WMO

Date:	14-05-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL40050.091.12