Fetal Cells from the maternal circulation for Noninvasive Prenatal Diagnosis Study (FC-NIPD Study), part I

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This first part of the research study aims to evaluate and optimize the Mitsui Chemicals Inc. fetal cell-based non-invasive prenatal diagnosis test (cbNIPD), its methodology, internal validation and quality control.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON56395

Source
ToetsingOnline

Brief title
NIPD-study

Condition

- Other condition

Synonym
N/A

Health condition

prenatal diagnosis

Research involving
Human

Sponsors and support

Primary sponsor: Mitsui Chemicals
Source(s) of monetary or material Support: Mitsui Chemicals

Intervention

Keyword: Fetal cells, NIPD, Nucleated Red Blood Cells

Outcome measures

Primary outcome

The enumeration of fetal nucleated cells isolated from 10 ml of maternal blood.

Secondary outcome

Optimization of storage, transport and handling of the blood samples.

Study description

Background summary

Of every 1000 pregnancies, 20 fetuses are affected by a genetic abnormality. Around 5% of these chromosomal abnormalities are trisomy 21 or Down syndrome, a condition for which many countries have screening programs offering testing to all pregnant women. Many other chromosomal abnormalities occur, of which 20% involve other aneuploidies, 25% microdeletions or - duplications, and the rest consists of inherited or de novo Mendelian or single gene disorders.

The gold standard for fetal genetic diagnosis is genetic analysis of amniocytes, which are fetal cells in the amniotic fluid. To obtain these cells, amniocentesis is required, an invasive procedure whereby a needle is inserted through the abdominal wall of the pregnant woman, through the wall of the uterus and through the fetal membranes. Amniocentesis has inherent risks, including rupture of the membranes, amniotic fluid loss, infection, fetal trauma, bleeding, immature or premature delivery and fetal death. These complications occur in 0.11-1.0% of procedures (Akolekar 2015). Furthermore, amniocentesis causes pain and discomfort, stress and anxiety for the women, is expensive and requires specialized skills and expertise of the operator. Therefore, this procedure is restricted to pregnancies considered to be at high risk for a fetal genetic disease (ACOG 2012).
Risk assessment is done by routine screening of all pregnant women. This screening is currently done by taking the woman and her partner*s history,

including age and use of teratogens, and offering a using a non-invasive prenatal screening test. The best currently available screenng test is called NIPT, which uses analysis of cell-free fetal DNA (cfDNA) in maternal plasma and has been increasingly adopted to predict aneuploidy (trisomy 21, 18 and 13) since 2011. However, NIPT remains only a screening test, it gives a non-definitive result, with false positives and false negatives, and therefore needs to be confirmed by an invasive diagnostic test, usually amniocentesis (Norton 2015, Gil 2015). cfDNA testing can also be false negative, although for the common trisomies quite rarely (Gil 2015). The standard techniques used in cfDNA analysis only allow quite reliable prediction for trisomy 21 and 18. For other aneuploidies (such as sex chromosome abnormalities) and for subchromosomal abberations, cfDNA is less reliable (Scibetta 2017, Lo 2019). Latest technological advances, using genomic analysis of cfDNA, appear to improve accuracy, but a recent Cochrane meta-analysis concluded that cfDNA testing cannot replace amniocentesis (Badeau 2017). Even if cfDNA analysis techniques further improve, this test will never achieve the same accuracy as amniocentesis, since the DNA fragments used in cfDNA testing originate from placental cells, and not fetal cells (Grati 2014). In addition, multiple pregnancy (in particular dichorionic) complicates the interpretability of cfDNA testing, and has failure rates up to 11% (Galeva 2019). In addition, maternal obesity, an increasing problem in obstetrics in general, is associated with a lower, and sometimes too low, fetal fraction of the DNA fragments to allow reliable testing (Rolnik 2018)

A second type of fetal screening is done using ultrasound. Around 18-20 weeks, and sometimes also already at 11-13 weeks, the fetus is examined for structural anomalies. When these are found, genetic testing is offered since many of the structural anomalies are caused by chromosomal aberrations. This genetic testing is also done using amniocentesis.

The presence of whole fetal cells in maternal blood was first described by Schmorl in 1893, a pathologist who found trophoblast cells in the lungs of women who died from preeclampsia (Lapaire 2007). In 1959, Zipursky et al described the presence of fetal red cells in maternal blood, which formed the basis of our understanding of Rhesus alloimmunization (Zipursky 1959). Since the late 1960s, it is known that from early in pregnancy onwards, fetal cells are present in the blood of the pregnant woman (Beaudet 2016). Several investigators, mainly around the 1990s, studied the potential to use these cells for fetal genetic diagnosis, but the attempts never made it into a clinically useful test (Bianchi 2002). There is however a renewed interest in the in many ways ideal prenatal diagnostic method using whole fetal cells from the maternal circulation (Rezaei 2018). Some investigators concentrated on trying to isolate trophoblast cells from maternal blood or cervical washings (Breman 2016, Vossaert 2018). However, since these cells are not true fetal cells, tests using trophoblast may still be less reliable than amniocentesis.

TL Genomics (Tokyo, Japan) developed innovative methods for enrichment and isolation of fetal nucleated red blood cells from the maternal circulation. Together with advances in genetic analysis techniques (Wapner 2012, Lord 2019), this could lead to replacement of cfDNA-based NIPT as well as amniocentesis, to

enable one-step, accurate and safe diagnosis of fetal genetic anomalies.

Study objective

This first part of the research study aims to evaluate and optimize the Mitsui Chemicals Inc. fetal cell-based non-invasive prenatal diagnosis test (cbNIPD), its methodology, internal validation and quality control.

Study design

Mitsui Chemicals Inc. developed a blood-cell separator chip technology, which can sort cells dependent on their size. This chip can isolate nucleated red blood cells of 11-13 micrometer diameter from maternal blood. In this selected population of cells from maternal blood, we aim to assess the percentage which is of fetal origin, and which thus can be used for prenatal diagnosis of fetal chromosomal abnormalities.

Intervention

The collection of 20mL blood at one occasion during the pregnancy. We aim to combine this blooddraw with other standard of care blood draws that take place during pregnancy.

Study burden and risks

Risks are limited to the loss of non-identifiable data. These risks are considered minimal, as data will be entered directly and de-identified into a protected database (RedCap).

Contacts

Public
Mitsui Chemicals

Shiodome City Center, 1-5-2 Higashi-Shimbashi Minato-ku
Tokyo 105-7122
JP
Scientific
Mitsui Chemicals

Shiodome City Center, 1-5-2 Higashi-Shimbashi Minato-ku
Tokyo 105-7122
JP

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Pregnant of viable singleton or twin pregnancy at the time of the blood draw (confirmed and dated by ultrasound);
• At least 18 years of age and able to provide informed consent;
• Pregnancy at the time of blood draw of at least a confirmed gestational age of 9 weeks 0 days.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Subject is pregnant with more than two fetuses or has had sonographic evidence of three or more gestational sacs at any time during pregnancy;
• Subject has a fetal demise (including natural or elective reduction) identified prior to consent;
• Subject has a history of malignancy treated with chemotherapy and/or major surgery, or bone marrow transplant.
• Subject is positive for any of the infectious tests on hepatitis B, hepatitis C, syphilis, HIV or HTLV-1.
• Subject has an obvious ectopic gestation.
• Subject is judged as inappropriate by a research rector.

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):	31-08-2020
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO

Date:	03-08-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	22-03-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	16-11-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	08-12-2023

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL72663.058.20