Prenatal diagnosis: MLPA and/or karyotyping

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Ethical review	Approved WMO
Status	Pending
Health condition type	Placental, amniotic and cavity disorders (excl haemorrhages)
Study type	Observational non invasive

Summary

ID

NL-OMON30149

Source
ToetsingOnline

Brief title
MLPA And Karyptyping, an Evaluation (M.A.K.E.)

Condition

- Placental, amniotic and cavity disorders (excl haemorrhages)

Synonym
Down Syndrome, trisomy 13/18/21/XY

Research involving
Human

Sponsors and support

Primary sponsor: Onze Lieve Vrouwe Gasthuis
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Down syndrome, karyotyping, MLPA, prenatal diagnosis

Outcome measures

Primary outcome

Diagnostic accuracy is assessed through a blind comparison of MLPA against the accepted gold standard (TKT)in a clinical setting. Sensitivity and specificity are calculated and discordant test results are recorded.

Technical performance including technical difficulties (i.e. equipment malfunction)and missing or inconclusive results are recorded, as well as missing results due to lack of amniotic fluid.

Turnaround time for laboratory processing and availability of test results of MLPA versus TKT, known at laboratory level and patientlevel are recorded.

Secondary outcome

1. Anxiety and distress as secondary outcome will be measured by available standardized questionnaires (STAI, PPC, IES, MOS-SF)which also have been used for similar studies(PhD Thesis Muller, 2006 in press; screening for irregular erythrocyte antibodies in pregnancy].

2. Cost as secondary outcome will focus on medical costs (including implementation and quality control).

If relevant the cost-effectiveness of TKT over MLPA will be calculated.

3. Using acommercially available kit(i.e.P095), trisomy 13, 18, 21 and sexchromosome abnormalities will be detected. Firstly, we will focus on detecting trisomy 21 and secondly, chromosomes 13 18, X and Y. The latter can be of uncertain clinical relevance and cause counselling difficulties. A panel

will assess these findings and will judge whether they are clinically relevant, irrelevant or of uncertain relevance. This might result in excluding/including probes from/into the MLPA aneuploidy kit in future testing. Differences inemerging unexpected or incomprehensible findings will be described qualitatively taking advantage of a recent study on this issue [VanZwieten,2004].

4. A standard patientpreference study (so called discrete choice evaluation)will allow quantification of the balance of all (dis)advantages of either test[Ryan,2005].

Study description

Background summary

For the past 30 years karyotyping is the gold standard in prenatal diagnosis for the detection of chromosomal aberrations in the fetus, in particular trisomy 21(Down syndrome). The main indications for traditional karyotyping (TKT) in the Netherlands are advanced maternal age and increased risk based on prenatal screening tests (PNS).
The annual numbers of maternal age-based invasive procedures for TKT are decreasing. The numbers of PNS are increasing, due to a shift of the maternal age distribution, with a relative increase of elderly pregnant women making use of PNS, and an increased demand of pregnant women, augmented by a change in government policy allowing PNS (combined test, triple test) for risk estimation of Down syndrome (DS).
targeted testing
Prenatal TKT provides genotypic diagnosis of DS and also detects other chromosomal aberrations. In the patient*s perception, some of thes e other chromosomal aberrations are unexpected, even after pretest counselling(van Zwieten 2004). Another problem is the uncertain clinical relevance of some of these other chromosomal aberrations. Unexpected and/or uncertain findings can cause patient anxiety, difficult counselling issues and potentially unnecessary pregnancy terminations(vanZwieten,2004).
MLPA (multiplex ligation-dependent probe amplification)is a new molecular genetic technique in prenatal diagnosis usingamnioticfluid.It is a potential alternative test for detecting aneuploidies. Compared to TKT, MLPA has 4

potential advantages:(1)the result is known in 2 days instead of 3 weeks, (2)the procedure is considerably less labourintensive,(3)the test requires less amniotic fluid (2-4ml in stead of 20ml)(4)MLPA is suitable for high throughput testing. Previous preclinical evidence suggests equivalence of MLPA and TKT regarding test performance (accuracy in detection of common occurring chromosome aberrations).

Study objective

The aim of this study is to evaluate the role of MLPA in a routine clinical setting for detecting firstly, DS and secondly, the most common chromosomal aberrations compared to TKT (gold standard) in prenatal diagnosis.
Is diagnostic accuracy of the MLPA P095 aneuploidy kit equivalent to that of TKT? In other words: can MLPA fully replace TKT, using amniotic biomaterial in an unrestricted way?
Does MLPA reduce anxiety for the patient by getting quicker results and less complex counselling issues?
Does substitution of TKT by MLPA improve cost-effectiveness of prenatal care?
What is the relevance of the differential pattern of unexpected findings in MLPA versusTKT?
What do pregnant women generally prefer, MLPA or TKT, given the most pertinent characteristics of both tests (includings equelae of the different availability of the test result)?

Study design

The study is designed as a diagnostic substitute study.

Study burden and risks

There will be no extra risk, associated with participating as the TKT result still is the gold standard.

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 women undergoing amniocentesis
the referral indication for amniocentesis is: 1)advanced maternal age, 2) increased risk after prenatal screening tests
informed consent is given

Exclusion criteria

patients with other referral indications, e.g. ultrasound abnormalities, previous child with chromosomal berration, structural balanced chromosome aberration of one of the parents.
language barrier

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2006
Enrollment:	4500
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL12992.067.06