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Comparison of false positive rates in prenatal combined screening and cell free DNA screening for trisomy 21

Submission date 26/07/2016	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 03/08/2016	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 10/10/2022	**Condition category** Genetic Diseases	[_] Individual participant data

Plain English summary of protocol

Background and study aims
Down's syndrome, also called also called trisomy 21, is a genetic condition that causes learning disability and characteristic physical features. Screening during pregnancy can determine the likelihood of a baby being born with Down's syndrome. The gold standard screening test is called the combined test because it combines an ultrasound scan with a blood test. The mother's age and the information from these two tests is used to work out the risk of the baby having Down's syndrome. However, recent research suggests that the test can be improved by adding another test called cell-free fetal DNA screening. Cell-free fetal DNA is DNA from the baby that is found circulating freely in the mother's blood stream. This additional test could improve screening by reducing the false-positive rate (the number of babies incorrectly diagnosed as having Down's syndrome). The aim of this study is to compare the false-positive rates of combined screening and cell-free DNA screening for Down's syndrome.

Who can participate?
Women with single pregnancies coming for Down's syndrome screening at 11-13 weeks of pregnancy

What does this study involve?
Participants undergo an ultrasound scan at 11-13 weeks of pregnancy. If fetal defects are found screening is not appropriate and invasive testing is performed. If no anomalies are found then participants are randomly allocated to undergo either cell-free DNA screening or combined screening. Both tests involve blood samples being taken. If there is a positive result invasive testing is offered. The numbers of false-positive cases in the two groups are compared.

What are the possible benefits and risks of participating?
There are no risks as all the tests are already considered to be standard procedures

Where is the study run from?
University of Tuebingen (Germany)

When is the study starting and how long is it expected to run for?
July 2016 to October 2017

Who is funding the study?
Cenata GmbH (Germany)

Who is the main contact?
Prof. Karl Oliver Kagan

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
2015 - 1

Study information

Scientific Title
Comparison of false positive rates in prenatal combined screening and cell free DNA screening for trisomy 21

Acronym
ReFaPo study

Study objectives
After a detailed ultrasound examination at 11 - 13 weeks with a normal result, cell-free DNA can reduce the false positive rate compared to combined screening based on maternal age, fetal nuchal translucency, PAPP-A and free beta-hCG.

Ethics approval required
Old ethics approval format

Ethics approval(s)
University of Tuebingen medical faculty ethics committee, 06/10/2015, ref: 572/2015BO1

Study design
Single-center randomised controlled trial

Primary study design
Interventional

Study type(s)
Screening

Health condition(s) or problem(s) studied
Prenatal screening for trisomy 21

Interventions
Following the normal ultrasound examination, randomization is performed into cell-free DNA screening or combined screening (maternal age, fetal NT, PAPP-A and free beta hCG).

In the cell free DNA (cfDNA) screening group, the risk for trisomy 21 will be calculated based on cell free DNA. For this analysis, blood will be taken and sent to CENATA GmbH who does the analysis. In general the analysis takes 3-5 days. The result will be a risk score. The case is considered to be screen positive if the risk is 1:100 or higher.

In the combined screening group, blood is taken for the analysis of PAPP-A and free beta hCG. The analysis will also done by a commercially driven laboratory. The risk will be calculated by the software of the Fetal Medicine Foundation UK. A risk for trisomy 21 of 1:100 or more is considered to be screen positive. In case of a screen positive result, invasive testing is offered. If the patient opts against invasive testing, we wait until the end of the pregnancy. Screen positive euploid cases are considered to be false positive cases.

All methods (screening by cfDNA, combined screening and invasive testing) are standard procedures in fetal medicine.

Intervention Type
Other

Primary outcome(s)
Number and proportion of false positive cases in each arm. False positive cases are defined as euploid cases with a risk for trisomy 21 > 1:100. The karyotype will either be obtained by invasive testing somedays after the screening test or after birth.

Key secondary outcome(s))
1. Number of cases that cannot be randomized (due to fetal defects, increased NT, multiple gestations). This data will become available at 11-13 weeks' gestation.
2. Time interval between randomization and return of the blood results
3. Number of cases without results in each study arm. This data will be become available latest 2 weeks after the blood sample is taken.
4. Number of women who opt for invasive testing. This data will generally be available within the consecutive 4 weeks after the screening test but theoretically the invasive test can be carried out through the pregnancy.
5. Acceptance of each screening test. The patient will be contacted by us to assess the acceptance level of each of the screening tests. This will be done 4 weeks after the screening test and after birth.

Completion date
01/10/2017

Eligibility

Key inclusion criteria
1. Patients coming for prenatal screening for trisomy at 11-13 weeks' gestation
2. Singleton pregnancies
3. Normal ultrasound examination without increased nuchal translucency thickness >3.5mm and without fetal defects. If NT is increased or there are fetal defects, screening is not appropriate and invasive testing is performed
4. Informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
1376

Key exclusion criteria
1. Increased nuchal translucency thickness
2. Fetal defects
3. Multiple gestations

Date of first enrolment
01/08/2016

Date of final enrolment
01/03/2017

Locations

Countries of recruitment
Germany

Study participating centre

University of Tuebingen
Department of Obstetrics and Gynaecology
Germany
72076

Sponsor information

Organisation
University of Tuebingen (Germany)

ROR
https://ror.org/03a1kwz48

Funder(s)

Funder type
Industry

Funder Name
Cenata GmbH (Germany)

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/01/2019	05/08/2019	Yes	No
Protocol file	in German version 1.0		10/10/2022	No	No