Information for research subjects and parents

Background

Many pregnant women want information about prenatal diagnosis and some choose to undergo a combined test, the CUB test, consisting of an ultrasound scan and a blood test. This test provides an estimate of the probability that the fetus has any of the most common chromosomal abnormalities (trisomy 13, trisomy 18 or trisomy 21). Women whose results indicate a high probability of trisomy 13, 18 or 21 are offered additional diagnostic testing, i.e. a biopsy from the placenta (chorionic villus sampling) or a test of the amniotic fluid (amniocentesis). However, these diagnostic tests raise the risk (less than 0.5% increase) of miscarriage. It is thus important to develop a test that does not increase the risk of miscarriage and that will reduce the number of women who must be offered invasive diagnostic tests.

A test called NIPT (non-invasive prenatal test) has recently been developed. It analyzes the unborn baby's DNA in a blood sample from the pregnant woman, in order to assess the probability of fetal chromosomal abnormalities. In this study we will be testing, in addition to the chromosomal abnormalities included in the CUB test, for triploidy, the 22q11.2 syndrome and sex chromosome abnormalities. Triploidy is incompatible with life. Learning disabilities, heart malformations and increased susceptibility to infections are among the consequences of the 22q11.2 syndrome. Sex chromosome abnormalities can lead to mild learning disabilities, growth restriction and infertility, among other problems. Individuals with 22q11.2 syndrome and sex chromosome abnormalities can also live a normal life without knowing about their syndrome. An early diagnosis can lead to that more adequate resources is used, less suffering, less examinations and less concern for parents and child.

Purpose/aim of the study

The aim of this study is to develop, evaluate and assess the quality of the NIPT, primarily investigating the reliability of the analysis for the above-mentioned syndromes. Blood samples will be taken. Some of this material will be used for chromosome analysis (NIPT) and some will be used to develop test components and analysis methods. Our goal is the possibility, in the future, to reliably diagnose chromosomal abnormality in an unborn child with a simple blood test from its mother. The study will be conducted in cooperation with the American company Natera, Inc, and its representatives will be monitoring the study.

Invitation to participate

Pregnant women aged 18-50, and has not already participated in the study in a previous pregnancy, will be invited to participate in the study after the CUB test. In order to be eligible to participate you also need to meet the following criteria's: you should expect only one child (it cannot initially have been a duplex pregnancy), be between 9+0 – 17+0 weeks pregnant or after 22+0 weeks pregnant, not have done NIPT earlier during this pregnancy, be able to understand the information for research subjects and parents, consent to participate and be willing to be informed about the results of the NIPT. Furthermore, in order to be included in the study, both parents (if there are two) must be able to understand the information and consent to the newborn infant being tested, as well as being able to understand and consenting to receiving information if the analysis indicates that the baby has any of the above-mentioned syndromes.

The study process

If you choose to participate in the study, a blood sample will be taken at the Ultrasound Clinic at the Department of Obstetrics and Gynecology at Sahlgrenska University Hospital/Östra. This study sample will be sent to the USA for development of the test, as well as for analysis of fetal DNA in your blood, which will be tested for the chromosomal abnormalities trisomy 13, trisomy 18, trisomy 21, triploidy, 22q11.2 syndrome and sex chromosome abnormalities. You will be informed about the results of the NIPT, but this test is not yet diagnostic. If the probability of the above-mentioned abnormalities is low in the NIPT, regardless the result of the CUB test, the test results will be sent to

you by mail. In around 0.9-4.6% of cases, the NIPT indicates no result, in which case we will call you and either offer a new NIPT or an appointment with a physician for more information and, possibly, an amniocentesis or chorionic villus sampling. If the NIPT indicates no result twice you will be offered a visit to a physician as soon as there is a time slot available. If the probability of any of the above-

mentioned abnormalities is high in the CUB test (1:2-1:50) and NIPT, or if only high risk at NIPT, one of the study staff will call you to schedule an appointment with a physician at Sahlgrenska University Hospital/Östra. When you see the physician, you will be given additional information and offered a chorionic villus sampling or an amniocentesis and possibly a more extensive ultrasound scan (if you are using anticoagulantia you may have to stop using this drug before your invasive testing, after consultation with your physician). No test results will be given by phone. Please note that if you have high risk in the CUB test (1:2-1:50) you will already have an appointment with a physician. In order to get good information and opportunity to ask questions you are encouraged to attend your physicians appointment even if you already received a low risk mail.

After the delivery, your newborn baby will also be tested, either by taking a few extra drops of blood (about 0.5 mL) together with the routine PKU test (which is taken on all newborn babies) or by 1-2 soft oral swabs being rubbed on the inside of the baby's cheeks for about one minute. The blood sample or swab is then sent for analysis of the chromosomal abnormalities trisomy 13, trisomy 18, trisomy 21, triploidy, 22q11.2 syndrome and sex chromosome abnormalities. Only if the analysis indicates that your baby has any of these syndromes and that we expect these to have a significance for the child's health at a longer term perspective, and if this condition has not previously been detected during pregnancy, we will contact you to schedule an appointment with a doctor so you can obtain more information and be offered further tests. The analysis of the newborn samples may take up till one year. Tests may also be taken from the placenta after delivery.

The study staff will peruse your and your baby's medical records until you are both discharged from the hospital or until 28 days after delivery. This means that the study staff can read everything that has been written in the medical records until 28 days after delivery, but the time when they are reading it could be after those first 28 days.

The information about you that will be sent together with the NIPT are test date and time, name, personal ID (Social Security number), week of pregnancy, number of fetuses, weight, height and if the pregnancy was conceived via IVF or oocyte donation. This information will not be decoded when the tests are sent to the USA for analysis since it is very important that the results will be sent to the right patient when you obtain them. Examples of other information concerning you that will be accessed for analysis are: results of any ultrasound scans done during pregnancy (for instance the CUB test and the routine scan at 18-20 weeks), the results of any chorionic villus sampling and/or amniocentesis you have undergone, as well as your own and your baby's medical condition during any previous pregnancies and the current pregnancy, delivery and the period immediately following delivery. This information will be coded before it is made available, so that it will not be directly traceable to your person. All study data is confidential.

In other parts of the world and in private clinics in Sweden, patients pay for NIPT themselves. In this study, you will not be charged for the NIPT. Instead, additional analyses will be performed in order to generally improve the test.

Testing

You will be tested by taking a blood sample of about 40 mL (about two tablespoons of blood), collected in four test tubes. These samples will be taken at the same time. Two of the test tubes will be used for the NIPT analysis, from this you will obtain result. From these two tubes lab metrics will be stored for quality respect (for example fetal fraction), this information will not be able to be linked to you. The other two test tubes will be analyzed in order to improve the NIPT. Genetic analyzes will be done on these samples, but it's only for research, and therefore, no test results will be given back to you. The blood sampling causes minimal to no pain. Your baby will be tested either by taking a few extra drops of blood (about 0.5mL), together with the routine PKU test, or

by rubbing 1-2 soft oral swabs on the inside of the baby's cheeks for one minute. The baby will be tested on one single occasion and testing causes minimal or no pain. Your placenta may also be sampled after delivery. Both the samples from you and from the baby will be sent to the USA for analysis.

Time required
Sampling of your blood and the testing of your baby will each require about 5-10 minutes.

Which tests are routine treatment or extra, non-routine tests?
The study tests on both you and the baby are not part of your routine treatment.

Risks
The study entails minimal risk for you and your baby since only a blood sample or oral swab are required. There are no additional risks for you or the baby involved in an extra ultrasound scan or a

biopsy from the placenta after delivery. The results of the NIPT will be revealed to you and the pertinent study staff, and they will thus be available for use in your care and/or treatment.

Benefits
Participation in the study may benefit you, as an individual patient, since you will be given the results of the NIPT, which investigates the probability of your unborn baby having trisomy 13, trisomy 18, trisomy 21, triploidy, the 22q11.2 syndrome or a sex chromosome abnormality. These results can be used in the management of your pregnancy. Furthermore, you will also be informed if the test results from your baby indicate that it has any of mentioned above syndrome. In that case, the results can be used to allocate the appropriate resources for your baby at an early stage. The results of the study are expected to contribute knowledge about whether it will be possible, in the future, to reliably and safely diagnose chromosomal abnormalities with a blood test from a pregnant woman. However, this will not benefit any individual patient while the study is ongoing.

Data processing
Data collected in connection with the NIPT will not be coded, which means that your name and personal ID (Social Security) number will be sent together with the samples to the USA for analysis. This will be done since the test results will be given to you and it is thus crucial to minimize the risk of results being mixed up. All other data, made available for analysis, that have been collected for development of the test and other study purposes (i.e. not related to the NIPT) will be coded, meaning that your name and personal ID (Social Security number) will be replaced with a code so that no individual can be identified. Personal data will be handled in accordance with the General Data Protection Regulation (GDPR). Patient data from the study will be compiled in a register and processed. These data will be confidential and no unauthorized person will have access to the register. Only the researchers in charge of the study will have the code "key". In the event that the study is published, no individuals will be identifiable.

Coded information from your medical records related to the study may be audited by the U.S. Food and Drug Administration (FDA) or government agencies in other countries where this NIPT may be considered for approval. In the event of regulatory visits, your medical records and consent form may be looked at by the U.S. FDA and/or other regulatory agencies, the Institutional Review Board, and the Biomedical Research Alliance New York.

Responsibility for personal data
Sahlgrenska University Hospital is responsible for handling personal data. You can contact the hospital's personal data controller (Susan Lindahl, tel +46 31- 343 27 15) if you want an extract of the registered personal data concerning you and if you want assistance to have the data corrected.

Biobank
As mentioned above, some of the study samples will not be coded. These samples will be destroyed

after the end of study or will be sent back to Perinatal laboratory. The other coded samples will be stored in a biobank and may only be used for purposes for which you have given consent. They can only be used for a future study if you have given renewed consent and after approval of the Ethics Board. You are fully entitled, without stating any specific reason, to request that your samples be destroyed or decoded, so that they are untraceable to your person. You can read more about this in the Swedish Biobanks in Medical Care Act (SFS 2002:297).

Confidentiality
All study staff are required to observe strict confidentiality.

Remuneration
No economic remuneration will be offered for participation in the study.

Participation is voluntary
You are not required to participate in the study to obtain care for yourself and your baby. Participation in the study is voluntary and can be terminated at any time without stating any reason. You will not be given worse treatment and your decision will not affect the care you are given if you choose not to participate in the study.

If you want to withdraw your participation: If you want to withdraw your participation in the study, contact the research midwife (se contact details below).

Collected information: The principal investigator have the right to retain the information collected before the date of withdrawn from the study and these data will still be part of the study.

Collected samples: If you no longer want us to use your samples, you have the right to have the samples destroyed.

For more information, contact the main researchers:

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