Analysis of Fetal DNA in Maternal Blood: Non-Invasive Fetal Diagnostic Tests for Blood Group and Sex Determination

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Summary and conclusions

There is a fetal diagnostic technique available today that involves analysing blood taken from the pregnant woman for the genetic characteristics of her fetus. Non-invasive prenatal diagnosis (NIPD), exploits the presence of cell-free fetal DNA in the blood of the pregnant woman, and often eliminates the need for invasive sampling of e.g. the placenta or amniotic fluid. Small amounts of cell-free fetal DNA are present in the pregnant woman's plasma during pregnancy but are rapidly eliminated from the mother's circulation following delivery.

The aim of this evaluation was to establish the accuracy of NIPD in the context of medically indicated fetal blood group and sex determination, and to discuss the health economic and ethical aspects. Sex determination of the fetus in the absence of any medical indication (e.g. for family planning) has not been evaluated. Using the technique for this purpose has been considered unethical in other contexts.

More than 200 scientific publications have been assessed during the evaluation, of which 30 have been assessed in detail. We have focused on three target groups for this technique:

Blood group determination

- Pregnant women immunised against RhD or other blood group antigens
- RhD-negative pregnant women who are not RhD immunised, i.e. screening

Sex determination

- Pregnant women with a medical indication for fetal sex determination as in e.g. X-linked diseases

The use of NIPD for fetal DNA analysis is the subject of active research and development in a variety of clinical fields and in screening for fetal blood groups.

SBU's appraisal of the evidence

- ❑ Some pregnant women have antibodies to (have become immunised against) the blood group of the fetus, which represents a risk to the fetus. The use of NIPD to determine the blood group of the fetus may help to improve the safety of medical care offered to these women and their unborn children.
- ❑ Screening for fetal blood group using NIPD, in combination with specific prenatal preventive measures (targeted RhD prophylaxis), could result in fewer RhD-negative pregnant women developing antibodies to RhD. The organisational and health economic consequences of introducing this type of screening have not been established.
- ❑ The use of NIPD to determine fetal sex when this is medically justified could improve the safety of medical care by reducing the need for invasive fetal diagnostic tests. The technique is not currently used for this purpose in Sweden.
- ❑ There is a lack of published research into the cost-effectiveness of using NIPD to determine fetal sex or blood group.

Summary

Blood group determination

Pregnant women immunised against RhD or other blood group antigens

A pregnant woman who has become immunised against RhD or another blood group, has during current or past pregnancy developed antibodies to a fetal blood group antigen. This is the case in about 1 000 pregnant women

in Sweden every year. The woman's antibodies may destroy the red blood cells of the fetus, which can be life-threatening for the unborn child. In some cases, this has serious consequences for the child, who may need blood transfusion either during pregnancy or after delivery. In rare cases the fetus/child cannot be saved.

NIPD was introduced a few years ago in Sweden for fetal blood group determination in pregnant women immunised against RhD or Rhc. Determination of fetal blood group establishes whether or not the fetus is at risk. If the fetus has a blood group antigen against which the mother has antibodies, the woman needs to be monitored with regular antenatal checks and, possibly, treatment. If the fetus does not have any of these antigens, further tests can be avoided and the parental anxiety in this regard can be alleviated for the remainder of the pregnancy. The use of NIPD can, therefore, help to improve the safety of medical care offered to these women and their unborn children. Used in the way just described, the technique is not thought to raise any significant ethical issues.

RhD-negative pregnant women without RhD immunisation (screening)

NIPD can also be used to screen all RhD-negative pregnant women, enabling the early determination of fetal blood group. About 85 percent of the Swedish population is RhD-positive. The other 15 percent of the population is RhD-negative and lacks the RhD protein, which is the case in about 16 500 pregnant women every year. About 60 percent of these RhD-negative women will carry an RhD-positive baby. In Sweden, RhD prophylaxis is given to these women after delivery, in order to reduce the risk of RhD immunisation.

The introduction of screening to determine fetal RhD status in all RhD-negative women is the subject of debate in Sweden and internationally. It involves a large number of tests and creates new demands on technical platforms. Screening to determine fetal RhD status using NIPD has recently been introduced in Denmark and the Netherlands and is the subject of a study by Stockholm County Council, which is estimated to be completed in 2012.

If NIPD is to be offered in the future to all RhD-negative pregnant women, the objective would be to give RhD prophylaxis during pregnancy (antenatal prophylaxis) only to those carrying an RhD-positive child, in order to reduce the risk of RhD immunisation. The use of NIPD to screen these women would, when combined with targeted RhD prophylaxis, have the potential to reduce the number of new cases of RhD-immunised women. This method could supersede the current practice of antenatal checks and postnatal fetal blood group determination. NIPD used for this purpose offers benefits to women and babies, compared to current practice, and is not considered to be ethically controversial.

Sex determination

NIPD is not currently used in Sweden for medically indicated sex determination but its introduction is planned. The method has the potential to reduce the need for invasive fetal diagnostic tests. If NIPD is used for this purpose, invasive diagnostic tests and late terminations can, in some cases, be avoided. This could reduce medical and psychological risk for the woman.

The use of fetal sex determination to plan families (i.e. sex selection as such) is considered unethical. Basic values of human dignity and respect would be threatened if the technique were to be used in this way. The issue has been considered by the Swedish National Council on Medical Ethics (SMER).

Patient benefit / evidence-graded results

- There is moderately strong scientific evidence that fetal *RHD* determination by NIPD has a sensitivity and specificity of nearly 99 percent (⊕⊕⊕○). These results are largely based on studies of RhD-negative pregnant women who are not RhD-immunised. Those studies that also included pregnant women who have been immunised against RhD showed similar results.

- The scientific evidence is insufficient to establish the sensitivity and specificity of blood group determination by NIPD in fetal *RHC*, *RHc*, *RHE* and *KEL1* (⊕○○○). It should, however, be noted that these analyses apply to only a few women and, if it is clinically important, the analysis could be repeated as required.

- There is limited scientific evidence that fetal sex determination by NIPD has a sensitivity and specificity of almost 99 percent (⊕⊕○○).

Economic aspects

The cost of fetal blood group determination by NIPD was about 2 900 SEK in 2010. The cost of the analysis represented 90 percent of the total cost. NIPD for immunised pregnant women is currently cheaper and has a lower risk of undesirable effects than invasive fetal diagnostic tests.

The health economic consequences of introducing NIPD for the screening of non-RhD-immunised RhD-negative pregnant women are not clear. The cost per analysis within the Swedish healthcare system has not yet been determined.

There is a lack of published research into the cost-effectiveness of using NIPD to determine fetal sex or blood group.

Four levels are used in grading the strength of the scientific evidence on which conclusions are based:

Strong scientific evidence (⊕⊕⊕⊕). Based on high or medium quality studies with no factors that weaken the overall assessment.

Moderately strong scientific evidence (⊕⊕⊕○). Based on high or medium quality studies with isolated factors that weaken the overall assessment.

Limited scientific evidence (⊕⊕○○). Based on high or medium quality studies having factors that weaken the overall assessment.

Insufficient scientific evidence (⊕○○○). Scientific evidence is deemed insufficient when scientific findings are absent, the quality of available studies is low, or studies of similar quality present conflicting findings.

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SBU evaluates healthcare technology

The Swedish Council on Health Technology Assessment (SBU) is a national governmental agency that assesses healthcare technologies. SBU analyses the benefits, risks, and costs of different methods and compares the scientific facts to prevailing practices in Sweden. SBU's goal is to provide stronger evidence for everyone engaged in shaping the delivery of health services.

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This assessment was published in 2011. Findings based on strong scientific evidence usually continue to apply well into the future. However, findings based on insufficient, limited, or contradictory evidence might have already been replaced by more recent findings.

The complete report is available in Swedish.

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