NON-INVASIVE PRENATAL DIAGNOSIS BASED ON THE PRESENCE OF EXTRACELLULAR FETAL NUCLEIC ACIDS IN MATERNAL CIRCULATION

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INTRODUCTION

Prenatal diagnosis is now part of established obstetric practice in many countries.

However, conventional methods of obtaining fetal tissues for genetic analysis, including amniocentesis and chorionic villus sampling, are invasive and constitute a finite risk to the unborn fetus. Approximately one procent end with abortion because of the procedure, even though the fetus is healthy.

Other methods also exist, that without risks, can give information about certain conditions that the fetus might have. But a certain diagnosis can not be given without several different examination methods by a specialist.

It has been a long-sought goal in human genetics to develop methods of obtaining fetal genetic materials for analysis, without putting a risk on the mother and fetus. Research in this field have been intensified the last years, mostly because of technologically improvements that have given us new techniques and new valuable information.

Based on analysis of fetal nucleic-DNA in maternal blood, pregnant women are able to get a diagnosis that is totally risk free for the fetus.

Unfortunately, with new technology there will always be new problems that need to be discussed and solved before they can be used in clinical practice. The ideal situation would be that there was some kind of world wide policy for the usages, unfortunately this is impossible.

I will look further into the clinical practice of prenatal diagnosis that already exists. Try to evaluate the usage and the negative and positive sides of them. I will also discuss the newer methods and the ethical problems that have arised, and how we might be able to approach them.

PRENATAL DIAGNOSIS

Prenatal testing is testing for diseases or conditions in a fetus or embryo before it is born. The aim is to detect birth defects such as neural tube defects, Down syndrome,other chromosome abnormalities,genetic diseases and other conditions. It can also be used to determine its sex.

Diagnostic prenatal testing can be by invasive or non-invasive methods. An invasive method involves probes or needles being inserted into the placenta, e.g amniocentesis, which can be done from about 14 weeks gestation, and usually up to about 20 weeks, and chorionic villus sampling , which can be done earlier (between 9.5 and 12.5 weeks gestation) but which is slightly more risky to the fetus. Non-invasive methods, can only evaluate risk of a condition and cannot determine 100% if the fetus has a condition. Non-invasive techniques include ultrasound and maternal serum screening . If an abnormality is indicated by a non-invasive procedure, a more invasive technique may be employed to gather more information.

The tests can be used to check for conditions such as Downs syndrome,spina bifida, cleft palate, Tay Sachs disease, sickle cell anemia, thalassemia, cystic fibrosis and fragile X syndome. In some cases, the tests are administered to determine if the fetus will be aborted.

Some screening tests performed on the woman are intended to detect traits or characteristics of the fetus. Others detect conditions in the woman that may have have adverse effects on the fetus, or that threaten the pregnancy.

Risk factors qualifying a pregnant woman for prenatal testing

Women over the age of 35.
Women who have previously had premature babies or babies with a birth defect, especially heart or genetic problems..
Women who have family histories or ethnic backgrounds prone to genetic disorders, or whose partners have these.
Women who have previously had several miscarriages
Women who have high blood pressure,lupus, diabetes,asthma or epilepsy
Women with multiple prenancies

The type of prenatal diagnosis done depends on the situation of the parents. If the woman is classified as being at high risk for a defect in the fetus, a more accurate but also more risky invasive technique may be used.

Reasons for prenatal diagnosis

1) to enable timely medical or surgical treatment of a condition before or after birth,

2) to give the parents the chance to abort a fetus with the diagnosed condition,

3) to give parents the chance to "prepare" for a baby with a health problem or disability, or for the likelihood of a stillbirth.

Having this information in advance of the birth means that healthcare staff can better prepare themselves and parents for the delivery of a child with a health problem.

Non-invasive methods

Ultrasound detection- Commonly dating scans from 7 weeks to confirm pregnancy dates and look for twins. The specialized nuchal transluscency screening at 11-13 weeks may be used to identify higher risks of Down syndrome. Later morphology scans from 18 weeks may check for any abnormal development.
Ultrasound scans do not propose any risk for the mother or the fetus.

Less invasive methods

Second trimester maternal serum screening

invasive methods

Chorionic villus sampling- Involves getting a sample of the chorionic villus and testing it. This can be done earlier than amniocentesis, but may

have a higher risk of miscarriage.

Amniocentesis- This can be done once enough amniotic fluid has developed to sample. Cells from the fetus will be floating in this fluid, and can be separated and tested.

Embroscopy and fetoscopy- These involve putting a probe with a video camera into a women's uterus to observe, or to sample blood or tissue from the embryo or fetus.

Ethical issues of prenatal testing

The option to continuing or aborting a pregnancy is the primary choice after most prenatal testing. Rarely fetal intervention corrective procedures are possible.
Knowing about certain birth defects such as spina bifida before birth may give the option of fetal surgery during pregnancy, or assure that the appropriate treatment and/or surgery be provided immediately after birth.

False positives and false negatives

Ultrasound of a fetus, which is considered a screening test, can sometimes miss subtle abnormalities. For example, studies show that a detailed ultrasound can detect about 80% of spina bifida.

Other screening tests, such as the triple test,can have false positives and false negatives. Even when the triple test results are positive, usually the pregnancy is normal, but additional diagnostic tests may be offered.

Both false positive and false negatives will have a large impact on a couple when they are told the result, or when the child is born. Diagnostic tests, such as amniocentesis, are considered to be very accurate for the defects they check for.

A higher maternal serum AFP level indicates a greater risk for anencephaly and open spina bifida. This screening is 80% and 90% sensitive for spina bifida and anencephaly.

No prenatal test can detect all forms of birth defects and abnormalities.

Amniocentesis has become the standard of care for prenatal care visits for women who are “at risk” or over a certain age. All obstetricians offer patients the triple test, HIV test and ultrasounds routinely. However, almost all women meet with a genetic counselor before deciding whether to have prenatal diagnosis.
It is the role of the genetic counselor to accurately inform women of the risks and benefits of prenatal diagnosis. Genetic counselors are trained to be non-directive and to support the patient's decision. Some doctors do advise women to have certain prenatal tests and the patient's partner may also influence the woman's decision.

EXTRACELLULAR FETAL NUCLEIC ACIDS IN MATERNAL CIRCULATION

The discovery of cell-free fetal DNA in maternal plasma in 1997 has opened up new possibilities for noninvasive prenatal diagnosis. Circulating fetal DNA molecules have been detected in maternal plasma from the first trimester onwards and can be robustly detected using a variety of molecular methods

The first marker that was developed for fetal DNA detection in maternal plasma was the Y chromosome, which is present in male fetuses . This approach constitutes a highly accurate method for the determination of fetal gender, which is useful for the prenatal investigation of sex-linked diseases .

Maternal plasma DNA analysis is also useful for the noninvasive prenatal determination of fetal RhD blood group status in RhD-negative pregnant women . This approach has been shown by many groups to be highly accurate and has been introduced as a routine service by the British National Blood Service since 2001 The latter development is important because this is the first routine use of noninvasive DNA-based prenatal diagnosis.

More recently, maternal plasma DNA analysis has been shown to be useful for the noninvasive prenatal exclusion of fetal ß-thalassemia major A similar approach has also been used for prenatal detection of the HbE gene

Other genetic applications of fetal DNA in maternal plasma include the detection of achondroplasia myotonic dystrophy , cystic fibrosis Huntington disease and congenital adrenal hyperplasia .It is expected that the spectrum of such applications will increase over the next few years.

Shortly after the documentation of the concentrations of circulating fetal DNA in maternal plasma in normal pregnancies, investigators studied its possible quantitative aberrations in pathologies.

The first disease that was associated with such quantitative aberrations of fetal DNA in maternal serum was preeclampsia , in which a fivefold elevation in the median circulating fetal DNA concentration was found. These results have now been reproduced by a number of other groups . It has recently been shown that at least part of such elevation might be attributable to the impaired clearance of circulating fetal DNA in preeclamptic pregnancies. In addition, fetal DNA concentration has also been found to be elevated before the onset of preeclampsia .In addition to preeclampsia, quantitative aberrations involving circulating fetal DNA have also been described in certain chromosomal aneuploidies preterm labor hyperemesis gravidarum and invasive placentation Taken together, these data suggest that it might be possible to use fetal DNA in maternal plasma or serum for predicting risky pregnancies.

IMPORTANT QUESTIONS SOCIETY MUST TACKLE

As we have seen,this new technology will give us new improved ways of prenatal diagnostics. It will help us to be able to improve prevention of many diseases .

There are many questions that will arise, if this new risk free method of diagnosis will become available for everyone. People are very different in their views, and the ethics is an important factor.

Will we see an increased demand for prenatal diagnosis , when the risk of abortion and loosing a healthy child is gone with the new risk free method?

How will the decisionprocess change with the introducton of these new methods? Will prenatal diagnosis become ”to available” or ”to easy? ”

When the risks are gone, will the genetic counseling be different? Will the governments demand of this type of counseling change?

Will we see changes in the societies view of prenatal diagnosis? Will the society put pressure on couples to accept the offer of risk free prenatal testing?

Should the testing be offered to everybody?

These are some of the questions I believe we must tackle in the near future. I believe we have many discussions regarding different issues in the future, and how each countries government will handle and regulate it.

FETAL SEX DETERMINATION-TESTS ON THE COMMERCIAL MARKET

”Whas it a boy or a girl?” is often the first question new parents are asked from the society. Many couples wants to know the sex of their child before it is born.
Sex determination has traditionally been determined by either ultrasound or invasive methods .
The sex can be determined by week 12 with ultrasound,when the genitals are developed so it is possible to see a difference between a boy and a girl.
At approximately 12 weeks, the genitals can be visualized at 80-100% of the pregnant women.

In July 2005, it was rapported that it is now possible to determine the sex of fetus through a commercial test bought online

The women takes a bloodtest from her finger and sends in the dry blood for analysis. The testpackage costs 275 american dollars, and the company gives the double amount back if the result shows to be wrong. The company claims that the test can be used already from week 5 of the pregnancy, and that it has an accuracy of 99,9%.
The test is supposely based on 20.000 births.

Baby Gender Mentor is the trade name of the commercial sex determination test.The test is made by Acu-Gen Biolab, Inc., a biotech company in Lowell, Massachusetts,United States.

The company says that the accuracy of the test exceeds that of conventional methods, and that their test offers "unsurpassed accuracy, unrivaled earliness, and uncompromised promptness".However, they have not made public any clinical evidence to support these claims. Customers and scientists have questioned the accuracy of the test, and

legal action is being pursued against Acu-Gen as well as a major supplier of the test.

It has been expected for a long time that such a test will soon reach the public through the commercial market. It had to come sooner or later.
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These types of test give people the possibility to abuse the technology by sorting children based on the sex.
In most countries the women can choose to have an abortion before week 12 (this number differs between countries).
We will probably see a rise in abortions taken because the fetus is of ”wrong” sex.
In many countries the biotechnological laws forbid to tell the sex of the fetus in the first trimester. Still,there is nobody that controll if the women have already bought a test online, and then demands abortion without anybody knowing why.

In Great Britain and USA there is a debate going on about the so called family balancing,where different methods help families with many children of same sex to have a child with the opposite sex. This test will probably have a great market in parts of the world.
There is a great preferance forboys in countries like India, and there is little doubt that there is selective abortion of female fosters and murders of little girl children.


BabyGenderMentor
• 99.9% Informative
• Confidential and Anonymous
• 5 Weeks after Conception
• Just a Fingerprick
• Results in 48 Hours

CONCLUSION

The discovery of cell-free fetal DNA and RNA in maternal plasma has opened up new possibilities for noninvasive prenatal diagnosis. Over the past 7 years significant progress has been made in our understanding of the biology and diagnostic implications of fetal nucleic acids in maternal plasma. It is hoped that further developments over the next few years will enable us to move even closer to the goal of widespread use of noninvasive nucleic acid-based prenatal diagnosis.

In theory it should be used on fetus early in the pregnancy without causing any risk to the mother and fetus. As we have seen there is a great potential for "abuse" of this technology.

Ideally the new methods could be used in cases where there is a high risk of the child inheriting a know disease in a family, or when there is suspicion of a certain genetic disease based on ultrasound finds.

It should also be available for use as an indicator for pre-eclampsia. As we know this is a life threatening disease for both mother and fetus, and it will be very useful if a test could predict this. As we know the fetal nucleic cells increase in the maternal peripheral blood of women in pre-eclampsia.Even in those without symptoms.

Countries as France, Netherlands and Great Britain are already using cell free fetal nucleic acids for detection of rhesus isoimmunisation.

A limitation of this method will be that it can probably not be used in multiple pregnancies.

It will probably not stop the usage of ultrasound, but hopefully the invasive methods that carries risk for the fetuses.

Unfortunately, what we see is that technology is running in front of the ethics. When new technological breakthroughs create ethical problems, the governenment usually answers with regulations with laws. In this situation I believe it will be difficult. We see that the methods greatly improves prevention of many conditions and diseases. Should it be up to the government to restrict the usage?


pkg foundation
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