Prenatal diagnostics

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Definitions

Prenatal diagnostics are regulated by the "Act of 5 December 2003 No. 100 relating to the application of biotechnology in human medicine, etc." which in § 4-1 states: *"For the purpose of this Act, prenatal diagnosis means the examination of fetal cells, a fetus or a pregnant women in order to obtain information about the genetic constitution of the fetus or to detect or exclude a disease or abnormality of the fetus".* The Ministry of Health requires approval of institutions, examination types and methods (§7). Ultrasound examinations on clinical indication and routine ultrasound at 18 weeks of gestation are not regulated by the Biotechnology Act.

Prevalence / Epidemiology

About 3% of all new-borns have abnormalities that have consequences, such as a disability or malformation that requires surgical treatment. The prevalence of trisomy 21, trisomy 18 and trisomy 13 increases with maternal age, particularly in women over the age of 35 years. Prenatal diagnostics has traditionally been regarded as the diagnosis of chromosomal diseases and certain structural malformations. Todays' prenatal diagnostics includes the extended term as stated in the definition above.

Indications

The indications are regulated by guidelines[2]

- Parents who previously have had a child with a chromosomal disease
- Parents who previously have had a child with a neural tube defect
- Parents who previously have had a child with a congenital metabolic disorder where it is possible to perform prenatal diagnostics
- Parents who previously have had a child with a severe X-linked recessive disease or where there is a high risk for the woman to be a carrier of such a disorder
- If one of the parents is a carrier of a chromosomal anomaly and thus have a high risk of having children with severe developmental disorder
- Parents who have an increased risk of having a child with a chromosomal disease due to the woman's age. So far prenatal diagnostics has been offered women above 38 years at term
- The woman has taken a teratogen (e.g. antiepileptic drugs).
- Ultrasound examination has shown signs of chromosomal abnormalities in the fetus
- In special cases where the woman or couple are in a difficult situation, and may not manage the extra burden of a disabled child

During the spring 2013 The Norwegian Parliament will probably discuss the introduction of early ultrasound (week 11^{0}-13^{6})[3] (see below) as an offer to all pregnant women in Norway.

Methods
The methods are divided into non-invasive methods (risk assessment) and invasive methods.

Non-invasive tests
• Ultrasound: According to guidelines on the use of ultrasound in pregnancy from the Norwegian Directorate of Health, when there is an indication for prenatal diagnostics, early ultrasound (week 11^0-13^6)[3] should be offered before invasive prenatal diagnostics. This provides an assessment of the risk of a chromosomal disease. An early ultrasound involves the measurement of the "crown-rump-length" (CRL) to determine gestational age. Other biometric measurements may be appropriate. An early ultrasound examination involves assessment of fluid accumulation in the neck region (nuchal transparency, "nuchal translucency", NT) as a marker for a chromosomal disease and structural heart defects. A thorough review of the fetal anatomy may reveal structural anomalies and identify specific markers for chromosomal disorders, such as absent ossification of the nasal bone. In multiple pregnancies, it is important to consider chorionicity, (di- and monochorionic multiples) as this is more difficult to resolve later in pregnancy.

Colour Doppler of the heart and pulsed Doppler of ductus venosus has been shown to improve the diagnostic accuracy of the NT-scan. Safety guidelines on the use of ultrasound from the International Society for Ultrasound in Obstetrics and Gynaecology (ISUOG) do not recommend routine use of Doppler in first trimester, only when indicated. If so, the power setting of the ultrasound equipment must be low with the thermal index for bone (TIB) ≤ 0.3.

• Biochemical analyses: Specific protein markers in the blood of the pregnant woman are used to provide a risk assessment for trisomy 13, 18 and 21. The so-called double test is performed in gestational week 8 to 13. The markers included are PAPP-A (pregnancy-associated plasma protein A) and free beta-hCG (chorionic gonadotropin-)[4]. St Olav's Hospital has a national function in performing the actual analyses.

• Biochemical test (blood test) and early ultrasound provides a sensitivity of approximately 65% and approximately 75%, respectively for trisomy 21. The combination of early ultrasound and blood test (CUB test) is the most widely used non-invasive method and increases sensitivity for trisomies to 90-95%. Risk calculation applies a false positive rate of 5% (specificity 95%) and a priori probability based on the age of the pregnant women[5] (IIa). Cut-off limit for risk assessment by CUB test is usually 1: 250. Invasive testing is offered at a risk of 1: 250 or higher.

Invasive tests
Invasive testing is performed if there is a recognized increased risk of a specific disease in the fetus or where early ultrasound or CUB test has shown increased risk of a disease that can be diagnosed by invasive diagnostics.
• Amniocentesis (AC): Performed after 15 weeks gestation with trans-abdominal ultrasound guided insertion. Approximately 15 ml of amniotic fluid is aspirated.
• Chorionic villus sampling (CVS): Performed after 10-11 weeks gestation with ultrasound-guided access by a trans-abdominal or trans-cervical approach depending on placental localization and operator experience.

Analyses by invasive testing
The method used is determined by the indication.
• PCR (polymerase chain reaction) or FISH (fluorescence in situ hybridization) gives a diagnosis for

trisomy in chromosomes 13, 18 and 21 within a week. If required, the sex chromosomes may also be identified.
• For a full karyotype, the relevant cells are cultivated before the actual analysis. The results will be available after 2-4 weeks.
• Monogenic hereditary diseases are diagnosed by PCR, in some cases MLPA (multiplex ligation-dependent probe amplification). Biochemical / enzymatic assays may be performed for certain metabolic diseases.

Future tests
The number of diagnostic examinations on free fetal DNA in the blood of pregnant women will probably increase significantly within a few years. These tests do not have risk of miscarriage. Today some laboratories abroad use free fetal DNA (fftDNA) in maternal blood for analysis of fetal Rhesus factor in rhesus negative women. fftDNA can be used for the diagnosis of trisomies and fetal sex[6]. According to the Biotechnology Act this method will require approval from the Norwegian Directorate of Health.

Referral, counselling, sampling
• Referral letter for prenatal diagnosis should be sent to the relevant department of medical genetics or a centre for prenatal diagnostics.
• Generally the Biotechnology Act does not require genetic counselling, just information. In the case of a genetic (inherited) disease, genetic counselling is required.
• All prenatal diagnostics should take place at an approved institution. These are Oslo University Hospital, Stavanger University Hospital, Haukeland University Hospital, NSFM at St Olav's Hospital and University Hospital of Northern Norway

Before sampling
• Documentation confirming the woman's Rhesus type should be included in the application or be forwarded.
• Before prenatal diagnostic examination an ultrasound examination is desirable to assess gestational age
• In the case of trans-cervical CVS there should be no vaginal infection (e.g. a candida infection will contaminate the tissue culture)

Information about the results / follow-up
• The department of medical genetics or fetal medicine centre are responsible for communicating the results to the patient or to the referring physician / department
• The department of medical genetics and the fetal diagnostic centre that has performed prenatal diagnostics should receive feedback on pregnancy outcome
• When prenatal diagnostics are performed on the basis of an ultrasound observation it is usually the department that treats the patient that informs her of the test result

Risk Factors / Complications
• Background risk of miscarriage is primarily dependent on the woman's age and gestational age when the examination is performed
• Today the estimated risk of miscarriage after AC or CVS is 0.5-1%[7,8] (Ia, Ib)
• Some have reported increased risk of amputation disorders in fetuses following CVS performed before week 9-10. This has not been verified in a large observational study initiated by World Health Organisation. It was recommended that CVS should not be performed before 8 ½ gestational weeks[9]

(IIa).

Patient information

• Online information from each centre is available. Anyone who wishes a fetal diagnostic test should have an appointment to receive medical genetic information unless they have been to such an appointment in a previous pregnancy.

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