Prenatal Diagnosis and Prenatal Screening — Methods and Tests

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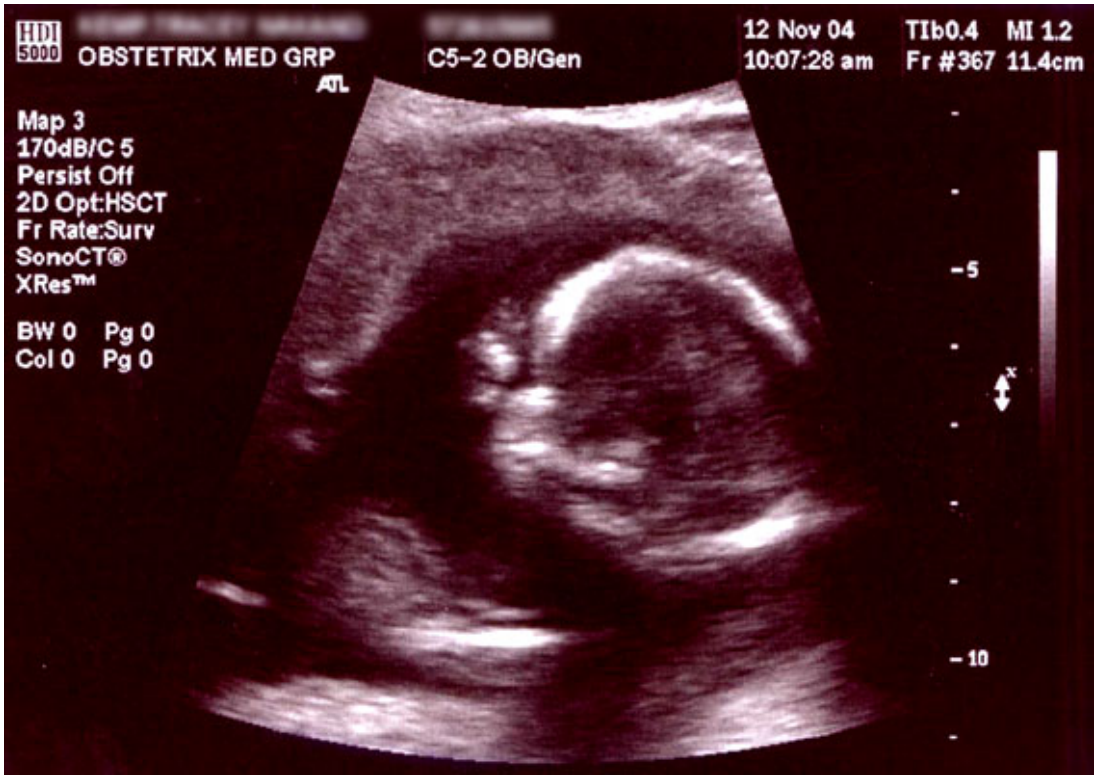
Prenatal screening is used in clinical practice to detect the necessity for carrying out more detailed and invasive tests for the diagnosis of aneuploidies and congenital or developmental birth anomalies. Ideally, prenatal screening should be made available to all pregnant women with non-invasive methods. More invasive testing is offered to those who are at increased risk. Ultrasonography is an excellent prenatal screening tool while prenatal diagnosis requires invasive tests like chorionic villus sampling, amniocentesis and fetal blood sampling for patients at increased risk.



Genetic Counseling

Genetic counseling is the process by which a trained health care provider **determines the risk of parents transmitting a genetic disease to their unborn fetus**. During this arduous process, the family trees of prospective parents are investigated in detail, analyzed inheritance patterns, and the **potential for transmission of the affected genetic trait**.

After ascertaining all facts, the prospective parents are counseled regarding the probability of their offspring inheriting the genetic trait, risks for recurrence in future

pregnancies and best management options available. Genetic counseling is indicated in the following cases:

- Prenatal screening tests suggestive of a birth defect
- Invasive tests suggestive of birth defects
- Family history of a genetic trait or disorder
- Previous child with a birth or genetic condition
- Maternal age over 35 years.

Molecular and Genome-Based Diagnostics

Currently, **biochemical, cytogenetic** and **molecular tests** are available to identify protein function, chromosome structure and the sequence of the DNA respectively and enable prenatal diagnosis of **aneuploidies** and inheritable conditions. Direct and indirect analysis of mutations based on the disease patterns can be used.

A better understanding of uniparental disomy (UPD), imprinting and triplet expansion disorders have helped to diagnose these conditions antenatally. Preimplantation genetic diagnosis during in-vitro fertilization with single blastomere biopsy and blastocyst biopsy can be routinely used nowadays.

Prenatal Screening and Diagnosis

Tests available for prenatal diagnosis include:

- Ultrasonography: evaluating nuchal translucency
- Amniocentesis
- Chorionic villus sampling
- Fetal blood cells in maternal blood
- Maternal serum alpha-fetoprotein
- Maternal serum beta-HCG
- Maternal serum estriol

Screening tests for aneuploidies can identify fetuses at risk for Down’s syndrome or other trisomies. This can be followed by a diagnostic procedure to confirm the diagnosis. Screening tests **help to reduce the number of invasive diagnostic procedures**.according to recent research, noninvasive prenatal screening using cell-free fetal (cff) DNA in maternal plasma can specify common aneuploidies (trisomies 21, 18, 13) in high-risk pregnant ladies. The disadvantage of screening tests is that they do not detect all cases of aneuploidies while invasive diagnostic tests are able to identify almost all existing genetic anomalies.

The choice of the test

The choice of the test depends on the maternal gestational age, obstetric history, the number of gestations, sensitivity and availability of the test, limitations of the test and options for termination of pregnancy, in case aneuploidy is diagnosed.

As **women above the age of 35 years are considered to be at a higher risk** for conceiving fetuses with trisomies, it is recommended that they undergo **chorionic villus sampling** (CVS) along with genetic counseling and amniocentesis totally based on age without any screening tests done before.

Women **under the age of 35 are recommended screening with either triple**

markers [human chorionic gonadotropin (hCG), unconjugated estriol and maternal alfa-fetoprotein levels] which have a 70 % detection rate **or quadruple markers** [human chorionic gonadotropin (hCG), unconjugated estriol , maternal alfa-fetoprotein levels and inhibin A levels] which have a 80 % detection rate of Down's syndrome. Combined with ultrasonography, these screening tests provide an accurate diagnosis of the condition.

First trimester screening tests

Nuchal translucency measurement, PAPP-A, free or total beta- hCG: this is processed through sonography to visualize the increased thickness of subcutaneous fluid at NT. The amount of fluid at the posterior aspect of the fetal neck is called nuchal translucency (NT) and can be measured on ultrasonography as early as the 6th week of gestation. Increased NT has been found to be associated with trisomies and congenital cardiac defects. NT combined with levels of free hCG and pregnancy-associated plasma protein A (PAPP-A) is used to screen for Down's syndrome in the first trimester with their combined detection rate being around 80 %.

Ultrasonography and fetal echocardiography can be offered to pregnant women if fetal NT is found to be at least 3.5 mm (and aneuploidy screen is negative and no chromosomal abnormalities have been detected) as there is still a high risk of congenital cardiac/abdominal wall defects and other genetic syndromes. It can detect the risk of Down syndrome and is recommended in 11 to 14 weeks of pregnancy.

A blood test named cell-free nucleic fetal acid [cfDNA] testing can also be opted to determine the risk of down syndrome and other chromosomal abnormalities in pregnant ladies who have a high risk of having a baby with a chromosomal abnormality. In this test, the analysis of small fragments of the DNA of fetus is analyzed from the pregnant mothers' blood as it is present in her blood in trace amounts. This test is recommended in the 10th week of the pregnancy.

First-trimester screening (FTS) is helpful, **as women diagnosed to have a malformed fetus or aneuploidy can be provided the options in the early gestation period** such as CVS, genetic counseling as well as second-trimester amniocentesis, especially if she is at high risk. In addition, FTS which includes PAPP-A and free beta- hCG testing has a 95 % sensitivity and a false positive rate of only 5 %.

First –trimester screening has a great advantage for the parent couples to take the decision of abortion if desired in case any chromosomal abnormality is detected as it is safest for the mother.

Second-trimester screening tests

Triple markers [human chorionic gonadotropin (hCG), unconjugated estriol, and maternal alfa-fetoprotein levels] can detect Down's syndrome in 70 % of the cases.

Quadruple markers [human chorionic gonadotropin (hCG), unconjugated estriol, maternal alfa-fetoprotein levels, and inhibin A levels] can detect Down's syndrome in approximately 80 % of the cases.

The high value of **alpha-fetoprotein** level in the blood determines the high risk of neural tube defect of the brain and spinal cord, birth defects of the abdominal wall and complications in late pregnancy such as, slow growth, miscarriage or death of the fetus.

A blood test is followed by ultrasonography and amniocentesis for confirmation of diagnosis and double checking of the result of blood tests.

Non-Invasive Prenatal Diagnosis Tests

NIPS –Non-invasive prenatal screening/ Fetal DNA test/Cell-free fetal DNA in maternal circulation

This is a new genetic test which **analyzes the DNA of the fetus from a sample of the maternal blood**. It can be performed anytime after the 9th week of gestation up to the 22nd week. A positive test is indicative of birth defects and further invasive tests may be warranted to confirm the diagnosis.

NIPS helps to detect trisomies like Down syndrome, trisomy 14 and 18, cystic fibrosis, hemophilia, etc. It can also reveal the gender of the fetus. The test has **higher sensitivity** compared to nuchal translucency as well as first-trimester screening tests and quad test. Currently, the American College of Obstetricians and Gynecologists Committee on Genetics recommends NIPS for high –risk women with

- Age above 35 years during pregnancy
- Positive first-trimester screening tests, e.g., triple or quadruple screen
- Ultrasound finding of an anatomical abnormality
- History of the previous trisomy
- History of a balanced translocation in a parent or partner's parent

Non-invasive prenatal testing is done in 10 weeks gestation and results get available in10-15 days.

Invasive Prenatal Diagnosis Tests

Indications for invasive prenatal tests are:

1. Advanced maternal age
2. Ultrasound screening indicative of fetal abnormalities
3. Previous history of fetal abnormality
4. Abnormal triple or quadruple marker tests (hCG, unconjugated oestriol and alfa-fetoprotein)
5. Maternal anxiety due to a history or family history of fetal malformations

Invasive tests include chorionic villus sampling (CVS), amniocentesis and fetal blood sampling (FBS). These tests are associated with an **elevated risk of complications**, e.g., limb injuries have been reported after CVS; miscarriages have been reported after amniocentesis and FBS.

While CVS is ideally performed between the 8th to 10th week of gestation, amniocentesis is performed in the second trimester between the 16th to the 20th gestational weeks. It cannot be performed earlier due to the risk of talipes and fetal loss. Similarly, FBS is not performed as often due to the associated high risk of miscarriages.

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