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EC GYNAECOLOGY
Review Article

Diagnostic of the Orofacial Genetic Abnormalities

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Received: December 21, 2018; **Published:** January 28, 2019

Abstract

The prenatal diagnosis involves a series of methods and procedures that can diagnose defects, malformation or hereditary disease during pregnancy. Nowadays, the prenatal diagnosis is becoming more and more routine approach in the detection of inherited diseases. It's included in the processing of all pregnant women by ultrasound. This approach has to accurately inform the family about the condition of fetus bearing by mother so that prospective parents can make a decision based on appropriate information about medical condition of their unborn child. The prenatal diagnosis also prevents some of the very difficult and fatal genetic defects.

In the group of noninvasive methods testing the maternal blood and ultrasound are included, while the invasive methods are amniocentesis, biopsy of chorion frondosum, cordocentesis and fetoscopy.

The preventive diagnosis brings many challenges. It takes great confidence and courage to take the appropriate decisions if fetus anomalies, even the slightest are diagnosed by prenatal diagnosis. Normally, each couple are waiting for the birth of a healthy, beautiful and bright child. Each confrontation with a defect often leads to difficalt dilemmas and frustrations. In this sense, many ethical issues are related to the prenatal diagnosis.

The preventive diagnosis are increasingly doing in order to discover and apply new ways of prenatal treatment in recent years. Early detection of the malformations is a prerequisite for the successful surgical intrauterine treatment. When gene therapy for multiple gene defects would possible be discover, prenatal diagnosis will have to be started early with the application of gene therapy in uterus and prevent irreversible damage of the fetus.

Keywords: *Prenatal Diagnosis; Genetic Diseases*

Introduction

Prenatal diagnosis involves a series of methods and procedures that can diagnose defect, malformation or hereditary disease during pregnancy [1,2]. Prenatal diagnosis is becoming increasingly routine in hereditary diseases, but it also enters the processing of all of the women during pregnancy (for example, through ultrasound). Prenatal diagnosis also provides prevention of some of the very severe infaust gene defects, hence, it can be preventively applied [1-4].

The indications of prenatal diagnosis include more anomalies, and chromosomal and genetic diseases that burden the family.

Methods of prenatal diagnosis that are used during the genetic load on the family with malformations are ultrasound, fetoscopy, RTG, alpha-fetoproteins. Methods for prenatal diagnosis that are used during the genetic load of the family with chromosome malformations are: amniocentesis, cordocentesis, chorion frondosum biopsy. While methods of prenatal diagnosis that are used during the genetic load of the family with genetic malformations are cordocentesis for extraction of DNA, amniocentesis, hormones in amniotic fluid, biopsy of fetal tissues through fetoscopy.

Indications for prenatal diagnosis are

- Previous child with malformations
- Previous pathological pregnancy (spontaneous abortions, polyhydramnios, oligo-amnion)
- Hereditary diseases in the family
- Malformations in the family
- Chromosome malformations in the family
- Mother's age more than 35,, and father's more than 40
- Mother's chronic illness
- Infections and parasitic diseases in pregnancy
- Consanguine marriages
- Carriers of the balanced translators
- Mother and father are heterozygotes for genetic diseases
- Elevated level of AFP in mother's blood
- Medical-treated sterility.

The objectives of the prenatal diagnosis are to provide a range of informed choices for parents at risk for getting a child with abnormalities, to provide support and reduce anxiety, especially among high risk groups, informing parents at risk for presence or absence of the genetic disorder, informing the parents about the results after affirmative genetic testing, giving parents the opportunity for appropriate information (psychological, pregnancy/childbirth, postnatal), and to enable prenatal treatment of a affected fetus, if it is possible.

Some of the diseases for which prenatal diagnosis is available include: congenital malformations, chromosomal diseases, non-genetic fetal diseases (Fetal infections, Hydrocephalus, Fetal effects of maternal drugs e.g. valproic acid), as well as individual genital diseases: multiple malformation syndromes Oramas, Craniosynostosis, Orofacial digital syndromes), haematological diseases (Thalassemias, Hemophilia) [5,6], metabolic disorders (Tay sachs, Wilson, MPS, CAH), and neuromuscular disorders (Huntington chorea, Myotonic dystrophy, DMD, Fragile X).

Methods for prenatal diagnosis are divided into: non-invasive (ultrasound, blood testing, fetal cell detection in maternal circulation, magnetic resonance imaging) [7]and invasive (amniocentesis, chorion frondosum biopsy, preimplantation genetic diagnosis (PGD)). the test scans the fetal diseases shown in table 1.

Disease	MSAFP	uE3	Beta hCG	Inhibin A (glycoprotein hormone)
Open NTD	Increased	No change	No change	No change
Downs syndrome	Decreased	Decreased	Increased	Increased
Trisomy 18	Decreased	Decreased	No change	No change

Table 1: *Triple test that scans fetal diseases.*

Legend: *Open NTD: Neural Tube Defect; free b HCG: Beta Human Chorionic Gonadotropin; uE3; Unconjugated Estriol; MSAFP: Alpha fetoprotein; Inhibin A: Glycoprotein Hormone.*

Screening of mother's serum is most often done in the first and second trimesters of pregnancy. Serum markers examined by the mother to detect Down's syndrome in the first trimester are the placental protein A (Preg. asso. Placental Protein A (PAPP-A)) [8], while the most significant fetal marker is the nuchal dial. Serum markers that are examined in the mother's second trimester to detect Down's syndrome are AFP, E3, hCG, and inhibitor A. With all these tests together Down's syndrome can be confirmed with 94% confidence.

Methods for detection of mutations are based on the method of hybridization (SSCP, ASO, array, melting curves) on the polymerization method (sequencing, PCR, allele discrimination), as well as those based on cleavage (RFLP, cleavage with nuclease).

In recent years, three-dimensional ultrasound (3D) and four-dimensional ultrasound apparatus (4D) have begun to play a greater role in prenatal diagnosis. They can be applied in the assessment of facial features, abnormalities of the central nervous system and skeletal defects. The limitations in the ultrasonic procedure are that the findings are based on the fetal attitudes, the estimated gestational age, the sonograph's experience, and the degree of severity of the anomaly.

Magnetic resonance is used in combination with ultrasound, usually at or after 18 weeks of gestation. It is a tool for examining women with large or complex anomalies and visualization of abnormality in relation to the whole body of the fetus. It is a risk-free method.

In the group of invasive methods of prenatal diagnosis include amniocentesis, cordocentesis, fetoscopy, and chorion frondosum biopsy that can be performed trans-abdominally and trans- vaginally.

The amniocentesis is performed in 16 - 18 weeks of the pregnancy, during the procedure 10 - 20 ml of the taken amniotic fluid is sufficient for the genetic testing. The supernatant can be used for biochemical testing (α-fetoprotein), the sediment is composed of amniocytes, while the chromosomal analysis is performed after two weeks of planting culture. The molecular DNA analysis takes a longer time.

Chorion frondosum biopsy is performed in or after 10 weeks of the pregnancy, CVS (Chorionic villus sampling) provides, i.e. early detection of fetal genetic abnormalities through analysis of trophoblast cells. The transabdominal biopsy of CVS can also be used, even in 3 trimesters when amniotic fluid is not available to us or when blood samples from the fetus cannot be taken. Chorionic biopsy (CVS) biopsy, if performed before 10 weeks of pregnancy, may be accompanied by an increased risk of defects in fetal limbs and oromandibular malformation [9].

Aspirated cells are from the trophoblast, and maternal cells from deciduate, which as a rule are located in the aspirate, must be eliminated before any sample analysis begins. The resulting chorionic villus consist of fast-dividing cells, so a direct chromosomal analysis can be performed that yields results within 24 hours, and for molecular analysis there is enough DNA that provides a guarantee for reliable molecular diagnostics. The whole procedure lasts 8 - 12 days.

The cordocentesis is a diagnostic test, which reveals the anomalies of the fetus through fetal blood. The cordocentesis is performed after 17 weeks of pregnancy. First, ultrasound determines the location where the umbilical cord connects to the placenta. With the assistance of ultrasound with a thin needle, it is accessed to the umbilical cord through the walls of the stomach and uterus. The thin needle is inserted into the umbilical cord to obtain a small sample of fetal blood. This invasive prenatal method can help diagnose fetal malformations, fetal infection (i.e. toxoplasmosis or rubella), determine the number of fetal platelets in maternal circulation, fetal anemia, and in isoimmunization. Complications that can occur include blood loss from the puncture site, infection, drop of the fetal cardiac frequency, premature rupture of membranes, fever, and leakage of the amniotic fluid.

The method of fetoscopy consists of inserting an endoscope into the amniotic area observing the fetus, requiring smaller abnormalities such as hexadactyly, skin changes, biopsy from the liver or skin, as taking blood from the umbilical vein (cordocentesis), if chromosomal mosaicism should be excluded. The method is performed lately in the pregnancy, in the second trimester. It is increasingly replaced by many good ultrasonic apparatuses, as well as with the possibility of detecting single gene anomalies with DNA from chorion frondosum.

A preimplantation diagnosis is performed only in several highly developed countries worldwide, in which *in vitro* fertilization centers exist. With the development of *in vitro* fertilization, the problem is growing the growing problem of satisfying the desire to ensure healthy offspring in couples who have undergone this procedure.

Pre-implantation genetic diagnosis (PGD or PIGD) is the genetic profiling of embryos prior to implantation. Preimplantation Genetic Diagnostics is considered in a similar fashion to prenatal diagnosis. For the implementation and used of the preimplantation genetic diagnostics (PGD), *in vitro*/assisted reproductive technology is required. With this method, it is possible that the fertilized oocyte can be cultured in laboratory conditions until it reaches the 8-cell stage. One of these cells can be isolated and tested using the PCR technique, and the remaining 7 blastomers can be implemented in the mother's uterus. The number of such born children is still limited, but it seems that the removal of one blastomer does not adversely affect the development of the fetus. The biggest advantage of this method is that the genetic information of both parents can be studied.

From cytogenetic studies, chromosomal analysis is most commonly performed, as well as FISH Fluorescence *in situ* Hybridization. With molecular genetics, direct DNA analysis, indirect DNA analysis, and DNA sequestration [10] are performed.

Today, geneticists and doctors deal mainly with attempts to come to a precise diagnosis of congenital genetic and hereditary diseases, to give a good genetic advice, to discover in the early stage some of the genetic diseases. The ultimate goal is of course the mapping of the human genome. The term gene therapy refers to a therapy that involves the insertion of DNA or RNA into a patient with a therapeutic aim.

So far, 106 protocols for gene therapy have been approved in the United States and they have been applied in 597 patients with various diseases. None of the above protocols showed any justification for routine application in clinical practice. Although more than 20 years there have been attempts to introduce genetic therapy in the treatment of many genetic diseases, this method is still at an early experimental stage [1]. Mapping the human genome began in April 2003, while in October 2004 the exact number of genes was determined.

Genomics is a scientific area that has emerged as a result of the achievements of molecular biology and the development of techniques that can determine the order of nucleotides in nucleic acid molecules.

The future of genomics is in the application of its achievements in many sciences, which certainly contributed to the development of new disciplines, such as: agrigenomics, pharmacogenomics, genomic medicine.

Conclusion

The moral test of every society and every government is to treat people with genetic diseases. Genetic research is necessary for the development of science, but also for the improvement and modernization of diagnostic and therapeutic procedures.

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Volume 8 Issue 2 February 2019