# THE ROLE OF PRENATAL DIAGNOSTICS IN THE PREVENTION OF CONGENITAL AND GENETIC DISEASES

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Annotation

In the review methods of prenatal diagnostics of congenital and genetic diseases are represented. Questions of prenatal screening of pregnant women as a means of decreasing child mortality and disability in Russia are discussed. The authors tell how to increase the effectiveness of prenatal diagnostics service in prevention of genetic pathology.

**Keywords:** prenatal diagnostics, congenital and genetic diseases, screening of pregnant women, medical and genetic consultation.

Prenatal diagnostics is a method of clinical medicine, which allows to evaluate on different stages of prenatal development the fetus, the risk of disease (congenital or genetic) in combination with families counseling (prenatal counseling). According to Baranov V.S. (1994), one of the founders of Russian prenatal diagnostic service, prenatal diagnostics (PD) is a new branch of medical genetics appeared in the 80s of XX connecting Obstetrics, Gynecology and Perinatology on the one hand and Human Genetics, Molecular Biology, Cytology, Embryology, Pathophysiology on the other [3].

That's why there are different methods used in prenatal diagnostics. First of all, it is the main non-invasive ultrasound (U/S.), which allows evaluating normal or abnormal structure of the organs of the fetus at various stages of development, further to determine the risk of congenital abnormalities, chromosomal aberrations, some genetic diseases [2]. The effectiveness of ultrasound depends on the technical condition of an apparatus and the skill of an ultrasonographer. It is known that over the past decade U/S apparatus has been improved that makes it possible to visualize subtle

organ failure of the fetus in a multiple spatial projections [11, 13, 19]. For example, 3-D ultrasound, Doppler, coronary angiography can currently detect up to 80-85% of congenital malformations in the II trimester of pregnancy (20-22 weeks) [15].

According to selective studies in Russia and other developed countries detection of congenital malformations in first-level health facilities is 20%, in the second level ones - 55%, and in perinatal centers it reaches 90% [14]. These data demonstrate that it is right to develop modern obstetrics and create perinatal centers as powerful, well-equipped facilities, having not only in-patient departments but also conducting a truly effective work to identify birth defects [12]. Large numbers of patients, significant staff with constant training, analysis and generalization of the experience can significantly improve the quality of diagnostics. As an example of high quality diagnostics is the work of the Scientific Center for Obstetrics, Gynecology and Perinatology of Russian Academy of Medical Sciences where the detection of congenital malformations is 94%. Every year, the department of functional diagnostics of the Center examines about 30,000 pregnant women and diagnoses 500 cases of congenital malformations. The introduction of three-dimensional ultrasound improves the diagnostic capabilities and improves detection of defects, especially smaller structures of the body (polydactyly, cleft upper lip, etc.) [6].

Nonetheless, deviations in the fetus development revealed through a variety of direct non-invasive diagnostic techniques with the help of ultrasound do not prove the presence of chromosomal and genetic diseases. In some cases the combination of specific ultrasound markers can suspect a presence of chromosomal pathology with a certain probability [16, 19]. Therefore the diagnosis of chromosomal and genetic diseases is carried out using special laboratory tests of samples of the fetus material (bioptates) obtained by different invasive methods of PD under the ultrasound control [15].

Invasive methods of obtaining fetal material for laboratory diagnostics are divided depending on the duration of pregnancy and the objectives of the examination. In the early stages of pregnancy in the I and II trimesters invasive chorion-biopsy and placenta-biopsy are used. In the later stages of fetal development in the II and III trimester amniocentesis (obtaining samples of amniotic fluid), and cordocentesis (obtaining the fetus blood with umbilical cord puncture) are used. For example, in accordance with the type of laboratory tests for cytogenetic research it is preferable to use specimens from chorion cells or fetus blood, for most biochemical studies to use amniotic fluid and blood. Higher quality DNA specimens are usually obtained from chorion-bioptates.

These methods are in place and substantially modified in the laboratory of Institute of Prenatal Diagnostics of Scientific Research Institute for Obstetrics and Gynecology named after D.O.Ott RAMS. According to data of the year 2005, more than 7 000 invasive procedures to obtain fetal

material for research (including 2 679 chorion-biopsy, 3 392 placenta-biopsy, 379 amniocentesis, 882 cordocentesis) were carried out [15]. According to data of the year 2007 in the Laboratory of Clinical Genetics of Scientific Center for Obstetrics, Gynecology and Perinatology RAMS 2 839 invasive procedures of prenatal diagnostics (chorion-biopsy, amniocentesis, cordocentesis) were made within 5 years. The number of complications (mostly abortions) was from 2.2 to 0.3%, on average 0.7%. As a result of these studies 91 cases of fetal pathology were detected. 97% were eliminated, and postnatal confirmation was 100% [6].

Since obtained through invasive procedures cells have fetus origin and their genotypic characteristics correspond to the body of the fetus as a whole, for the prenatal diagnostics of the fetus reliable and efficient cytogenetic (method of karyotyping of chromosomal specimens obtained from chorion cells or placenta) and molecular-genetic research methods (method of direct or indirect DNA diagnostics) are used most commonly [15].

Biochemical, cytogenetic and molecular-genetic analyzes should be routine for that laboratory where they are carried out by qualified personnel. Prenatal diagnostics can give the following results:

• If the fetus has serious illness – termination of pregnancy is recommended.

• If the suspected pathology of fetus was excluded – the pregnancy is prolonged.

•When the suspected pathology has been excluded and other fetal abnormalities are found.

•If ambiguous data (balanced adjustments *de novo*, mosaic options, the new gene mutations, etc.) has been obtained – often further or additional prenatal study (on available specimen or specimen obtained by additional invasive procedure, often cordocentesis ) are made.

•When congenital defects or multiple congenital defects and chromosomal disorders are excluded – prenatal consultation is necessary. It should include consultation of obstetrician-gynecologist, geneticist and pediatric surgeon to determine the possibility (feasibility) to continue pregnancy, to calculate the risk of monogenic diseases and to decide if the correction of defects is possible.

•It was possible to decrease the high risk of a particular disease, but the probability of the disease remained significant [8].

One of the most difficult problems of PD is the ethical aspect of PD that inevitably arises in all its stages.

Particular problems are caused by the fact that in the majority of genetic diseases diagnostic opportunities are ahead from therapeutic ones. Therefore, the only measure to prevent the birth of the ill fetus is still a prenatal diagnostics of the disease followed by termination of pregnancy if the family agree. [5] An alternative but still unaffordable for many families method is the pre-implantation diagnostics.

Thus, the role of medical and genetic counseling to provide complete information about the features of the clinical manifestations of the disease is becoming more important. The principle of freedom of choice in reproductive decisions for families should be saved but this choice should be informed. The individual choice can be affected by personal attitude to human life, the desire to prevent human suffering, social and economic conditions in the absence of adequate treatment and social support to the disabled and the chronically ill. Traditionally, abortion was considered ethically acceptable when there was a risk of severe genetic fetus disease. This view was formed when it was possible to diagnose prenatally a small number of severe hereditary diseases. Nowadays when it is possible to diagnose less severe disease, to identify genes of susceptibility to multifactor diseases, to investigate genes of normal signs discussions about ethical aspect become more and more actual [26].

The aim of prenatal diagnosis is to prevent the birth of children with severe congenital and genetic diseases. To select a risk group on the congenital defects, chromosomal and monogenic diseases among the general mass of pregnant women in a given region so-called screening is carried out. Total screening may study 80-90% of women. In many regions of Russia, due to the lack of trained personnel and inadequate infrastructure, screening is often used as selective method. According to leading experts, the main screening programs in PD should include:

*Ultrasound screening.* It is made three times during pregnancy (10-14, 18-22 and 30-32 weeks). Depending on the examination ultrasound screening is divided into Level 1, Level 2, Level 3. Early detection of congenital defects (CDF) and markers of chromosomal aberrations in the I trimester greatly facilitates decision on prolongation of pregnancy and therapeutic abortion during this period is 3-5 times safer for a woman's life than at a later time [17]. For example, congenital heart disease (CHD) occupy a leading position in the structure of congenital anomalies of the fetus, making 16-40 % of cases, often combined with a chromosomal abnormality. Every year in Russia about 10 000 children with CHD are born [2]. Diagnostics is often difficult to perform. Screening for fetal CHD is possible at 12-14 weeks by consistent detection of markers: thickening of nuchal fold more than 3 mm, the rate of blood flow in diastole through ductus venosus less than 2 cm/s. Later, when chromosomal aberrations has been excluded, the algorithm of consistent detection of CHD markers allows to detect a high-risk group of isolated heart defects [20, 21, 22, 23, 25]. The use of high-density, high-frequency transvaginal (TV) detectors allows visualizing the basic structure of the fetal heart, discharge of the great vessels, to carry out Doppler sonography study at 13-14 weeks of pregnancy [24].

*Biochemical screening.* It identifies the main marker serum proteins in the mother's blood: alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), free (unconjugated) estriol, pregnancy-

associated plasma protein A (PAPP-A), free β-subunit of human chorionic gonadotropin ( β-hCG). The concentration of the main marker proteins varies depending on the duration of pregnancy and the condition of the fetus.

Simple blood test is not enough to find out if the risk of congenital malformations is high or not. At the first stage of a computer calculation the numbers obtained in laboratory diagnostics are transferred into so-called MoM (multiple of median), characterizing the degree of deviation of an indicator from median. MoM = [value of the indicator in the patient's blood serum] / [median of the indicator for the duration of pregnancy]. At the next stage of the calculation the correction of MoM according to various factors (body weight, women, race, the presence of certain diseases, smoking, multiple pregnancy, etc.) is made. As a result there is so-called corrected MoM. On the third stage corrected MoM is used to calculate the risk. Software is specially installed for used in laboratory methods determining indicators and reagents. It is unacceptable to calculate risk using analyzes made in different laboratories. The most accurate calculation of risk of fetal abnormalities is made using ultrasound findings, performed at 10-13 weeks of pregnancy. Since the value of the index and median have the same units of measurement, the value of MoM has no units. If the MoM value of a woman is close to 1, the value of the index is close to the average in the population. If the MoM value is greater than 1, the value of the index is above the average in the population. If the MoM value is lower than 1 – the value of the index is below the average in the population. In the analysis forms next to the absolute values of the index there are corrected MoM values for each index [9]. The interaction between the members of the laboratory, clinical specialists and experts in the instrumental diagnostics is necessary at all stages of the diagnostic process as the calculation of the risks of prenatal screening is a complex procedure performed together. This technique involves the clinical history and clinical examination of the pregnant woman, ultrasound examination of the fetus and the data of immunochemical blood test. It cannot be properly processed and implemented without any participant of the diagnostic process. [7]

*Cytogenetic screening.* It determines a higher risk for chromosomal aberrations based on the family's reproductive history (age of the mother, one of the spouses carriage of a chromosomal aberration, a prior child with multiple congenital defects or chromosomal diseases). Karyotyping of the fetus at various stages of fetal development requires the use of complex techniques, which includes a variety of methods for preparing and colour staining chromosomes specimens, each of which has its own advantages and disadvantages. The efficiency of diagnostics depends on the quality and quantity of fetal material, and its accuracy is determined by a resolution of the analysis methods, the choice of which is chosen according to the indication for PD and gestational age. Before performing invasive intervention it is necessary to evaluate the adequacy of the obtained

fetal material to specific objectives of the study [10].

*Molecular screening.* As in Russia at the present time only 70 mono-gene disorders are technically available for molecular genetic testing, it is possible to conduct their prenatal diagnostics. However, the existing organizational problems, lack of specialists, the high cost of diagnostics, as well as the inhomogenuity of the ethnic composition of the regions of the Russian Federation, the specific spectrum of mutations among the population of Russia significantly limit the introduction of molecular screening to the Health Care of the Russian Federation. In the Russian Federation candidates for the molecular-genetic screening are monogenic diseases such as cystic fibrosis, phenylketonuria, congenital adrenal hyperplasia, spinal muscular atrophy (Werdnig Hoffmann disease). [15]

*Immunological screening.* It allows early detection of the presence of potential pathogens of infectious diseases causing abnormalities in the development of the fetus, such as rubella virus, cytomegalovirus, herpes virus, the causative agent of toxoplasmosis. For example, infection of the fetus with virus rubella can follow the mother's infection at any stage of gestation. In this case the outcome of rubella is highly dependent on gestation. The probability of infection of the fetus at less than 8 weeks of pregnancy is 54%, at 9-12 weeks – 34%, at 13-24 weeks – 10-20%, and no more than 12% since the end of the second term [4]. The most common fetus malformations that occur when infected with rubella virus, are retardation, deafness, cataracts, retinopathy, aorticopulmonary window, patent ductus arteriosus, hypoplasia of the pulmonary artery (or valve stenosis), hepatosplenomegaly [18]. Another important prenatal immunological test is to determine mother's Rh when the pregnancy is immunoincompatible. [1]

Prenatal genetic screening of pregnant women is a part of a national program on prenatal diagnostics. In Russia the Order №316 MH RF of December 30, 1993 "On Further Development of Medical Genetic Services of the Ministry of Health of the Russian Federation" and the Order №457 MH RF of December 30, 2000 "On Improving Prenatal Diagnostics in the Prevention of Congenital and Genetic Disorders in Children" played an important role in its formation. These orders not only regulated the structure of the whole PD service in Russia, but also defined the interrelation of its various departments taking into account existing peculiarities of the organization of medical genetic services in the regions of the Russian Federation. In 2010 the Resolution of the Russian Government № 1141 of December 27, 2010 to support regions with PD subsidies from federal budget was given. These subsidies financially provided procedures of prenatal diagnostics of children developmental disorder.

Thus, nowadays the role of prenatal diagnostics as basic part of prenatal medicine is constantly growing. In Russia there are significant reserves for PD development and decreasing

child mortality and disability. Firstly, there is an improvement in population awareness about importance of medical-genetic consultation as well as improvement in quality of prenatal diagnostics (specialists' trainings, high-quality equipment, different methods used). Secondly, it is increasing role of prenatal centers in providing quality of prenatal diagnostics in regions.

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