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Prenatal diagnosis (A Review)

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ABSTRACT

In 2 to 3% of pregnancies, congenital malformations are diagnosed during pregnancy or shortly after birth. These abnormalities, with surpassing premature birth, are the most common cause of death in infants in the United States and account for 20% of these deaths (1). Preventive diagnosis, diagnosis of malformations, fractures, and chromosomal anomalies are some of the most important genetic syndromes in the fetus. Components included within the category of prenatal diagnosis include typical screening tests to find an aneuploidy and neural tube defects, invasive diagnostic tests such as percutaneous and amniocentesis sampling, screening and diagnostic tests suggested to individuals exposed to a specific genetic disorder, and the diagnosis of structural malformations with the help of specialized ultrasound and other methods of embryo imaging. The AFP screening of the mother's serum generally takes place between weeks 15 and 20. This should be done through the protocol, including quality control, consultation and follow-up. The amount of AFP is measured in nano-grams per milliliter and is reported by the median number (MoM) of the non-affected population. Converting outcomes to MoM standardizes AFP level distribution and allows comparison of results from different communities and labs percent reported.

Introduction:

In 2 to 3% of pregnancies, congenital malformations are diagnosed during pregnancy or shortly after birth. These abnormalities, with surpassing premature birth, are the most common cause of death in infants in the United States and account for 20% of these deaths (1). Preventive diagnosis, diagnosis of malformations, fractures, and chromosomal anomalies are some of the most important genetic syndromes in the fetus. Components included within the category of prenatal diagnosis include typical screening tests to find an aneuploidy and neural tube defects,invasive diagnostic tests such as percutaneous and amniocentesis sampling, screening and diagnostic tests suggested to individuals exposed to a specific genetic disorder, and the diagnosis of structural malformations with the help of specialized ultrasound and other methods of embryo imaging. The purpose of prenatal diagnosis is to provide accurate information on the short-term and long-term prognosis, the risk of recurrence, and possible treatments, thereby improving counseling and pregnancy outcomes (2).

Various screening tests:

By the mid-1980s, prenatal diagnostic tests for fetal aneuploidy were recommended only on the condition of "high maternal age". However, age alone is a poor screening test, since about 70% of down syndromes are seen in women younger than 35 years old. About 3 years ago, Merkatz et al. (1984) observed that the low level of AFP in the mother's serum during 15-20 weeks is a sign of Down syndrome pregnancies; therefore, screening for younger mothers became important, as well (3). Over the past two decades, four major advances in the field of aneuploidy screening have taken place;

1. Adding the measurement of miscellaneous serum anilities to the second trimester screenings increased the detection rate of Down syndrome in the four-mark test by about 80% (Table 1).
2. In women younger than 35 years of age, the rate of Down Syndrome Detection by screening the first trimester in the 11-14th week of pregnancy (using the measurement of fetal neck trans-lucensia with serum analytes) is comparable to that of the second trimester screening (4).
3. The combination of first and second trimester screening rates has reduced Down syndrome rates to 90-95% (5).
4. Detection of extracellular embryonic DNA in the mother's serum, in order to detect triazomes 21, 18, 13 in high risk pregnancies, has become a screening test, with a detection rate of 98% and a false negative rate of 5.5% 0% (6).

With the exception of the measurement of embryonic extracellular DNA, each aneuploidy screening test performed in the first or second trimester is based on a composite likelihood ration; the risk associated with maternal age is multiplied by this ratio. Concerning decreasing the risk of Down syndrome, this principle is implemented according to ultrasound findings. The risk level for each woman is clear and is indicated by a ratio (1: x). However, each screening test has a predetermined amount, in which the test result is considered "positive" or, in other words, abnormal. Traditionally, this threshold is defined for the second trimester test as far as the risk of having a fetus with Down syndrome in a 35-year-old woman (about 1 in every 385 pregnancies). Women with positive screening tests results should be advised to propose a diagnostic test to determine fetal karyotype through sampling of pericardium or amniocentesis (7).

Table1. Some Down Syndrome Screening Strategies and their diagnosis value:

Strategy	Analyte	Diagnosis rate
Screening during the first trimester	NT, PAPP-A, hCG or free B-nCG	79-87
NT	Just NT	64-70
Triple test	MSAFP, Hcg or free B-nCG, uE3	61-70
Quad test	MSAFP, Hcg or free B-nCG, uE3, inh	72-81
Integrated screening	First trimester screening and Quad test (the results are preserved until the completion of Quad test)	94-96
Consecutive step by step screening	• First trimester screening and Quad test • - After screening for the first trimester, 1% of the diagnostic test population is recommended • Quad test is conducted on 99% of cases and the results are kept until the Quad test is completed.	90-95
Consecutive conditional screening	• First trimester screening and Quad test • - After screening for the first trimester, 1% of the diagnostic test population is recommended • Quad test is conducted on 15% of cases and the results are kept until the Quad test is completed. • After the first trimester screening, in 84% of the cases, no other test is done, no analyzes are measured. (Highly parallel genomic sequencing)	88-94
Exogenous DNA extraction (in high-risk pregnancies)		98

Based on a positive 5% screening rate:

Free hCG-β: free form of Hcg (Human chorionic gonadotropin) beta subunit; inh: Inhibin Daire alpha; MSAFP: Mother's serum alpha-phytoprotein; NT: Cervical transplantation; PAPP-A: Uneartransplant-derived plasma A protein: non-conjugated sterile (8).

Screening mother's serum Alpha Phyto-Protein level (MSAFP)

AFP is a glycoprotein produced by the yolk sac in early pregnancy, followed by the liver and the digestive tract of the fetus. AFP is the main protein in the embryo and embryo serum and is the equivalent of albumin (9).By 13th week, AFP concentrations increases steadily in the embryo and amniotic fluid, and then decreases rapidly. On the contrary, after 12 weeks, the concentration of AFP increases steadily in the mother's serum. The incidence of normal AFP gradient between the embryo and maternal serum is 1: 50,000. Embryo coating defects (such as NTD and abdominal wall defects) allow AFP to be fed into amniotic fluid, thereby increasing the level of AFP in the mother's serum (10).More than 30 years ago, it was shown that in the 16th to 18th weeks of pregnancy, the serum AFP level is also greater than twice the median (MoM) in a large number of women with anencephaly or Spina Bifida fetuses (11). Since the mid-80s, MSAFP concentration has been widely measured as a screening test for NTD.

The AFP screening of the mother's serum generally takes place between weeks 15 and 20. This should be done through the protocol, including quality control, consultation and follow-up. The amount of AFP is measured in nano-grams per milliliter and is reported by the median number (MoM) of the non-affected population. Converting outcomes to MoM standardizes AFP level distribution and allows comparison of results from different communities and labs percent reported (12). The positive predictive value of the test is only 2 to 6 percent (the positive predictive value means that the person who has increased the level of AFP actually has an embryo). The reason for the lack of specificity of the test is the overlapping of the distribution of AFP levels in both pregnancy and non-infected pregnancies.

Increased MSAFP:

One of the algorithms that is used to evaluate the level of the maternal AFP is starts with a standard ultrasound (if not already done), because ultrasound can withstand the three most common causes of increased AFP. The three causes are: lower than estimated true gestational age; multiple pregnancy, and fetal death. In practice, all cases of anencephaly and many cases of Spina Bifida are diagnosed or at least suspected of being performed by standard ultrasound in the second trimester (13). When the pregnancy and the abnormal screening result are confirmed, diagnostic evaluations are recommended to the patient.

Many abnormalities of the fetus and the placenta increase AFP (Table 2). The likelihood of one of these abnormalities or the adverse outcome of pregnancy increases with increasing levels of AFP. If the AFP level is more than 7 MoM, more than 40% of pregnancies will be abnormal (14).Based on what was stated above, if the high level of AFP is confirmed in the mother's serum, shoe should receive genetic counseling and ask for a diagnostic test (such as amniocentesis or ultrasound examination). Some women have risk factors that even require diagnostic tests, even if the level of AFP is normal. These risk factors include: a history of NTD, a first-degree relative with NTD, insulin-dependent diabetes, and exposure to drugs that increase the risk of NTD in the first trimester.

Table2. Incidence of abnormal AFP concentrations in the mother's serum:

Increases AFP level
Gestational age estimated less than actual
Multiple pregnancy
Fetal death
Neural tube defects
Gastro-scale
Emmaphalloceles
Cystic Higroum
Bowel obstruction or esophagus
Liver necrosis
Renal anomalies - Polycystic kidneys, kidney agenesis
Congenital nephrosis, urethral obstruction
Extratogical
Imperfect osteogenesis (osteogenesis imperfecta)
Teratom Saccharoccinea
Congenital Skin Defects
Pilonidal cysts
Corio angioma pair
Thrombosis between pins or pairs

The abruption of the placenta
Oligo Hydramnios
Preeclampsia
Limit of fetal growth
Tranum or mother's hepatoma
Decrease AFP level
Obesity
Diabetes mellitus
Triozomi 21 or 18
Trophoblastic disease of pregnancy
Fetal death
More than real estimated pregnancy age

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