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Review Article

Physiology Section

Prenatal Markers of Foetal Complications

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ABSTRACT

Prenatal markers are commonly used in practice to screen for some foetal abnormalities. They can be biochemical or ultrasonic markers in addition to the newly used cell free Deoxyribonucleic Acid (DNA) estimation. This review aimed to illustrate the applications of the prenatal screening, and the reliability of these tests in detecting the presence of abnormal chromosomes such as trisomy-21, trisomy-18, and trisomy-13 in addition to neural tube defects. Prenatal markers can also be used in the anticipation of some obstetrical complications depending on levels of these markers in the mother's circulation. In the developed countries, prenatal screening tests are regularly used during antenatal care period. Neural tube defects, numerical and structural chromosomal abnormalities, in addition to some obstetrical problems are commonly screened for, by using prenatal tests. Maternal education about the importance of performing these tests should be done in order to improve the detection rate of foetal abnormalities and some pregnancy complications.

Keywords: Detection, Neural tube defects, Screening

INTRODUCTION

Prenatal diagnosis refers to the discovery of foetal abnormalities before birth, while screening is the method of surveying group of people, using a special indicator or several indicators and establishing specific level or cut-off levels, in order to recognise those in the group who are at increased risk for a specific disorder [1]. The prenatal screening methods were implemented in practice since 1980, mother's serum was assessed for presence of numerical or structural foetal chromosomal abnormalities. In 1984, a relationship between decreased levels of serum Alpha Fetoprotein (AFP) in the pregnant mother and Down's syndrome was found [2]. After that, the maternal serum tests (biochemistry) and precise ultrasonographic imaging in the second trimester were developed and permitted the recognition of pregnancies with high risk [1].

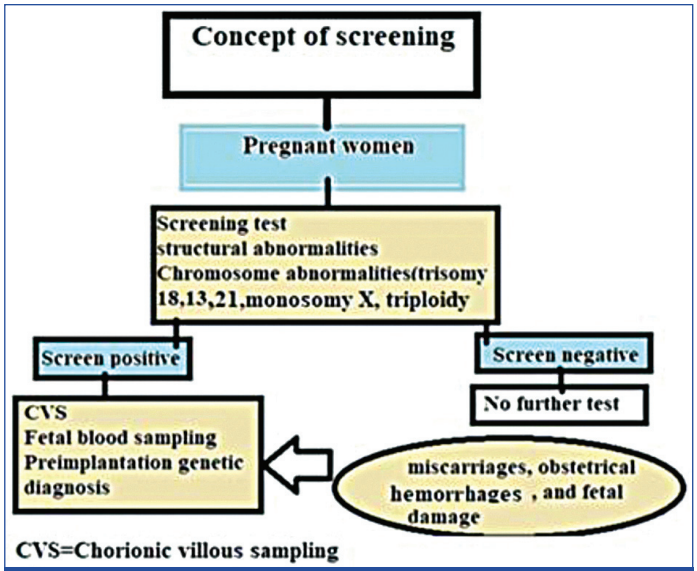
Later in the 1990s, the screening during pregnancy has been shifted to first trimester via combining the age of the mother, Nuchal Translucency (NT) in the foetus, free beta Human Chorionic Gonadotropin (β-HCG), and Pregnancy-Associated Plasma Protein-A (PAPP-A) in mother's serum [2]. More recently, the prenatal screening methods have been diverted to genomic screening that measures (free foetal DNA) in the mother's blood [1]. If there are abnormal levels of maternal markers, associated with no foetal chromosomal disorders, this may reflect presence of obstetrical complications [3]. [Table/Fig-1] shows the concept of prenatal screening. Prenatal markers can aid in the detection of the disorder, in addition to its prognosis and treatment. Markers can identify the biological condition and they can discover the changes in the components of tissues or fluids of the body more accurately [4].

It is essential to understand the difference between the diagnostic test and the screening test, the diagnostic test confirms the presence of the anomaly in the foetus that is thought to be at risk, whereas the screening test searches for the possibility of the abnormality in the foetus in an obviously normal pregnancy [5].

This review sheds the light on the applications and the importance of prenatal screening in the detection of chromosomal disorders and adverse pregnancy outcomes.

MATERNAL BIOMARKERS

Foetal chromosomal aberrations, such as Down's syndrome and Edward's syndrome and unfavourable obstetric complications



[Table/Fig-1]: Concept of prenatal screening.

including preeclampsia, preterm deliveries, gestational diabetes, and foetal growth restriction might not be detected merely by taking full history and by evaluating patients' risk factors especially in nulliparous females.

Prediction of these outcomes within the first three months of pregnancy (first trimester) may allow sufficient time for early intervention like starting a prophylactic management, and trying to identify the severity of the consequences via the follow-up of complicated cases using prenatal markers. This emphasises the importance of research in this area to find more prenatal tests with good prediction rates [5,6].

Congenital anomalies represent about 7% of neonatal deaths, and a lot of them have no well-known pathophysiological cause, since specific and robust laboratory tests are not always available [7]. Physicians depend on tests such as ultrasound and Magnetic Resonance Imaging (MRI). Biomarker including the prenatal markers, are shown to be powerful screening tools to predict disease and health of human, because they mirror an individual's state of health [7]. There is a common method that categorises pregnant women into high or low risk groups based on the possibility of presence or absence of unfavourable foetal or maternal outcomes [8].

Looking for foetal aneuploidy in the first trimester is considered the most widely employed test in the beginning of pregnancy for the prognostication of a successive pregnancy complications, such as, delivering an infant with abnormal chromosomes. This made it necessary for the new development of screening plans by the aid of several biomarkers in early pregnancy for guessing other pregnancy complications that may affect the foetus later on and cause complications, such as preeclampsia, preterm birth, gestational diabetes, and foetal growth limitation [9].

Indications for Prenatal Maternal Biomarkers in Diagnosing and Screening Tests

It is important to screen for possible foetal anomalies in order to minimise the possibility of unwanted results, to establish a proper way of care throughout pregnancy and to identify high risk groups [10]. Women above 35-year-old, presence of a previous child with Down's syndrome or other chromosomal disorders, translocation carrier state in parents, and history of genetic defects in family are common indications of prenatal screening [11].

PREECLAMPSIA

Gestational hypertension and preeclampsia can lead to maternal and foetal death and morbidity (e.g., prematurity) all over the world [12]. The mechanism of increasing blood pressure in pregnancy is not totally understood but mostly it is associated with endothelial dysfunction because of the imbalanced angiogenic controller factors and oxidative stress biomarkers [13].

Preeclampsia is the most common serious problem in pregnancy, with incidence of 2-8% throughout the world [14]. The application of several biomarkers in expecting these results has been studied, involving Doppler- indices of uterine artery [15,16]; indicators of the function of placenta, like Pregnancy associated Plasma Protein A (PAPP-A) and plasma-protein 13 [17]; inhibin A and activin A, placental growth factor and Vascular Endothelial Growth Factor (VEGF) [18], and the inhibitors of them, soluble FMS-like tyrosine kinase-1 and soluble endoglin [19].

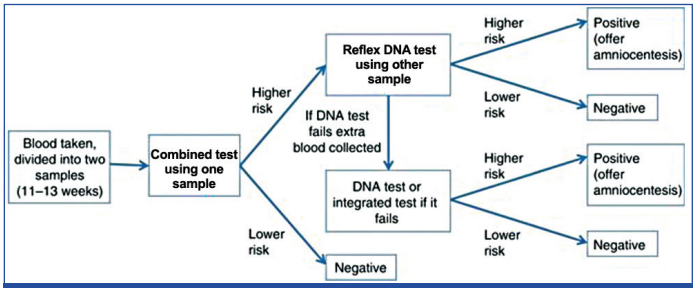
Many promising biomarkers have been suggested, either each one alone or several ones together, although many studies prefer combination of them for satisfactory sensitivity and specificity, to be of clinical importance that may help in predicting women who will possibly have preeclampsia. Biomarkers serum levels in mother's circulation either increase or decrease during pregnancy in preeclampsia [10,20].

Many studies have reported that the combination of average blood pressure measurement, doppler of uterine artery, placental growth factor, and PAPP-A, discovered about 80.8% to 93% of preeclampsia cases with a false positive rate of 5-10% [20-22]. Other promising biomarkers like antiangiogenic factors such as sFlt-1, sEng and pro-angiogenic factors like VEGF have been used and studied [10]. The discovery of neutrophil-gelatinase associated lipocalin and its relation to the endothelial damage during preeclampsia made the researches work hard to demonstrate its importance and its cut-off values [23,24]. Recently, maternal serum cell free foetal DNA (cfDNA) has become the new gold standard test for screening for aneuploidy, and preeclampsia with a sensitivity and specificity reaching upto 100% [25].

ANEUPLOIDY

Screening in the beginning of pregnancy (first-trimester) for trisomies twenty one, eighteen and thirteen by adding the age of the pregnant mother, foetal Nuchal Translucency (NT) thickness, foetal heart rate and serum β-hCG, in addition to PAPP-A can discover upto 90% of patients with trisomy 21 and upto 95% of those with trisomies 18 and 13, at a false rate of positivity of nearly 5% [26].

cfDNA in the blood of pregnant mother can discover upto 99% of trisomy 21 conditions, and upto 98% of trisomy 18 conditions and 92% of trisomy 13 conditions with false positive results ranges between (0.1 and 0.3%) [27- 31]. It's involvement in the routine tests depends on the outcomes of combined testing in the 11-13 weeks of pregnancy rather than being an essential first place method [32]. In some places in the world there is an additional prenatal screening for single gene disorders like Cystic Fibrosis (CF) and Fragile X-Syndrome (FXS) [33]. [Table/Fig-2] shows the suggested strategy for applying the combined test and the cfDNA test according to the results of each one [33].



[Table/Fig-2]: Flow diagram of reflex DNA screening protocol [33].

CONGENITAL ANOMALIES

Accurate laboratory tests are not available for most of the congenital anomalies, so physicians depend on ultrasound imaging and MRI. Biomarkers from maternal plasma are considered very promising [34]. By measuring certain molecules in maternal blood, one can predict the type of deformity and can manage the after birth treatment or estimate the prognosis of the abnormality. For instance, to diagnose the dysfunction of the left ventricular systolic action, tests depending on urinary N-terminal pro-brain natriuretic peptide test is accompanied by a plasma N-terminal pro-brain natriuretic peptide test that can aid in detecting left ventricular systolic dysfunction in congenital heart diseases [35].

Biomarkers are analysed to discover certain abnormalities, and help in management of patients postoperatively like cardiac cases with congenital heart diseases. Actually the importance of screening tests is diminished sometimes by the fact that many of the congenital defects are present in newly born babies from pregnant mothers with no or low risk factors [36].

SOME BIOCHEMICAL MATERNAL MARKERS AND THEIR INDICATIONS

1- Alpha-Fetoprotein (AFP)

This is a type of protein made by the baby in the uterus and is measured in pregnant mother's serum starting from the sixth week of pregnancy, reaching maximum level in week (thirty four) of gestation.

High values of it are found in: pregnancies of twins, problems in the skin, failure of some organs, congenital nephropathy, cystic hygroma, hepatic necrosis, defects in the neural tube, and defects in the abdominal wall. Diminished levels of it are recorded in cases of disorders in the chromosomes, problems of the placenta, hydrops foetalis, trophoblastic disorders, and pregnant women with diabetes [37].

2- Human Chorionic Gonadotropin (HCG)

This hormone is formed throughout the period of pregnancy, and is released by cells that form the placenta, after fertilisation and attachment to the walls of the uterus. It can first be measured in blood, approximately (eleven days) after the start of pregnancy and almost 12-14 days after conception in test that is done on urine. It approaches its maximum value in the first (8-11) weeks of pregnancy [38].

A low concentration can refer to a mistake in the calculation of pregnancy establishment or the possibility of miscarriage or blighted

ovum, and it may refer to the presence of ectopic pregnancy. An increased HCG concentration in pregnancy means, wrong calculation of pregnancy, or molar pregnancy [39].

3- Unconjugated Estriol (uE3)

It is one of group of three natural oestrogens, which are estriol, estradiol and estrone. In women who are not pregnant, the main oestrogen hormone is estradiol that is formed by the ovaries. While throughout pregnancy, estriol is secreted by the placenta and foetus and turns up the most abundant one. Maternal serum uE3 levels is measured as an indicator of the health of the foetal-placental complex and in evaluating gestational problems [26].

4- Inhibin-A

Inhibins are glycoprotein hormones. Inhibin has a negative feedback function on FSH secretion from the pituitary. Inhibin-A is the major type of inhibins in pregnant mother's blood starting from the fourth week of pregnancy. The exact biological action of inhibin-A in pregnancy is that it could be an excellent indicator of the function of placenta more than β-hCG since it has less half-life. It can be used in anticipating miscarriage, Down's syndrome, preeclampsia, and foetal growth restriction in the first and/or the second three months of pregnancy (second- trimester) [32].

5- Pregnancy Associated Plasma Protein-A (PAPP-A)

This protein is produced by the foetus and the placenta throughout pregnancy. It has some functions, like preventing the foetus from recognition by the mother's immune-mechanism, matrix- mineralisation and angiogenesis. It is also applied as a diagnostic test in the first and second trimesters of pregnancy for aneuploidies, like Down's syndrome [33].

6-Cell Free DNA (cfDNA)

cfDNA can be defined as DNA fragments which are found outside the cell nucleus. They are formed mainly by apoptotic or necrotic process; they also exist in fluids of the body, that's why they can be used as bioindicators of disease or abnormal conditions. Circulating cfDNA, double-stranded molecule, has a less molecular weight than genomic DNA, in the type of short pieces, ranging between seventy and two hundred base pairs in length.

Cell free DNA clinical applications include sex determination, identification of single gene disorders, detection of paternally inherited allele, isoimmunisation, screening for aneuploidies, anticipation of presence of pregnancy complications such as preeclampsia, preterm birth and small for date [1].

CONCLUSION(S)

Maternal serum biomarkers, in association with other modalities like ultrasound can improve detection rates of complicated pregnancy or abnormal outcomes. Increased education and the introduction of such measures should be implied as appropriate, also labeling women as high risk should be taken carefully into consideration. Prenatal screening is now an important and well applied part of regular care and observation during pregnancy period in developed countries. Disorders being commonly screened for involve neural tube defects in the foetus, numerical and structural chromosomal abnormalities in addition to some maternal complications.

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