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THE IMPORTANCE OF BIOCHEMICAL AND ULTRASOUND MARKERS IN PRENATAL DIAGNOSIS: CURRENT METHODS AND DEVELOPMENT PERSPECTIVES

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List of abbreviations:

NIPT – Non-Invasive Prenatal Testing
PAPP-A – Pregnancy-Associated Plasma Protein A
cfDNA – Cell-Free DNA
β-hCG – beta subunit of human chorionic gonadotropin
AFP – alpha-fetoprotein
uE3 – unconjugated estriol
NT - nuchal translucency
CRL - crown-rump length
NB - nasal bone
DV - ductus venosus
AFI - amniotic fluid index
FL - femur length

Abstract

Objective:
This paper explores the role of biochemical and ultrasound markers in prenatal diagnosis, emphasizing their importance in early detection of chromosomal and structural abnormalities in the fetus. It aims to characterize the most relevant diagnostic markers, evaluate the sensitivity and specificity of current methods, and discuss modern advancements such as non-invasive prenatal testing (NIPT).

Materials and Methods:
The study is based on a review and analysis of current literature and clinical data regarding the most frequently used biochemical markers—PAPP-A, β-hCG, AFP, uE3, and inhibin A—and their integration into first and second trimester screening protocols, including the double, triple, and quadruple tests. The complementary role of ultrasound parameters such as nuchal translucency (NT), nasal bone (NB), venous duct flow (DV), and femur length (FL) is also discussed. Furthermore, the paper reviews algorithms like FMF and PRISCA and compares them with modern methods such as NIPT, focusing on detection rates and clinical application.

Main Results:
The combination of biochemical markers and ultrasound significantly enhances the sensitivity and specificity of prenatal screening, especially for trisomy 21, 18, and 13. The use of integrated approaches—such as the FMF algorithm—achieves a detection rate of up to 95% for Down syndrome when both NT and biochemical markers are included. NIPT shows the highest accuracy, with sensitivity exceeding 99% for the main chromosomal aneuploidies. However, limitations exist, particularly in the context of multiple pregnancies and structural defect detection.

Conclusion:
Biochemical and ultrasound markers remain fundamental tools in prenatal screening, providing crucial information for risk stratification and early intervention. The integration of traditional methods with advanced technologies such as NIPT offers a comprehensive approach to fetal health assessment. Continuous refinement of diagnostic algorithms and broader access to non-invasive testing are key directions for future development, aiming to improve both prenatal care quality and patient safety.

Keywords: prenatal diagnosis, biochemical markers, ultrasound markers, PAPP-A, NIPT

Introduction.

Introduction to prenatal diagnosis

Prenatal diagnostics is an important element of modern maternal and fetal care, which, among other things, allows assessment of the mother's health status or early detection of genetic, metabolic and anatomical disorders of the child. Thanks to dynamic progress in the field of biochemistry and ultrasound imaging, doctors can more and more effectively assess the state of health of the developing child, while minimising the risk to mother and fetus. This will translate into an improved treatment process and sound therapeutic decisions in both the fetal and perinatal periods.

Modern prenatal diagnosis is based on two main pillars: biochemical markers and ultrasound. Biochemical markers, such as PAPP-A, β-hCG, AFP, uE3 or inhibin A, provide valuable information on placental function and potential genetic abnormalities in the fetus. They are the basis for screening tests such as the double, triple or quadruple tests, which allow the risk of Down syndrome, Edwards syndrome and other disorders to be estimated. These tests are complemented by ultrasound, which allows a direct assessment of the fetal anatomy and the detection of characteristic ultrasound markers such as nuchal translucency, parietal-septal length or the presence of a nasal bone.

Non-invasive prenatal diagnosis, based on the analysis of free fetal DNA circulating in the mother's blood, has also played an increasingly important role in recent years. This is one of the most sensitive methods for detecting trisomies 21, 18 and 13, as well as selected microdeletions and single-gene diseases.

This thesis aims to present the key biochemical and ultrasound markers used in prenatal diagnosis. Their mechanisms of action, scope of application and importance in assessing the risk of birth defects and chromosomal aberrations will be discussed. Special attention is also given to screening methods, their effectiveness and the limitations to be considered in interpreting the results.

The scope of work includes:

- Characterisation of the most important biochemical markers, such as PAPP-A, β-hCG, AFP, uE3 and inhibin A, and their use in first and second trimester screening tests.
- Discussing the role of ultrasound in prenatal diagnosis, including the importance of ultrasound markers such as nuchal translucency, parietal-substance length, assessment of the nasal bone and venous tract flow.
- Analysis of the effectiveness of individual diagnostic methods, their sensitivity and specificity in detecting fetal defects.
- Comparison of classic prenatal diagnosis methods with modern techniques such as NIPT, and discussion of their advantages and limitations.
- Outline the practical application of prenatal diagnosis in daily medical practice and its impact on clinical decision-making regarding further management of pregnancy.

- The aim of the paper is to provide a comprehensive knowledge of the diagnostic methods used in pregnancy, highlighting their importance in detecting potential abnormalities and enabling early medical intervention.

Biochemical Markers in Prenatal Diagnosis.

Characterisation of biochemical markers

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

It belongs to the glycoproteins produced mainly by the trophoblast and placenta during pregnancy. Its function is to regulate fetal growth and development and to modulate the maternal immune response to pregnancy. Its concentration increases during the first trimester, specifically between the 10th and 14th weeks of pregnancy. It is during this period that the PAPP-A determination has the greatest diagnostic value. A low level of PAPP-A in the first trimester (about 0.5 MoM on average for trisomy 21) can indicate chromosomal aberrations in the fetus, including Down syndrome, Edwards syndrome and other trisomies. However, the PAPP-A assay alone is not sufficient as a stand-alone screening test - its interpretation should take into account other parameters such as β-hCG levels and nuchal translucency (NT) on ultrasound. [5], [8], [17]

Beta-human chorionic gonadotropin (β-hCG)

It is a glycoprotein hormone produced by trophoblast cells from as early as day 10-12 after conception. Its main role is to stimulate the corpus luteum to produce progesterone, which is essential for the maintenance of pregnancy and the normal development of the endometrium. After an initial sharp rise in maternal serum β-hCG, its level begins to gradually decrease between 10th and 20th week of pregnancy. The value of the free β-hCG subunit is an important marker in prenatal diagnosis, as its deviation from the norm may indicate the presence of chromosomal aberrations in the fetus. Its elevated level may indicate trisomy 21, twin pregnancy or myoma. On the other hand, a decreased level may suggest trisomy 18 or trisomy 13. It should be borne in mind that the final interpretation of the results requires the consideration of other markers, such as PAPP-A, AFP or uE3, as well as parameters obtained from ultrasound examination. [5], [9]

Alfafetoprotein (AFP)

It is a plasma protein that is produced by the fetus early in pregnancy, mainly by the liver and yolk follicle. Its level in the mother's serum gradually increases during pregnancy, peaking around week 32, and then begins to fall. In the amniotic fluid, AFP concentration increases between weeks 10 and 14, after which it also begins to decrease. The AFP concentration in the pregnant woman's serum is an important part of prenatal diagnosis,

especially in the second trimester, when its determination is a part of the triple and quadruple tests. Abnormal values may indicate congenital abnormalities in the fetus, including neural tube defects and chromosomal aberrations. [6]

Unconjugated estriol (uE3)

It is one of the three main estrogens, along with estradiol (E2) and estrone (E1). Unhydrolysed estriol (uE3) is its biologically active form, which is formed through the cooperation of the placenta, the fetus and the fetal liver. Unlike total estriol (which also includes metabolites), uE3 is not converted in the maternal liver, making it a more specific indicator of placental and fetal function. Non-hydrolysed estriol is a part of the triple and quadruple test used to assess the risk of chromosomal aberrations and fetal defects. Its level increases gradually during pregnancy. Reduced uE3 levels can indicate- trisomy 21, trisomy 18, Smith-Lemli-Opitz syndrome (a defect in cholesterol synthesis affecting brain and genital development), fetal adrenal insufficiency or placental dysfunction. In contrast, elevated uE3 levels are usually not clinically relevant, but can occur in cases of multifetal pregnancy. [7]

Inhibin A

It is a glycoprotein, belonging to the TGF-β (transforming growth factor beta) family. It is secreted mainly by the granulosa cells of the ovary in women and the placenta during pregnancy. Its function is to inhibit the secretion of folliculotropic hormone (which regulates the menstrual cycle) by the pituitary gland and to participate in placental implantation and development. During pregnancy, inhibin A concentration gradually increases, reaching its highest values in the third trimester. Inhibin A is one of the parameters of the quadruple test, which is used to assess the risk of fetal aneuploidy, especially trisomy 21 when its level is elevated or trisomy 18 when the concentration is reduced. [8]

Use of biochemical markers in prenatal diagnosis

Double test (PAPP-A, β-hCG)

It is one of the primary screening tests used in prenatal diagnosis during the first trimester of pregnancy. It involves determining the concentration of the two previously mentioned biochemical markers in the mother's blood:

- pregnancy Associated Plasma Protein-A (PAPP-A),
- beta-human chorionic gonadotropin (β-hCG).

It allows the assessment of the risk of trisomy 21, trisomy 18 and trisomy 13. An additional benefit of the test is the assessment of the pregnant woman's risk of pre-eclampsia and fetal hypotrophy. It is often combined with an examination of nuchal translucency, parietal-axillary length and heart rate (ultrasound examination). It is then called a composite test, the result of which is calculated by a specialised computer programme, using also the age of the patient, the age of the fetus and the obstetric history.
It is performed between the 11th and 14th week of pregnancy.
In terms of interpreting the results, a reduced PAPP-A level may indicate an increased risk of trisomy 21 and 18 and other pregnancy complications such as preeclampsia or fetal growth restriction. Elevated β-hCG levels are characteristic of Down's syndrome, while reduced levels may suggest Edwards syndrome. The duplicate test is non-invasive, meaning that it carries no risk of miscarriage, but in the event of an abnormal result, additional tests are needed to confirm or rule out a genetic defect. [7], [8], [9], [17]

Triple test (AFP, uE3, β-hCG)

It belongs to the screening tests of the second trimester of pregnancy, where the risk of certain birth defects, e.g. bifida, spina bifida, amenorrhoea or cerebral hernia, and chromosomal aberrations in the fetus, e.g. trisomy 21, trisomy 18, is assessed. It involves the analysis of three biochemical markers in the mother's blood:

- alfafetoprotein (AFP),
- unconjugated estriol (uE3),
- beta-human chorionic gonadotropin (β-hCG).

The triple test is performed between 15th and 20th weeks of pregnancy.

As for the interpretation of its results, an elevated AFP level suggests the possibility of neural tube defects. Low levels of AFP and uE3 and high levels of β-hCG may indicate trisomy 21, while reduced levels of all three markers are characteristic of trisomy 18. However, if it indicates the possibility of any fetal abnormality, further testing is indicated due to its low sensitivity and high rate of false positives. [7], [9], [17]

Quadruple test (AFP, uE3, β-hCG, inhibina A)

It is a screening test of the second trimester of pregnancy. It is performed for the risk of chromosomal aberrations and certain birth defects in the fetus. It involves the analysis of three biochemical markers in the mother's blood:

- alfafetoprotein (AFP),
- unconjugated estriol (uE3),

- beta-human chorionic gonadotropin (β-hCG),
- Inhibin A.

The test is performed between the 15th and 20th weeks of pregnancy.
Moving on to interpretation, elevated AFP levels may indicate possible neural tube defects (spina bifida, amenorrhoea), low levels of AFP and uE3, high β-hCG and inhibin A suggest an increased risk of Down's syndrome, while reduced levels of all markers may speak of trisomy 18 (Edwards syndrome).
It is now mainly used when first trimester tests were not performed or were inconclusive. However, it is increasingly being replaced by non-invasive prenatal diagnosis (NIPT) in many countries. [7], [9], [17]

Non-invasive prenatal diagnosis (NIPT)

Non-invasive prenatal diagnosis (NIPT) is an advanced screening method based on the analysis of free fetal DNA (cffDNA) circulating in the mother's blood. It is one of the most modern tools in prenatal diagnosis. It most commonly covers the three main trisomies of chromosomes-21, 18, 13. However, there are also extended tests that allow the risk of selected microdeletion syndromes in the fetus to be assessed. Analysis of free fetal DNA also allows the evaluation of sex chromosomes and, in certain clinical cases, the detection of single-gene diseases.

Free fetal DNA is short fragments of genetic material mainly derived from trophoblast cells (the outer layer of the placenta) that circulate in the blood of the pregnant woman, accounting for about 10% of the total free DNA (the rest belongs to the mother). Its presence can be detected as early as the 5th week of pregnancy, but it is not present in sufficient quantity for reliable testing until the 10th week. As for the sensitivity of the test for the previously mentioned trisomies, it is as follows - 99.7% for trisomy 21, 97.9% for trisomy 18, 99% for trisomy 13.

As can be seen, NIPT is particularly effective in detecting the most common chromosomal trisomies, which have a significant impact on fetal development. However, it also has limitations, such as low effectiveness in multiple pregnancies or failure to detect structural defects in the fetus. On the other hand, the advantages are its complete non-invasiveness, which makes it safe for both mother and fetus, as well as its highest sensitivity. However, it must be remembered that NIPT is a screening test and not a diagnostic test, so its results need to be confirmed in the case of suspected abnormalities. [2], [10], [11], [15]

Ultrasound Markers in Prenatal Diagnosis.

Crown-Rump Length (CRL)

This is the length of the fetus measured from the top of the head (parietal) to the buttocks, i.e. excluding the lower limbs. It is one of the key measurements taken during the first trimester of pregnancy (up to about week 14) to determine gestational age (with an accuracy of ±3-5 days), to determine the expected date of delivery and

to assess early normal fetal development. This is the most accurate method for determining gestational age (especially up to the 12th week of pregnancy). Formula for gestational age based on CRL:

Gestational age (weeks) = CRL (mm) + 6.5

A normal result confirms proper fetal development, while deviations may suggest growth abnormalities, errors in the date of conception or risk of miscarriage. [4]

Nuchal translucency (NT)

This is a naturally occurring space located in the nuchal region of the fetus that is filled with fluid. It is a physiological swelling resulting from insufficiency of the lymphatic and circulatory systems. It is usually visible on ultrasound between the 11th and 14th weeks of pregnancy. Elevated nuchal translucency can result from a variety of abnormalities, including genetic (trisomy 21, trisomy 18 or trisomy 13), cardiac (congenital heart defects) or structural (bone dysplasia or connective tissue disease). Normal is defined as a value of less than 3 mm (but it should be correlated with the age of the mother and the CRL). An elevated NT value does not automatically indicate a disease, but requires further diagnosis. [3], [9]

Nasal bone (NB)

It is a fine-boned structure that forms the upper part of the nasal dorsum. It develops early in prenatal life, but does not begin to ossify until around the 10th week of pregnancy. It can be assessed during ultrasound examination between the 11th and 14th weeks of gestation. Its absence or hypoplasia may indicate an increased risk of genetic defects (most frequent trisomies - 21, 18, 13, Noonan, achondroplasia, skeletal defects or bone dysplasia). We speak of a normal NB when, on ultrasound examination, a hyperechoic structure is visualised in the facial profile. Its absence, hypoplasia or altered shape should be recommended for further diagnosis. [4]

Flow in the venous line (DV)

The ductus venosus is a short vascular structure that plays an extremely important role in the fetal circulation. It is located in the liver and connects the umbilical vein to the inferior vena cava, allowing it to bypass the hepatic circulation and direct the blood coming from the placenta, which is rich in oxygen and nutrients, directly to the fetal heart. After birth, the venous duct closes and becomes a venous ligament. Assessment of the flow in the venous conduit is performed between the 11th and 14th weeks of pregnancy as one of the screening tests. We speak of normal flow when we have a biphasic wave present, consisting of a positive systolic wave, a diastolic wave and a positive wave in the arterial phase. The blood flow is continuous and directed towards the fetal heart. A DV abnormality can tell us about the presence of genetic defects, chromosomal aberrations, heart defects, or vascular or placental abnormalities. Any abnormality should be verified by further diagnostics. [4], [12]

Amniotic Fluid Index (AFI)

It is an indicator of the amount of amniotic fluid used in ultrasound to assess the fetal environment. It is a key element in assessing fetal wellbeing and placental function. It is performed in the second and third trimester of pregnancy. It is the sum of the length of the largest pocket dimensions of all four quadrants of the uterus expressed in millimetres or centimetres. The normal value is considered to be between 5 and 25 cm, below this we speak of small-foramen, above this we speak of multiforme. There can be many causes for these conditions, both on the part of the mother and the baby. For example, problems with the placenta, defects of the urinary tract, rupture of the membranes, intrauterine growth retardation, gestational diabetes of the mother, defects of the digestive system or genetic disorders or intrauterine infections. Mild abnormalities may not need intervention, whereas severe thrombocephaly or polyhydria will already need further diagnosis. [13]

Femur Length (FL)

It is a parameter measured during ultrasound examination during pregnancy, which determines the length of the fetal femur. FL is one of the basic indicators of fetal biometry, used to assess the baby's growth and body proportions. It is performed in the second and third trimester of pregnancy. In correlation with gestational age, it is used to determine the approximate age of the fetus and its body weight. Small deviations may be physiological, while significant ones are an indication for further diagnosis. [14]

Combining ultrasound with biochemical tests.

The combination of ultrasound and biochemical tests in prenatal diagnosis significantly increases the effectiveness of detecting genetic and structural defects in the fetus. By using both methods, it is possible to estimate the risk of genetic diseases more accurately, assess fetal development and detect pregnancy complications at an early stage. An example is the combined test where the sensitivity for trisomy 21 is 85-90% when only NT and biochemical tests are used. However, by adding additional ultrasound markers (e.g. nasal bone, DV), the efficiency increases to around 95%.

Modern medicine uses advanced mathematical algorithms that integrate biochemical, ultrasound data and individual patient characteristics to estimate the risk of trisomies and other genetic disorders as accurately as possible. With these methods, doctors can accurately assess the health of the fetus and plan further diagnostics.

The algorithm developed by the Fetal Medicine Foundation (FMF) is currently one of the most precise genetic defect risk assessment systems used worldwide.

The trisomy risk assessment model takes into account:

- mother's age- the risk of trisomy increases with a woman's age, especially after the age of 35,
- measurement of nuchal translucency- this is a key parameter assessed by ultrasound between the 11th and 14th week of pregnancy (the higher the NT value, the greater the risk of trisomy),
- the concentration of biochemical markers in maternal serum:
    - PAPP-A- reduced values may suggest a risk of Down's syndrome or other chromosomal defects,
    - β-hCG- elevated levels are associated with an increased risk of trisomy 21,
- presence or absence of a nasal bone - in many cases of children with Down syndrome, the nasal bone is not visible in the first trimester, which increases the risk of this trisomy
- blood flow in the venous tract- abnormal flow in this structure may indicate an increased risk of genetic defects,
- abnormal flow across the tricuspid valve- abnormal flow may be another marker for increased risk of trisomy 21.

The data collected is entered into a computer system which, based on complex statistical calculations, converts it into specific risks expressed as, for example, 1:1000 (low risk) or 1:50 (high risk).

The PRISCA (Prenatal Risk Calculation) algorithm is an older method used mainly in the second trimester of pregnancy and is used in laboratories to assess the risk of Down syndrome and other trisomies. It is less precise than the FMF algorithm, but can still provide valuable information for patients who did not test in the first trimester. It analyses: maternal age and biochemical markers (PAPP-A, β-hCG, AFP).

The most modern and precise method of assessing the risk of genetic defects is NIPT (Non-Invasive Prenatal Testing). This test analyses the free fetal DNA (cffDNA) that circulates in the mother's blood. It detects trisomy 21, 18 and 13 with over 99% sensitivity. It can also detect sex chromosome disorders (e.g. Turner syndrome, Klinefelter syndrome). Some variants of NIPT allow the assessment of microdeletions and other rare chromosomal aberrations. It can already be performed from the 10th week of pregnancy and its sensitivity is the highest among screening tests.

The combination of FMF algorithms, PRISCA and the modern NIPT test allows a very accurate assessment of the risk of genetic defects in the fetus. Each of these methods has its own advantages and limitations, so the decision to use them should be adapted individually to the patient. The greatest diagnostic efficiency is achieved through a combination of biochemical tests, ultrasonography and analysis of free fetal DNA (NIPT). [1], [2], [9], [11]

Summary and future research directions.

Modern technologies in prenatal diagnosis, including artificial intelligence used in analysing ultrasound images and interpreting biochemical test results, advanced genetic testing and personalisation of tests, are contributing to increasingly accurate risk assessment and earlier detection of birth defects. However, their

development also raises ethical questions that require consideration of the individual needs of patients and appropriate support in the decision-making process. In the future, further developments in prenatal diagnosis may allow more effective treatment of conditions while still in the fetal life stage, increasing the chances of healthy development of the child.

Disclosure

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