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Review article

Advantages and Limitations of Currently Available Methods of Prenatal Diagnostics

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SUMMARY

Introduction/Aim. Pregnancy is one of the most important and enjoyable but often one of the most stressful periods in a woman's life. The most common fears that occur in this period of life are related to the health of the baby, the course of pregnancy, and childbirth. In order to get more information about the health status of a baby, there are a lot of prenatal diagnostic procedures which can be recommended to the pregnant women. Different studies have shown that in some healthcare systems health-care providers have gaps in knowledge in some areas of prenatal diagnostics and testing, primarily due to the constant advancement of prenatal diagnostic technology, introduction of new tests, and improvement of availability, specificity and sensitivity of the already existing prenatal tests. The aim of this paper was to systemize the current knowledge and provide medical professionals with new and detailed insight into the currently available methods of prenatal diagnostics, their informativeness, application, indications, contraindications, and possible complications in order to improve the current medical practice.
Methods. Internet search engines were used to find and select relevant literature data.
Conclusion. Constant monitoring of technology advancement, continuous education of health-care providers and publishing of new findings about currently available methods of prenatal diagnostics, represent necessary preconditions for improving the current medical practice and health of the patients.

Keywords: **healthcare providers, medical practice, prenatal diagnostics, prenatal testing**

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INTRODUCTION

Pregnancy is one of the most important and enjoyable but often one of the most stressful periods in a woman's life (1).The most common fears of future parents that occur in this period of life are related to the health of the baby, the course of pregnancy and childbirth (2). When it comes to the health of the baby, this fear is justified given the fact that 3% to 5% pregnancies are severely complicated by congenital malformations or genetic disorders of the foetus (3). These conditions not only impact the child's quality of life constituting the leading cause of infant and child mortality but also extend their influence on the overall well-being of the family, the health system, and society (4).

In order to get more information about health status of the baby, there are a lot of prenatal diagnostic procedures which can be recommended to the pregnant women (5) by health-care professionals during official visits.

Different studies have shown that in some healthcare systems, health-care providers have gaps in knowledge of some areas of prenatal screening and testing primarily due to the constant advancement of prenatal diagnostic technology, introduction of new tests, and improvement of availability, specificity, and sensitivity of the already existing prenatal tests (6, 7). Thus, the introduction of continuous medical education and continuous publishing of new findings in prenatal diagnostics for health-care providers involved in prenatal counselling is necessary.

Further, trained medical professionals are not only people that recommend pregnant women certain type of medical procedures and tests and who interpret their results. Beside official consultations, patients also frequently seek advice from people around them who do not have adequate medical education but have a lot of unverified information. This commonly leads to the confusion of patients during the process of deciding which method of prenatal diagnostics to undergo (8), because the patients themselves make the final decision on whether or not to undergo a certain procedure.

The aim of this paper was to systematize the current knowledge and provide medical professionals and patients with better insight into the currently available methods of prenatal diagnostics, its application, indications, contraindications, and possible complications in order to improve the current medical practice and health of patients.

METHODS OF PRENATAL DIAGNOSTICS

The landscape of prenatal diagnostics represents a mosaic of diverse methodologies, each contributing to our ability to understand and monitor the health of an unborn child. The term "prenatal diagnostics" encompasses an array of techniques, from non-invasive screenings to more comprehensive diagnostic procedures.

Each method has its unique strengths and applications, offering a window into the development of the foetus and, when necessary, signalling potential concerns. Although a large number of different procedures are available today, they still cannot fully guarantee that the child will be born healthy, because at today's level of development of medicine and technology, it is not possible to detect all possible diseases and pathological conditions in foetuses. The main goals of prenatal diagnostics development are to expend its range to early period of pregnancy, and to increase the range of detectable diseases and conditions. Additionally, early diagnostics will enable timely foetal therapy, introduction of early preventive measures, or at the request of the pregnant woman, consideration of possible termination of pregnancy in case the foetus has severe mental and physical impairment (9, 10). Information about foetal condition allow parents, as well as health care professionals, to better prepare themselves psychologically, socially, financially and medically for the birth of a child with a health problem (9, 11, 12).

The terms prenatal diagnostics and prenatal testing are commonly used in the reference literature and practice. Since they are very similar, it is very important to explain the difference between them. In the broader sense of the word, prenatal diagnostics represents the application of non-invasive and invasive procedures, while in the narrow sense, this term represents only the application of invasive diagnostic procedures. On the other hand, prenatal testing or screening represents only the application of non-invasive procedures in order to assess the health status of the foetus (9, 13, 14).

Very often, patients do not understand the difference between screening and diagnostic tests and particular consideration has to be paid to that during a consultation period. It is of great importance to ex-

plain to patients the meaning of the results of certain tests, especially that negative results do not guarantee that the baby will be born healthy (15).

According to the American College of Obstetricians and Gynecologists, women of all ages should be offered some kind of prenatal testing, regardless of maternal age or other risk factors (16, 17). Ideally, possibilities of prenatal testing according to maternal age, health status, family history etc. should be discussed during the first obstetric visit (14).

NON-INVASIVE PRENATAL TESTS

Non-invasive prenatal tests, otherwise called screening tests, are recommended to pregnant women without risk to the foetus and themselves. Their results indicate the likelihood of genetic disorders and congenital malformations in the foetus. Their results are not enough to make the definitive diagnosis, but with positive results of these tests, pregnant women are further referred to some of the definitive invasive diagnostic tests. It is recommended that non-invasive tests should be performed first, and then invasive tests, if there is still a need for them. Initially, prenatal genetic testing are focused primarily on identifying trisomy 21 (Down syndrome), but now it is possible to detect a wide range of congenital malformations and hereditary disorders (9, 16).

Today, the following methods of prenatal screening are commonly used in practice:

- Ultrasonographic screening;
- Maternal serum screening;
- Screening of free circulating foetal DNA in the mother's blood;
- Screening of foetal cells in the mother's blood;
- Screening of parents for carrying a specific hereditary disorder, i.e. determining the status of parental carriers in specific genetic disorders (9).

Ultrasonographic screening

Ultrasonography represents routine foetal screening in gynaecology, which is used for accurate determination of the week of gestation, assessment of foetal growth, localization of the placenta, determination of multiple pregnancies, and for the diagnosis of congenital malformations. The great advantage of this method is its non-invasiveness, so its use is not risky for the mother and foetus. Nowadays, it is applied routinely in gynaecological practice and it is considered that at least four ultrasound examinations are needed during pregnancy in different time intervals (18).

The first ultrasound examination is needed after the absence of menstrual bleeding. An examination should be performed to determine whether the pregnancy is in the uterus and whether it is vital (19).

The second ultrasound examination is performed in the period from weeks 11 to 14 and is called ultrasound foetal screening: the head, torso, arms, legs, organs that have begun to develop can be seen, as well as certain changes that could show that the foetus does not develop properly. It is very important to establish that the development of the foetus is normal and that the pregnancy can continue or that the foetus does not develop properly and terminate the pregnancy. Ultrasound foetal screening parameters such as nuchal translucency (NT), nasal bone presence, and ductus venosus flow may indicate an increased likelihood of chromosomal aberrations in the foetus (Figure 1) (19, 20).

The third ultrasound examination is performed in the period from the 20th to 24th week of pregnancy, and then the morphology of the foetus, growth and development of the foetus, placenta placement, amniotic fluid amount and more detailed echoanatomy of the foetus are examined, because the organs are larger and can be visualized better (21).

The fourth ultrasound examination is performed in the period from the 30th to the 32nd week of pregnancy, and then the baby's growth, the amount of amniotic fluid, and the appearance of the placenta are analyzed, and also it is assessed whether the baby is progressing well. Some structural abnormalities detected by ultrasound may indicate chromosomal disorders in the foetus. The use of ultrasonography is also important as an aid in performing invasive procedures such as chorionic villus sampling, amniocentesis, and cordocentesis (22).

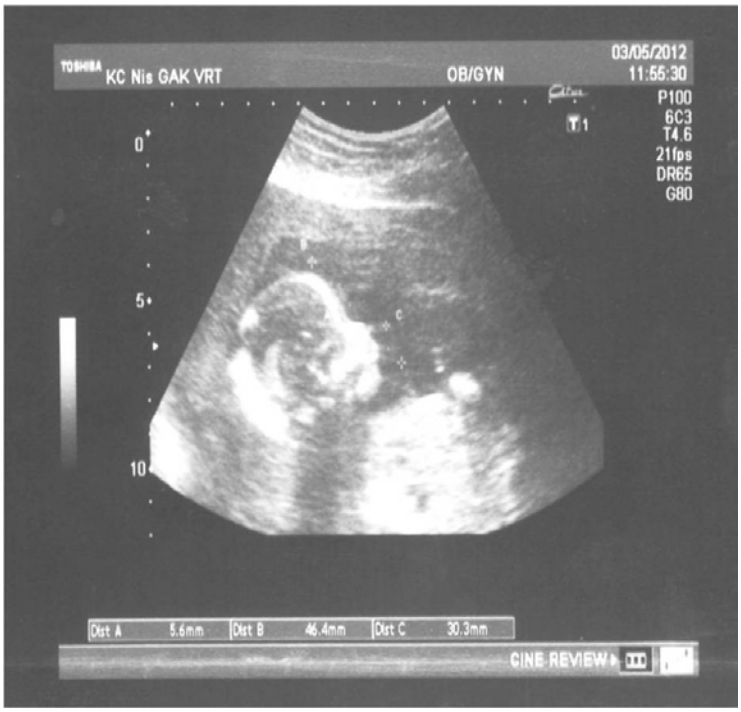

Figure 1. *Ultrasound of the foetus in the 12th week of pregnancy*

There are no absolute contraindications to either transabdominal or transvaginal ultrasound, except for patient refusal (23). While this method is safe for both the mother and foetus, healthcare providers should appropriately inform patients about the ultrasound's limitations before proceeding (24).

Maternal serum screening

Maternal serum screening involves the use of concentrations of certain metabolites from maternal serum and ultrasonographic measurements to assess the risk of the foetus carrying one of the most common trisomies, anencephaly or neural tube defect. There are several different tests, depending on the period of pregnancy in which they are performed, as well as the type of metabolite whose concentrations are used.

The double test is part of a more comprehensive screening in gynaecology called the first trimester screening (25). It is classified not as a definitive but as a predictive test, which means that its results report the probability of the most common trisomies in the foetus (trisomies of chromosome 21, 13 and 18). To calculate the risk, this test uses the levels of free beta-human chorionic gonadotropin (beta-hCG) and pregnancy-related plasma protein A (PAPP-A) in blood. Beta-hCG and PAPP-A levels may be either higher or lower than normal in pregnant women with Down syndrome, Patau syndrome and Edwards syndrome. However, for risk assessment, i.e. calculation of probability of chromosomal aberrations in the foetus, the test also uses the ultrasonographic parameter nuchal translucency (NT) (19), as well as the age and weight of the mother. In addition to the measures of nuchal translucency (NT) in the ultrasound findings, the presence/absence of the nasal bone as well as the flow through the ductus venosus are stated (20). The entered parameters are further processed by software, and the result is issued in the form of probability (Figure 2). The test itself is performed between the 11th and 14th week of pregnancy. It is important to remember that the result only indicates whether there is an increased risk that the foetus is a carrier of any of these trisomies. The foetus is thought to be more likely to have trisomy if test results show a risk greater than 1: 250 (26).

Down's syndrome screening program

Patient:
ID. No.: 38 - Hospital Number: A 2299 .
DOB: **7/6/1977** ; maternal age at EDD: **35** years. EDD:10/2/2012.
Gestational age based on biometries: CRL of 54 mm, which is equivalent to 12 weeks and 1 days at date of ultrasound: 3/21/2012 .Real gestational age at screening date: **12 weeks and 2 days.** Screening date: **3/22/2012**. Single-fetus pregnancy.

Screening profile: Combined First Trimester. Software used: SsdwLab 5.

Gaussian markers
Level of **Free ßhCG** 26.68 mIU/ml at 3/22/2012 : **0.87** MoM.
Level of **PAPP-A** 1830 mIU/l at 3/22/2012 : **0.97** MoM.
Level of **NT** 1.3 mm (CRL of 54 mm) : **0.91** MoM.
Marker values have been corrected by, weight (68 Kg), smoker.

Down's syndrome Risk; 1 : 6910 calculated as Risk at screening date. **Low Risk.** The maternal age related risk for Down's syndrome is 1: 244 .

Edwards' and Patau's syndrome Risk; Less than 1 : 100000 calculated as Risk at screening date. **Low Risk.**

3/27/2012

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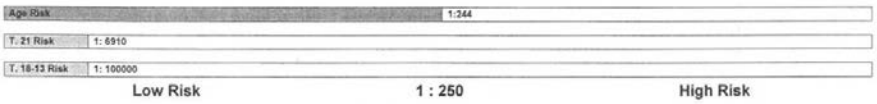


Figure 2. *The results of the double test*

Result of Down's Syndrome Screening Test

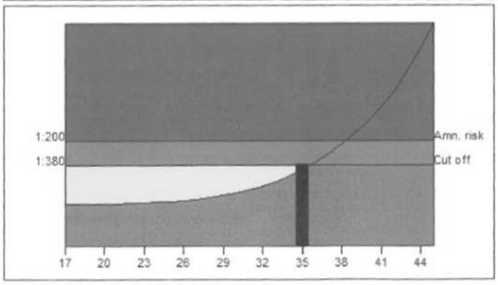
Name		Sample N°	6563	Diabetes	no
		Birthday	6.7.1977	Twin pregnancy	no
Doctor		Age	35,2	Day of serum taking	21.4.2012
		Weight	70 kg	Day of result report	23.4.2012

Results of measured serum value and risk value

AFP	30,30 ng/ml	1,02 MoM
HCG	29375,00 U/L	1,57 MoM
fE3	2,10 ng/ml	0,56 MoM

Gestation age

Gestation age on the day of serum taking 16 + 2



Triple Test
1:368

Age Risk
1:446

TRISOMY 18 SCREENING
The risk for trisomy 18 is < 1:10000. There is no statistical indication for trisomy 18 risk.

NEURAL TUBE DEFECTS (NTD) SCREENING
The risk for spina bifida/anencephaly is < 1:10000. There is no statistical indication for spina bifida/anencephaly.

Figure 3. *The results of the triple test*

The triple test is part of the second trimester screening and is used as a screening test for Down and Edwards syndrome, as well as neural tube defects, omphalocele, gastroschisis, etc (27). Risk assessment is based on the measurement of alpha fetoprotein (AFP), human chorionic gonadotropin (hCG) and unconjugated esteriol (E3) in the serum of pregnant women, in relation to age, body weight, and week of gestation (Figure 3). The test is performed in the second trimester of pregnancy from the 15th to 18th week of pregnancy, by taking the blood of a pregnant woman. The parameters are always analyzed together because individually they do not give informative result. If the finding shows an increased risk, pregnant women are referred for additional tests such as ultrasound and amniocentesis (28). Recently, another biochemical marker, inhibin A, was included in the second trimester biochemical screening as a fourth parameter. This unified test was called the quadruple test and it is also more accurate than the triple test. As with the double test, the entered parameters are processed by a software and the result is issued in the form of probability (29, 30).

Screening for free circulating foetal DNA in the mother's blood

In recent years, non-invasive prenatal testing (NIPT) has been increasingly used as a screening method in the world, where one of the methods is based on the analysis of free circulating foetal DNA (cffDNA) in the mother's blood (31, 32). Most of the free circulating DNA (cfDNA) in the mother's blood comes from the mother, while the foetal component (cffDNA) comes from placenta. From early pregnancy, cffDNA is present in the mother's blood and quickly disappears from the mother's circulation a few hours after birth, making it specific for pregnancy. Basic principle of this method lies in the fact that fragments of foetal DNA that are circulating, when combined, carry information about the entire foetal genome. If the foetus has e.g. Down syndrome, there will be slightly more DNA fragments specific for chromosome 21 in the mother's circulation. With technological progress, it has become possible to perform extremely precise counting of individual molecules and thus detect small changes in the number of chromosome of interest in the blood (33).

This test is very accurate with high sensitivity (99%) and specificity (99.5%) for Down syndrome, which can be performed starting from the 10th week of pregnancy when the mother's circulation has sufficient quantity of cffDNA. Except for Down syndrome, this method can be used for screening other chromosomal aneuploidies, various unbalanced structural aberrations (deletions and duplications) and more recently for single gene disorders (34). Results that do not agree with the karyotype of the foetus can be the results of several conditions. False positive results can occur due to chromosomal rearrangements or maternal mosaicism, maternal malignancy, placental mosaicism or due to loss, i.e. the disappearance of one of the twins in a twin pregnancy. False-negative results can also occur due to low cffDNA levels or laboratory and technical problems. As such, this test is not a diagnostic test and confirmation of a positive result by invasive testing is necessary (35).

Indications for screening free circulating foetal DNA in maternal blood are:

- Age of mother (> 35);
- Positive screening of maternal serum in the first and second trimester;
- Presence of ultrasonographic soft markers (soft markers of aneuploidy are nonspecific, often transient, and easily detectable during the second and third trimester ultrasound. The most commonly studied soft markers of aneuploidy include thickened nuchal fold, and mild foetal pyelectasis;
- Maternal anxiety;
- Previous child with trisomy (34, 35);

This type of screening is not recommended in the case of the following conditions:

- Suspected monogenic disease in the foetus;
- Malformation of the foetus detected by ultrasound;
- Infection;
- Balance translocations in one of the parents;
- Multiple pregnancies (34,35).

The main advantages of this method are that it is absolutely non-invasive, possess high sensitivity and specificity, and also reduces the need for invasive testing.

Screening of foetal cells in the mother's blood

It has been known for decades that some developing foetal cells enter into mother's circulation and that this process begins in the very early pregnancy. After many years of partial success and fail-

ure, advances in genetic analysis have heightened interest in foetal cells for prenatal diagnostics (36).

Although extremely rare, circulating foetal cells (CFCs) in the mother's blood possess a complete foetal genome. The mother's circulation is dominated by nucleated erythrocytes, trophoblast cells, as well as foetal leukocytes (37). The method itself is performed between the 10th and 18th week of pregnancy. Technological progress allows isolation even of a few circulating foetal cells from a few millilitres of maternal blood. After isolation of cells, the next step represents the whole genome amplification. The amplified whole genome is further analyzed by microarray method or next generation sequencing (38, 39).

Currently, non-invasive prenatal testing is mainly focused on methods that analyze free circulating foetal DNA in the mother's blood. Although these methods can very reliably detect the incidence of common aneuploidies (trisomies of chromosome 21, 13, and 18), they are not as effective in detecting duplications or deletions as well as monogenic disorders. This is mainly due to the fact that the foetal DNA circulating in the mother's blood is fragmented and mixed with the mother's DNA. Intact foetal cells circulating in the mother's blood can overcome this deficiency of cell-free NIPT (cfNIPT) because they are the source of pure and whole foetal genomes. Currently, the greatest difficulty in performing this method is the isolation of intact foetal cells. There is hope that with the development of technology, this difficulty will be overcome and that genetic analysis of circulating foetal cells will become a routine diagnostic procedure (40).

Parental screening for carriers of a specific inherited disorder

Although the screening of parents for the carriers of a specific hereditary disorder is primarily done before pregnancy occurs, it is possible to conduct it also during pregnancy. The blood of both parents is taken for analysis and subjected to molecular genetic methods for the diagnosis of monogenic diseases. In the case of positive results in parents, and depending on the disease and type of inheritance, as well as whether one or both parents are carriers of the harmful allele, some of the methods of invasive diagnostics by which foetal cells are taken and which are further subjected to molecular genetic tests can be performed (41).

INVASIVE METHODS OF PRENATAL DIAGNOSTICS

Invasive tests are considered definitive diagnostic tests that determine the existence of chromosomal aberrations and monogenic diseases. They carry a dose of risk and it is important to perform them only when they are really necessary. Given their invasive nature, involving the extraction of tissue samples for further analysis and carrying potential risks for the mother and foetus, the final decision on whether these tests will be performed is made by the parents. Although invasive prenatal diagnostic tests have very high diagnostic reliability in assessing hereditary basis, they are not without risks, including but not limited to foetal loss, foetal injury, rupture of membranes, and maternal infection (42 - 44).

Amniocentesis

Amniocentesis is a procedure involving the aspiration of several millilitres of amniotic fluid from the amniotic cavity, commonly employed for prenatal diagnosis of aneuploidy, congenital diseases, and infections. This invasive test stands as the most frequently performed procedure in prenatal diagnostics. The process entails aspirating 10 - 20 ml of amniotic fluid, typically conducted by a gynaecologist between the 16th and 20th week of gestation (45). Prior to the intervention, meticulous disinfection of the abdominal skin is imperative, followed by the insertion of a fine needle into the amniotic cavity, guided by ultrasound. While the amniocentesis procedure itself is not classified as painful, pregnant women often describe it as an uncomfortable experience. The aspirated amniotic fluid contains cells from the urogenital tract and fibroblasts from the foetal skin, and the natural compensation of the removed amniotic fluid occurs seamlessly. The obtained sample is then forwarded for further examination. While some types of analyses can be conducted immediately using amniotic fluid cells, the majority of cell analyses require cultivation for 2 - 3 weeks to yield a satisfactory quantity of cells for DNA and chromosome analysis. Complications associated with amniocentesis encompass miscarriage, leakage of amniotic fluid, sepsis, and foetal lung dysfunction. It is well-established that approximately one pregnancy loss occurs per 200 amniocentesis

procedures. Consequently, it is imperative that amniocentesis be undertaken only when there is a specific and compelling reason for it (43, 46).

Indications for amniocentesis are:

• Abnormal results of screening tests, abnormal ultrasonographic findings, previously affected foetus, abnormal parental karyotype;

• Increased risk of specific genetic disorder;

• Infective diseases of the mother that can be transmitted to the baby (44);

• Anxiety and the request of the mother (typically not considered indications but may be performed in exceptional cases);

• Advanced maternal age (although being over 35 years old is not a standalone indication for invasive testing);

• Evaluation of foetal lung maturity post 34 weeks of gestation;

• Assessment of bilirubin in amniotic fluid and evaluation of the severity of alloimmunization in Rh isoimmunized pregnancies;

• Relief of maternal discomfort during hydramnios and administration of intraamniotic drugs (47).

There are no absolute contraindications for amniocentesis. However, relative contraindications encompass:

• Infections;

• Patients undergoing anticoagulant therapy;

• Cases involving oligohydramnios (46).

Depending on the specific case, the following analyzes can be further performed on the sample obtained by amniocentesis:

1) Cytogenetic and molecular-cytogenetic analyses

Routine karyotyping is the most common but not the only type of cytogenetic analysis which can be performed on amniotic cells. Since the cultivation of cells is mandatory for routine kariotyping, 3 weeks usually pass before the results are obtained (48). These results give information on the total number of chromosomes and the existence of structural aberrations visible under the light microscope, commonly larger than 7 - 8 Mb, and sometimes larger than 4 - 5 Mb. A normal finding does not exclude the existence of submicroscopic structural aberrations as well as monogenic diseases. In case when there is suspicion of submicroscopic chromosomal rearrangements, molecular cytogenetic analyses as fluorescence *in situ* hybridisation (FISH) (49) or molecular karyotyping (50) are commonly required.

2) Molecular analyses

With these methods, changes of less than 100 kb in genetic material can be detected, up to the level of one nucleotide that underlies monogenic diseases (51).

3) Biochemical analyses

Biochemical analyzes of amniotic fluid are performed when there is a risk of congenital metabolic errors (mucopolysaccharidosis, familial hypercholesterolemia, adrenoleukodystrophy, homocysteinuria etc.) and also to assess maturation and renal function of the foetus in the amniotic fluid during pregnancy (52).

4) Diagnosis of foetal infections by microbiologic evaluation of amniotic fluid (53)

Chorionic villus sampling

Chorionic villus sampling (CVS) is a diagnostic procedure conducted between the 10th and 13th week of pregnancy, involving a biopsy of chorionic tissue for prenatal genetic testing. A key benefit of CVS is the prompt availability of genetic test results during pregnancy, enabling patients to consult a gynaecologist, seek early referral to paediatric specialists, or consider options for terminating pregnancy in the event of abnormal results (54).

The chorion plays a crucial role in placental formation as placenta originates from its cells. Although those cells are not part of the foetus, they are usually genetically identical to it. Using a hollow needle, the doctor takes a small amount of chorionic tissue from a location identified through ultrasound guidance. In order to avoid malformations of foetal limbs, which sometimes this procedure can cause, it is commonly performed after the 11th week of pregnancy. The first results are available after one to eight days. The advantage of CVS is early diagnosis and, if necessary, a chance to verify the results with other invasive methods (55, 56).

There are several indications for chorionic villus sampling:

• Abnormal results of non-invasive prenatal screening;

• A previous child with a structural birth defect;

• Previous child with detected chromosome aberration;

• Aberrant karyotype of the parent;

• The parent is a carrier of an inherited disorder;

(54, 57).

The potential risks associated with undergoing a chorionic villus biopsy are similar to those of amniocentesis, commonly encompassing the possibilities of pregnancy loss, bleeding, infection, and scrotal rupture, but also sometimes unreliable results (54, 58).

A thorough examination of complications following chorionic villi sampling revealed an overall foetal loss rate of 2 percent at any time during pregnancy. While sampling of chorionic villi, there exists a rare possibility of obtaining maternal tissue instead of trophoblasts, leading to inaccurate results. Chorionic villus sampling results can also unveil placental mosaicism, occurring in 1% - 2% of cases, wherein a mismatch between the placental and foetal karyotype is observed (59). Although foetal mosaic status is present in 10% of cases, detecting such mosaicism increases the risk of placental dysfunction and perinatal complications, including foetal growth restriction and maternal hypertension (54, 60). After discovery of mosaicism, amniocentesis is recommended. The likelihood of cell culture failure, amniotic fluid leakage, or infection after chorionic villus sampling is minimal, being less than 0.5% (61).

Diagnostic analyses that can be performed on amniotic cells can be also applied to trophoblast cells:

1) Cytogenetic and molecular-cytogenetic analyses;

2) Molecular analyses;

3) Biochemical analyses.

Cordocentesis

It represents intrauterine foetal blood sampling by percutaneous umbilical cord puncture. It is performed under ultrasound control after the 18th week of gestation. Foetal blood is aspirated in the amount of 1 - 3 ml, depending on the gestational age and further planed analyses. The most common indications are rapid determination of karyotype, hemoglobinopathy, coagulopathy, metabolic disorders, immune defect, viral infection, toxoplasmosis, assessment of intrauterine asphyxia in high-risk pregnancies. Complications of cordocentesis are rare, with reflex foetal bradycardia occurring most often. Potential risks linked to this procedure encompass infections, premature rupture of membranes, preterm birth, placental abruption, hemorrhage, alloimmunization, and pregnancy loss (62, 63).

The most common indications for diagnostic cordocentesis are:

- Rapid karyotyping;
- Treatment of foetal hemolytic disease;
- Addressing a serious early foetal growth deficit;
- Confirmation of suspected congenital infection (62).

The development of molecular genetics techniques is slowly reducing the need for cordocentesis as a diagnostic method, so it is certain that there will be less and less need for it in the coming years.

Preimplantation diagnostics

Preimplantation genetic diagnosis (PGD) is a technique which involves the examination of genetic material in the early embryonic cells derived from embryos obtained through *in vitro* fertilization (IVF). This process encompasses the analysis of three primary sources of genetic material: polar bodies from oocytes, blastomeres from cleavage-stage embryos, and trophectoderm cells from blastocyst-stage embryos. Following genetic testing, embryos in which no changes in the genetic material were found are selectively transferred to the uterus (64).

PGD serves as important reproductive tool, particularly for couples at an elevated risk of passing on genetic disorders to their offspring. Selection of embryos free from identified genetic changes offers prospective parents to proactively avoid potential issues like health complications and the emotional and financial challenges associated with pregnancy termination (65).

Preimplantation diagnosis can be used for determination of the sex of embryo in sex-related disorders (66), for identification of monogenic diseases (67) and various chromosomal aberrations in the developing embryo (68 - 70). The first technique used for the detection of chromosomal aberrations during PGD was FISH. Nowadays, the methods such as RTqPCR (quantitative reverse transcription polymerase chain reaction), aCGH (array comparative genomic hybridisation), SNP arrays (single nucleotide polymorphism arrays), karyomapping techniques and next generation sequencing (NGS) are commonly used for the detection of chromosomal aberrations, while multiplex PCR, whole genome amplification (WGA), SNP arrays, and NGS are used for the detection of mutations in developing em-

bryos (64).

Currently, the choice of the technique applied in specific case depends on the type of analysis requested (determination of the sex of embryos, mutation testing or chromosomal analysis). Advancements in technology are moving towards discovering a universal method that can simultaneously diagnose various types of genetic conditions. This progress aims to enable the selection of the most optimal embryo with the highest potential for successful implantation (65).

Although this method acts as an ideal solution by which the genetic basis of the embryo is checked even before implantation and thereby avoids numerous complications, it also has limitations and disadvantages. It is a technically very demanding method that can only be performed in highly specialized centres and its application is limited only to patients undergoing IVF. Also, it can only detect changes in genetic material of a small number of embryonic cells which means that even though the tested cells have a normal genetic basis at the time of detection, genetic changes in other cells can be missed and also during later development errors in genetic material may occur, which both can affect the health of the newborn child (71).

CONCLUSION

Prenatal diagnostics involves the application of various medical procedures which are able to detect a wide range of diseases and conditions before birth. Commonly, they are recommended to patients by health-care professionals during official visits, but the patients themselves make the final decision on whether or not to undergo a certain procedure. Different studies showed that in some healthcare systems health-care providers have gaps in knowledge in some area of prenatal screening and testing primarily due to the constant advancement of prenatal diagnostic technology, introduction of new tests, and improvement of availability, specificity and sensitivity of the already existing prenatal tests. Constant monitoring of technology advancement and continuous education of health-care providers about currently available methods of prenatal diagnostics, their informativeness, application, indications, contraindications, and possible complications represent necessary preconditions for improving current medical practice and health of the patients.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Prednosti i ograničenja trenutno dostupnih metoda prenatalne dijagnostike

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SAŽETAK

Uvod/Cilj. Trudnoća je jedan od najvažnijih i najprijatnijih, ali veoma često i najstresnijih perioda u životu žene. Najčešći strahovi koji se javljaju tokom trudnoće vezani su za zdravlje bebe, tok same trudnoće i porođaj. Kako bi se stekao uvid u zdravstveno stanje bebe, danas postoji mnogo procedura prenatalne dijagnostike, koje se mogu preporučiti trudnicama. Različite studije pokazale su da u pojedinim zdravstvenim sistemima kod zdravstvenih radnika postoje praznine u znanju o pojedinim oblastima prenatalne dijagnostike i o testiranju, prvenstveno zbog stalnog unapređenja tehnologija prenatalne dijagnostike, uvođenja novih testova, kao i povećanja dostupnosti, specifičnosti i osetljivosti već postojećih prenatalnih testova. Cilj ovog rada bio je da sistematizuje dosadašnja znanja i pruži medicinskim radnicima nov i detaljan uvid u trenutno dostupne metode prenatalne dijagnostike, njihovu informativnost, primenu, indikacije, kontraindikacije i moguće komplikacije, radi unapređenja dosadašnje medicinske prakse.
Metode. Korišćeni su internet pretraživači za selekciju adekvatne literature i podataka.
Zaključak. Stalno praćenje tehnološkog napretka prenatalne dijagnostike, objavljivanje novih saznanja o trenutno dostupnim metodama, kao i kontinuirana edukacija zdravstvenih radnika iz ovih oblasti, neophodni su preduslovi za unapređenje dosadašnje medicinske prakse i zdravlja bolesnika.

Ključne reči: **zdravstveni radnici, medicinska praksa, prenatalna dijagnostika, prenatalno testiranje**