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RECOMMENDATIONS

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Recommendations for prenatal diagnostics of the Polish Society of Gynaecologists and Obstetricians and the Polish Society of Human Genetics

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INTRODUCTION

The natural expectation of every pregnant woman is to give birth to a healthy baby. As such, the purpose of obstetric care is to assess and monitor the course of pregnancy and the development of the foetus. In the overwhelming majority of cases, it is possible to confirm that the foetus is undergoing normal development. Obstetric care is provided by a doctor and a midwife and is based on health promotion, screening and medical consultation. Such treatment has a positive effect on the mental state of the pregnant woman and the attitude of both parents to the child.

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The standards and organization of obstetric care in Poland are set by the Regulations of the Minister of Health. They define the quality of medical procedures, as well as the competencies of obstetricians and midwives, based on the rights and benefits of pregnant women.

All foetuses are at risk of malformations or genetic diseases. Furthermore, even a physiological course of pregnancy does not exclude the possibility of abnormalities or genetic syndromes postnatally. Such congenital defects may be diagnosed based on standard tests such as ultrasound examination.

However, foetuses of mothers with a positive history of genetic disorders or other risk factors may be at a higher risk of developmental disorders than the general population. For example, older mothers are at a higher risk of chromosomal aberration and teratogenic factors may increase the risk of foetal abnormalities. Women at high risk can take advantage of the Prenatal Testing Program NFZ created to provide genetic counselling, non-invasive screening and genetic tests.

The Polish Society of Gynaecologists and Obstetricians and the Polish Society of Human Genetics recognize that every pregnant woman, regardless of age, course of pregnancy, and history of previous pregnancies, should be informed about the possibility of performing prenatal tests. This applies in particular to abnormal pregnancies.

Prenatal testing is used in the diagnosis of a range of abnormalities which may have an impact on the pregnancy, delivery, health, and even life of the woman and the child.

Prenatal tests form the basis of both obstetric and postnatal care. Based on their findings, future parents can be informed in an understandable way and without undue stress to obtain their consent for further medical treatments.

Furthermore, if needed, their results allow early referral to a specialist for further monitoring, or to a particular hospital for childbirth.

The results of prenatal tests also allow the parent to provide informed consent regarding the medical and prophylactic care of the foetus and newborn, and can be used to support genetic counselling.

Prenatal tests also provide information about the location of pregnancy and abnormalities of the placenta. They may protect the health and even life of the pregnant woman in cases such as placenta accreta (caesarean scar pregnancy).

Non-directive counselling should be provided both before and after prenatal tests.

It is important to make parents aware of the limitations of prenatal testing. It is necessary to emphasize that, such diagnostics are restricted to detecting specific defects or developmental disorders. Normal test results do not guarantee the birth of a healthy child.

1. GENERAL PROVISIONS

1.1. The recommendations of the Polish Society of Gynaecologists and Obstetricians and the Polish Society of Human Genetics present the principles and conditions for performing screening tests and genetic tests in the prenatal period.

1.2. All pregnant women should be informed about the possibilities, goals, and limitations of prenatal testing.

1.3. All women should be informed about the tests that are reimbursed by the health insurance and about commercially-available tests. The Polish Society of Gynaecologists and Obstetricians and the Polish Society of Human Genetics will make efforts to get reimbursement for every prenatal test recommended based on medical knowledge.

1.4. Both screening tests and genetic tests are voluntary and require informed consent from the pregnant woman.

1.5. A pregnant woman has the right to withdraw from the proposed screening and genetic tests at any stage, regardless of the type of clinical indication and without giving any reason for her decision. Withdrawal should not affect the quality of further obstetric, neonatal, genetic counselling, or other specialist services of maternal and child care.

1.6. The recommendations specify competencies and requirements for those who order, perform and evaluate the results of genetic tests.

1.7. Laboratories that perform screening tests and genetic tests must meet the legal requirements for medical diagnostic laboratories.

1.8. The purpose of screening tests is to find pregnant women who have an increased risk of selected chromosomal aberrations in the foetus. The goal is also to exclude any complications of pregnancy and to find any defects of the foetus. Based on the magnitude of the risk, obstetric care can be continued in the reference centre or the woman can be referred to a specialist in clinical genetics, who will decide about further genetic testing.

1.9. Screening tests are non-invasive tests. Ultrasound examination should be carried out by a physician with certificates of the Foetal Medicine Foundation (FMF) and the Polish Society of Gynaecologists and Obstetricians. Recommended markers of foetal development should be assessed. Blood should be taken from the pregnant woman to test biochemical markers and/or to analyse foetal cell free DNA in the mother's blood.

1.10. Genetic tests are carried out after obtaining samples of the foetal cells in an invasive way. Genetic tests are ordered by a specialist in clinical genetics after genetic counselling. The indications for genetic tests are based on screening tests and the risk of malformations and

genetic diseases in the foetus. Reimbursement of these services is defined by the Minister of Health.

1.11. A specialist in obstetrics or feto-maternal medicine who orders genetic tests without the advice of a specialist in clinical genetic should have experience in genetic counselling.

1.12. When samples are sent from other medical units, the unit which performs the genetic test should specify the content of medical records necessary for the test evaluation.

1.13. The skills of doctors performing ultrasound examinations and laboratories performing screening and genetic tests should be regularly audited.

2. PROCEDURES IN PREGNANCY SUPERVISION

2.1. A medical history regarding health and risk factors should be collected during the first visit.

Comment:

Family and obstetric history should be collected. Any exposure to harmful factors during the pregnancy and in the preconception period should be recorded. Cases with infertility, repeated miscarriages or foetal death, malformations, chromosomal aberrations, intellectual disability, and family history of monogenic diseases deserve particular attention.

The essential parts of the medical history are presented in the attached questionnaire (App. 1). The questionnaire should be completed during each pregnancy.

2.2. Based on the risk factors given in the medical history, the obstetrician should refer the pregnant woman to a specialist in feto-maternal medicine or a specialist in clinical genetics.

Comment:

A specialist in feto-maternal medicine or in clinical genetics can order additional genetic tests. If an increased risk of genetic disease is suspected, the obstetrician is obliged to inform the pregnant woman about the necessity of genetic counselling. In which case, the woman should visit a specialist in clinical genetics with complete medical records. If any genetic test is indicated, no further screening tests should be performed. The unit performing the genetic test is obliged to prepare a complete algorithm of the diagnostic procedure.

2.3. The goal and limitations of prenatal tests should be explained to the patient, especially the differences between screening and diagnostic tests.

2.4. The recommended screening tests are the combined test and NIPT (non-invasive prenatal testing). Pregnant women should be informed about the goals and limitations of the tests. Of the two, the NIPT has the highest sensitivity and the highest positive predictive value, and the lowest percentage of false-positive results.

2.5. Ultrasound examinations should be performed on every pregnant woman (as recommended by the Polish Society of Gynaecologists and Obstetricians).

Comment:

The first-trimester ultrasound examination (foetal crown-rump length — CRL 45–84 mm) may be performed as part of the combined test. If foetal malformations are found, the patient should be referred to the feto-maternal medicine centre or a specialist in clinical genetics. In such cases, the specialist in clinical genetics follows the procedure presented in section 5.1.1.

2.6. Screening tests should be performed on any pregnant woman who does not have any other indications for genetic tests.

3. SCREENING IN PREGNANCY

Screening should be offered to every pregnant woman, regardless of her age. In cases with a history of genetic diseases, the pregnant woman should be referred immediately for invasive genetic testing. Additionally, the collected sample should be used to exclude chromosomal aberrations.

The Polish Society of Gynaecologists and Obstetricians and the Polish Society of Human Genetics recommend screening tests that include the combined test (p. 1) and NIPT (p. 3).

3.1. Combined test consisting of ultrasound (NT, CRL, FHR) and double test (free beta-hCG and PAPP-A).

3.1.1. The combined test should be offered to every pregnant woman. The test consists of an ultrasound examination [measurement of foetal crown-rump length (CRL), nuchal translucency (NT), foetal heart rate (FHR)] and the double test free human chorionic gonadotropin (beta-hCG) and pregnancy associated plasma protein A (PAPP-A).

3.1.2. The pregnant woman should be clearly informed that the combined test is only a screening test used to assess the risk of Down syndrome (chromosome 21 trisomy), Edwards syndrome (chromosome 18 trisomy), and Patau syndrome (chromosome 13 trisomy). The pregnant woman should be informed about the possibility of false-positive and false-negative results.

The pregnant woman should be informed about further diagnostic procedures.

The goals and potential risks of invasive procedures should be discussed. The woman should

be informed about the associated risk of loss of pregnancy, which in some cases may be even higher than the probability of the aneuploidy in the foetus.

3.1.3. Any evaluation of free beta-hCG subunit and PAPP-A must be performed with validated methods based on standards used in medical laboratories.

3.1.4. These tests should be evaluated by external quality control. Only a procedure accredited by the Foetal Medicine Foundation (FMF) should be used. The method to calculate the risk of foetal aneuploidy should be also accredited by the Foetal Medicine Foundation (FMF).

3.1.5. The double test (free beta-hCG + PAPPA) should not be performed if the NIPT test has been carried out previously, or if there is any indication for invasive diagnostics based on ultrasound examination.

3.1.6. The pregnant woman should be informed about the additional benefits offered by the double test, like the assessment of the risk of pre-eclampsia (PE) and foetal growth restriction (FGR).

3.1.7. The pregnant woman has the right not to undergo the screening test, and this information should be added to the medical record.

3.1.8. If the pregnant woman decides not to undergo the double test, the risk of aneuploidy can be assessed based only on ultrasound examination (*i.e.*, CRL, NT, FHR measurement). If the ultrasound examination identifies a high risk, the double test or NIPT should be offered again. Based on the results of these tests, the woman should be referred to genetic tests. When NT ≥ 3.5 mm or foetal defects have been diagnosed, invasive diagnostics should be always ordered.

3.1.9. The obstetrician/feto-maternal specialist should discuss the result of the combined test with the pregnant woman. A second-trimester ultrasound examination (18–22 weeks of gestation) should be offered when the risk is low (less than 1:1000).

3.1.10. NIPT should be proposed in cases with an intermediate risk (between 1:300 and 1:1000) (see 3.3.). Second-trimester ultrasound (18––22 weeks of pregnancy) is also recommended in cases with intermediate risk.

3.1.11. Women with high risk (risk greater than 1:300) should be referred to a feto-maternal specialist or a specialist in clinical genetics. NIPT or invasive testing should be offered to women with risks between 1:100 and 1:300. The advantages and disadvantages of each test should be presented. Second-trimester ultrasound is also recommended at 18–22 weeks of pregnancy.

3.1.12. Invasive genetic testing is indicated in women with a risk higher than 1:100. NIPT is not recommended in cases with a risk higher than 1:100. Information about indications for invasive tests should be provided both orally and in writing. Second-trimester ultrasound is also recommended (at 18–22 weeks of pregnancy).

3.1.13. A pregnant woman has the right to invasive diagnostics, regardless of the combined test results. The woman should be informed about the risk of invasive diagnostics.

3.2. Biochemical tests of the second trimester (triple or quadruple tests) are not more recommended because of their low sensitivity and the high percentage of false-positive results.

3.3. Test based on the analysis of cell-free foetal DNA (cffDNA) in the mother's blood (NIPT non-invasive prenatal testing).

3.3.1. The risk of the most common aneuploidies (trisomy of chromosomes 21, 18, 13) and other selected chromosomal aberrations in the foetus can be assessed with the cell-free foetal DNA (cffDNA) test. The test should be offered to a woman found to have risk 1:300 to 1:1000 in the combined test.

3.3.2. If the risk identified in the combined test is from 1:100 to 1:300, NIPT or invasive genetic diagnostics should be offered.

3.3.3. If the risk in the combined test is greater than 1:100, an invasive genetic test should be offered (see Diagnostic genetic tests for details).

3.3.4. An ultrasound examination should be performed before blood sampling for NIPT.

3.3.5. There is no evidence that calculating the risk of microdeletion in the foetus yields any benefits. The positive predictive value of NIPT in microdeletion syndromes is still low. Because the risk of false-positive results is high it may lead to increasing number of unnecessary invasive diagnostics.

4. FOETAL HEART ASSESSMENT

Screening of foetal heart defects is an element of obstetric ultrasound examination based on the recommendations of the Polish Society of Gynaecologists and Obstetricians.

The indications for a detailed assessment of the foetal heart structure are:

— abnormal structure of the foetal heart on obstetric ultrasound,
— foetal arrhythmia,
— increased nuchal translucency (NT > 95th percentile), absent or reversed flow in the ductus venosus, absence of nasal bones, tricuspid valve regurgitation in the first trimester of pregnancy,
— non-cardiac defect in the foetus,
— hydrops fetalis,
— an increased risk of a chromosomal aberration in the foetus (based on family history, combined test, or NIPT test),
— foetal chromosomal abnormality or monogenic disease,
— monochorionic twin pregnancy,
— a metabolic disease in a pregnant woman (*e.g.*, phenylketonuria),
— diabetes in the pregnant woman,
— presence of autoimmune antibodies in pregnant woman [anti-Ro (SSA); anti-La (SSB)],
— infection with the risk of inflammation of the heart muscle,
— exposure to teratogenic factors during pregnancy: *e.g.*, retinoic acid, ACE inhibitors, selected antiepileptic drugs, SSRI drugs,
— exposure to alcohol or drugs during pregnancy,
— a heart defect in a pregnant woman, the father of the foetus, or first-degree relatives.

If the above-mentioned indications are present, the structure of the foetal heart should be thoroughly assessed by a specialist in obstetrics and gynaecology with appropriate qualifications (certificate of foetal heart examination of the Polish Society of Gynaecologists and Obstetricians). If abnormalities in the structure or function of the foetal heart are found, the pregnant woman should be referred to a specialist with certificate of proficiency in foetal echocardiography.

5. DIAGNOSTIC GENETIC TESTS

5.1. Qualification for testing:

5.1.1. A pregnant woman is qualified for diagnostic genetic tests by a specialist in clinical genetics on the basis of genetic counselling. Genetic counselling should be given to both parents. They should have the possibility to ask questions and express their doubts. The specialist in clinical genetics should verify indications for the genetic test and present the goals and limitations of the test. It should be indicated that normal results do not guarantee the birth of a healthy child. The genetic test is not able to exclude all genetic diseases. The pregnant woman should be informed that it may be necessary to repeat the genetic test. The genetic counselling procedure should include information about the risk of invasive procedures and the advantages and limitations of the diagnostic test. The crucial information should be provided in writing.

5.1.2. The consent of the pregnant woman is needed before any invasive procedure can take place (App. 2). This consent should be attached to medical records. The consent should contain information about indications for genetic testing and the risk of complications of invasive procedures.

5.1.3. Consent is required once for the invasive procedure and again for the diagnostic genetic test (template: App. 3). This consent should contain information about the indication for prenatal diagnostic, risk of test failure, need to repeat the test, and the possibility to perform the test in other diagnostic units. The consent should contain information about the storage of the biological samples for a future genetic test, and a clause on the protection of personal data. The consent should also include a declaration by the woman whether she would like to learn the results of the test, or if she would not.

5.1.4. Genetic counselling should clarify all doubts regarding the consent to a genetic test.

5.1.5. The Polish Society of Human Genetics is responsible for standardizing the pattern of consent forms listed in points 5.1.2.–5.1.3.

5.1.6. Consent for the invasive procedure and consent for genetic testing may be combined in one document.

5.2. Collection of material for diagnostic genetic testing. Feto-maternal specialists or obstetricians experienced in performing invasive diagnostics (certified by the Polish Society of Gynaecologists and Obstetricians) should choose the method for collecting biological samples for the genetic test (chorionic villi sampling, amniocentesis, cordocentesis).

5.3. Ordering diagnostic genetic tests.

5.3.1. The invasive procedure should be preceded by genetic counselling from a specialist in clinical genetics.

5.3.2. Because of the limited number of specialists in clinical genetics, the first genetic counselling can be provided by a feto-maternal specialist or obstetrician who has been appropriately trained. Genetic counselling should meet the criteria presented in pp. 5.1.1.–5.1.4.

5.3.3. The training undergone by obstetricians in genetic counselling which meets the criteria presented in pp. 5.1.1.–5.1.4. should be organized, supervised, and certified by the Polish Society of Human Genetics.

5.3.4. Samples for the genetic test should be sent to the diagnostic unit together with necessary medical records. The sending unit should gather information from the diagnostic unit on what data is needed. A copy of the consent for genetic testing should be sent to the diagnostic unit (p. 5.1.3.).

5.3.5. The unit performing the genetic test should provide a referral form. The form should contain the data of the sending doctor, pregnant woman, ordered test, and any other crucial data. It should also carry the information on how to return the result.

5.4. Biological samples for the prenatal genetic test can be obtained by chorionic villi sampling (p. 5.7.1), amniocentesis (p. 5.7.2.), or cordocentesis (p. 5.7.3).

5.5. Before collecting the biological samples, the pregnant woman should give written consent to the invasive procedure as presented in paragraph 5.1.2.

5.6. The risk of invasive procedure complications is currently lower than reported in previous years. The risk is even lower than 1% in units with experience in invasive procedures.

5.7. The diagnostic laboratory records the macroscopic and microscopic features of the biological samples sent for the genetic test. This information may be crucial for evaluating the results of the genetic test. Any comments regarding the received samples should be reported to the doctor who ordered the genetic test.

5.8. Invasive procedures.

5.8.1. Chorionic villus sampling

Chorionic villus sampling allows the collection of material between 11 + 0 to 14/15 weeks of pregnancy. After 15 + 0 weeks of pregnancy, amniocentesis is the preferred method. Because of the possibility of mosaicism which may be present only in the placenta, the genetic test results should be evaluated with ultrasound examination and family history. Chorionic villus sampling is recommended in cases with foetal malformations and in cases with a high risk of lethal monogenic disease.

To account for the risk of mosaicism present only in the placenta, chorionic villus sampling should not be proposed in cases with a high risk of foetal aneuploidy associated with maternal age, in cases found to be high risk based on biochemical results (double test) or cffDNA test. In such situations, it is recommended to perform amniocentesis after 15 + 0 weeks of pregnancy (see 5.7.2.).

Chorionic villus sampling can be used for the cytogenetic test (evaluation of the foetal karyotype) after short incubation or culture of the cells. DNA can be isolated from trophoblast villi for molecular tests.

5.8.2. Amniocentesis.

It is recommended to perform amniocentesis for genetic testing after 15 + 0 weeks of pregnancy. The procedure involves the sampling of amniotic fluid using a needle inserted into the uterus.

Comment:

In samples contaminated by blood, i.e., an admixture of blood or bloody amniotic fluid, it can be difficult to perform the genetic test. It is also difficult to perform the genetic test from the amniotic fluid obtained by amniocentesis before 15 weeks of pregnancy because of the low cell number.

5.8.3. Cordocentesis

Cordocentesis is a collection of foetal blood from the vessels of the umbilical cord. This can be performed after the 18th week of pregnancy. It is especially useful in cases of oligohydramnios, after 22 weeks of pregnancy or to verify mosaicism in the previous test where the samples were obtained by amniocentesis or chorionic villus sampling.

Cordocentesis can be used for genetic testing if the test was not previously successful in the material obtained by amniocentesis.

Remark:

5.8.3.1. In cases of cordocentesis for the cytogenetic test, heparin should be used to prevent coagulation of blood samples.

5.8.3.2. In cases of cordocentesis for the molecular test, EDTA should be used to prevent coagulation of blood samples.

5.8.4. Other possibilities of obtaining biological samples for genetic tests. In unique cases, cytogenetic and molecular tests may be performed using cells isolated from the urine of the foetus, when bladder puncture has been performed for other reasons. The tests can also be performed in fluid obtained after amnioinfusion. In such cases, the test may not be successful and this information should be provided to the pregnant woman.

5.9. After invasive diagnosis in RhD-negative pregnant women, efforts should be made to prevent RhD immunization.

6. TYPES OF DIAGNOSTIC GENETIC TESTING

The pregnant woman should be informed about the goals and limitations of a genetic test before collecting the samples. The pregnant woman should be informed that it may be necessary to do the genetic test also in both her and the biological father of the foetus to evaluate the results in the foetus. Before the test, the pregnant woman should consent to the genetic test in writing (App. 3).

6.1. Classical and molecular cytogenetics methods

6.1.1. Classical cytogenetics methods are used to detect numerical and structural chromosomal aberrations.

The most frequent genetic abnormalities found in prenatal testing (over 70%) are trisomy, monosomy and polyploidy. Structural chromosomal aberrations are less common, but are frequently observed in genetic syndromes with phenotypic features caused by microdeletions (less frequently, microduplications) of different chromosomes.

It is especially important to diagnose unbalanced translocation in the foetus, where one of the parents may be a carrier of a balanced translocation; in such cases, there is a high risk of foetal abnormality in each subsequent pregnancy. The presence of balanced translocation in one parent is a typical indication for prenatal testing. Such cases require special attention during genetic counselling.

6.1.2. Fast molecular testing (qPCR, FISH, MLPA, BoBs, dPCR) can obtain a result within 48–72 hours. The diagnosis obtained from the fast molecular test should be confirmed by karyotype from the cell culture. In some cases, the karyotype allows the risk of chromosomal aberrations in the next pregnancy to be calculated; the procedure applies to carriers of balanced translocation, including the fusions of acrocentric chromosomes (13-15 and 21-22).

Comment:

Aneuploidy can be accurately diagnosed using fast molecular testing if ultrasound markers of chromosomal aberration are present or a high risk of chromosomal aberration is observed in the NIPT test.

6.1.3. Higher sensitivity and specificity than classical cytogenetic techniques can be obtained by array-based comparative genomic hybridization (aCGH). aCGH allows the detection of not only aneuploidy but also the microdeletions and microduplications causing typical genetic syndromes. By analyzing copy number variations (CNV), aCGH is able to detect many structural micro rearrangements causing loss or excess genome fragments.

By comparing the aCGH results with available databases it is possible to evaluate whether the observed CNV is responsible for the abnormal phenotype. Some aCGH results require verification by using classical cytogenetic methods or FISH (fluorescence in situ hybridization). It is also recommended, in selected cases, to perform cell culture with classical cytogenetic method regardless of the aCGH results.

6.1.3.1. In addition to aCGH, another CMA (chromosomal microarray analysis) method is SOMA (SNP Oligonucleotide Microarray Analysis). However, while aCGH is recommended for use in prenatal testing in many guidelines, SOMA is only used by some centres due to the difficulty in interpreting the results.

6.1.3.2. aCGH is a quick method with a wide diagnostic range and therefore it is recommended as a first-line prenatal test especially in cases with foetal malformations and other developmental abnormalities without clear etiopathogenesis. aCGH can be additionally performed in the case of birth defects and normal foetus karyotype.

6.1.3.3. In some cases, it is difficult to evaluate the results of aCGH in the foetus. Many CNVs, indicating microduplications or microdeletions, have been observed also in healthy subjects. In some cases, it might be necessary to perform aCGH also in parents to compare their results with those of the foetus.

6.1.4. Normal results of classical and molecular cytogenetics should be provided to the pregnant woman by a specialist in obstetrics and gynaecology, a feto-maternal specialist, or a specialist in clinical genetics. They should discuss them with pregnant women. Abnormal results should be provided by a specialist in clinical genetics together with genetic counselling.

6.2. Molecular testing of monogenic diseases:

6.2.1. Genetic tests for monogenic diseases should be ordered by the specialist in clinical genetics. Family history and results of ultrasound examinations should be taken into account.

6.2.2. In some cases, a genetic test should first be performed on a family member affected by the genetic disease. The results can then be used to decide on the prenatal test for the foetus. This strategy is usually faster and cheaper.

6.2.3. It might be necessary to perform NGS (next-generation sequencing) in a foetus with abnormalities of unknown etiopathogenesis. NGS should be ordered by the specialist in clinical genetics after consultation with the specialist in laboratory medical genetics or with experienced molecular biologists.

6.2.4. Biochemical, enzymatic and immunocytochemistry methods, as well as others, can be used to diagnose monogenic diseases in foetus. The analysis can be performed in samples of amniotic fluid, amniocytes, and cells from amniocyte culture. If the disease causing the mutation is already known in the family, chorionic villi sampling should be the preferred method to obtain biological samples. The specialist in clinical genetics should order the test and choose the laboratory unit.

6.3. Evaluation of the results of genetic tests:

The results of the genetic tests should be discussed with the pregnant woman or with both parents. The impact of genetic abnormalities on the foetus should be explained. The perspectives of medical treatment should be presented. Genetic counselling regarding the consequence for other family members should also be provided. All information must also be provided in writing, and this should be noted in the medical records. The pregnant woman should be informed about the limitation of the genetic test when its results are normal.

7. PROCEDURE IN CASE OF SEVERE DEVELOPMENTAL DEFECT IN THE FOETUS

The pregnant woman or both parents should be informed about specialist care and perinatal palliative care in case of a severe developmental defect or incurable disease in the foetus.

8. SPECIFIC CASES OF PRENATAL TESTING

8.1. First prenatal testing in a foetus with CRL > 84 mm (foetal crown-rump length).

In the case of a foetus with CRL > 84 mm, it is recommended to perform the full ultrasound examination. In addition, NIPT (non-invasive prenatal testing) should be ordered and the mother should be informed about the possibility of invasive genetic testing.

8.2. Prenatal testing in multiple pregnancy:

In the case of multiple pregnancy, ultrasound examination should be performed according to the guidelines of the Polish Society of Gynaecologists and Obstetricians.

A screening test (combined test/NIPT) can be performed in twin pregnancy. The pregnant woman should be informed that the screening test has lower sensitivity in a twin pregnancy than in a single pregnancy. In the case of pregnancies with three or more foetuses, screening tests should not be performed. Invasive genetic testing can be used for all multiple pregnancies. The pregnant woman should be informed that the risk of the invasive procedure is higher in multiple pregnancy than in a single pregnancy. Invasive procedures should be performed for each foetus separately, even in the case of monochorionic pregnancy. In exceptional cases, the amniotic fluid can be taken only from one foetus.

8.3. Prenatal testing after preimplantation genetic testing

As the combined test has a lower sensitivity than the preimplantation test, the combined test should not be ordered if the preimplantation test for aneuploidy has been performed; in such cases, NIPT should be considered. Full ultrasound examination should be performed in the first trimester of pregnancy, according to the guidelines of the Polish Society of Gynaecologists and Obstetricians. Invasive genetic testing should be performed in cases with abnormal foetal development. The invasive testing should be ordered by a feto-maternal specialist or a specialist in clinical genetics. Further procedures should be the same as presented above in the guidelines. The double (biochemical) test should be ordered to screen for pre-eclampsia and foetal growth restriction.

Conflict of interest

All authors declare no conflict of interest.

APPENDIX NO. 1.
Questionnaire of the prenatal medical history

Patient name .....

PESEL (Polish national identification number) .....

Age over 35	Yes	No
Which pregnancy is it?		
Have you experienced two or more miscarriages?	Yes	No
Was fertilization obtained as a result of infertility treatment (‚in vitro')	Yes	No
Are your children healthy and developing properly?	Yes	No
Were any genetic diseases found in the foetus/child in the previous pregnancy?	Yes	No
Have there been any genetic abnormalities in your immediate family?	Yes	No
If so, which ones?		
Have there been any defects or other abnormalities in your immediate family?	Yes	No
If so, which ones?		
Has anyone in your family demonstrated intellectual disabilities?	Yes	No
If so, which ones?		
Have you been exposed to harmful factors, drugs harmful to the foetus, stimulants, radiation?	Yes	No
If so, on what?		

....

Date Doctor's signature Signature of the patient or authorized guardian

APPENDIX NO. 2.
Informed consent form for intrauterine procedure

Patient name .....

PESEL (Polish national identification number) .....

1. INDICATIONS FOR INTRAUTERINE PROCEDURE

.....

2. METHODS OF INTRAUTERINE PROCEDURE

After a detailed analysis of the case, we propose to carry out the following procedure: a needle will be inserted through the abdominal wall into the uterine cavity, followed by:

— amniocentesis (amniotic fluid intake)
— chorionic villus sampling
— cordocentesis (taking blood from the vessels of the umbilical cord)

The aim of the proposed treatment is to obtain material for genetic and/or biochemical research.

3. POSSIBILITY OF COMPLICATIONS

As a result of taking material for testing, the following complications may occur:

— triggering excessive contractile activity of the uterus
— premature rupture of foetal membranes, with an outflow of amniotic fluid
— premature separation of the placenta/chorion
— intrauterine infection
— damage to the foetus
— umbilical cord tamponade in case of cordocentesis
— periodic tachycardia or foetal bradycardia
— miscarriages
— premature birth

4. TALKING TO YOUR DOCTOR

Please ask us about anything you would like to know in connection with the planned procedure. We will be happy to answer all your questions.

5. PATIENT STATEMENT

I fully understood the information contained in this form and the information provided to me during the conversation with the doctor. I was given unlimited opportunities to ask questions, and all of them were answered and explained satisfactorily.

After reading the content of this form and talking to the doctor, all my requirements have been met for:

— diagnosis
— proposed and alternative diagnostic tests

I am aware of the possible complications associated with the intrauterine procedure.

I agree to have the diagnostic test performed on me (this should be emphasized):

- amniocentesis
- chorionic villi sampling
- cordocentesis

.....	.....	.....
Date	Doctor's signature	Signature of the patient or authorized guardian

APPENDIX NO. 3.
Informed consent for genetic testing

Patient name .....

PESEL (Polish national identification number) .....

Indications for genetic testing: .....

I give my informed consent to the collection of biological material of the foetus and the performance of genetic tests related to the suspicion or clinical diagnosis of a genetically-determined disease.

I agree to have the following tests performed (appropriate to emphasize):

- cytogenetic test (assessment of the foetal karyotype)
- aCGH test
- molecular test

I declare that:

I was informed about the goal of the ordered genetic test, its sensitivity, the limitations of the method and its importance for further diagnostic and therapeutic procedures	Yes	No
I agree to store the genomic DNA sample after the diagnostic procedure has been completed	Yes	No
I agree that my sensitive data will be archived and processed by the performing unit in accordance with the Regulation of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)	Yes	No
I agree to perform the test in another unit/department	Yes	No
I have been informed to which laboratory the biological material will be sent *(applies to tests performed outside of Poland)*	Yes	No
I was informed about a possibility that the test will fail and the test may need to be repeated	Yes	No
I want to be informed about the result of the test	Yes	No

....

Date Doctor's signature Signature of the patient or authorized guardian