GENETIC COUNSELING CENTRE
PRENATAL SCREENING OF CHROMOSOMAL ABNORMALITIES
INVASIVE PRENATAL DIAGNOSTICS

PRENATAL DIAGNOSTICS

NON-INVASIVE CHROMOSOMAL ABERRATION DIAGNOSTICS
FROM MATERNAL BLOOD - MaterniT21™ PLUS
2D, 3D/4D ULTRASOUND

PREDIKO
Knowledge and Information for a feeling of certainty
Good knowledge is an important component of Prenatal Care. Our endeavours are to provide our expectant mothers with the best degree of information about modern diagnostic methods in pregnancy. Only a well-informed expectant mother can correctly decide and select the most appropriate prenatal diagnostics for herself.

What are Chromosomes?
The human body is made up of cells. Each cell contains the same genetic information. This information is stored in the cell cores in structures which are called chromosomes. Chromosomes are made up of double helixes of DNA (Deoxyribonucleic acid) fibres carrying the genetic information. Each human cell contains 46 chromosomes. Sex cells – eggs and sperm – contain half that number of chromosomes.

What does Chromosomal Aberration mean?
Sometimes, human cells may contain a different number of chromosomes, or they may have chromosomes with differing constructions. These aberrations occur in the course of impregnation – i.e. the fusion of the egg and sperm – and have a negative effect on the physical and mental development of the afflicted individual. In all, about one hundred such syndromes are known. One the most well-known and frequent of these is Down’s Syndrome.

What is Down's Syndrome?
Down’s Syndrome is a chromosomal aberration whereby the cells contain a redundant (extra) copy of the 21st chromosome. Therefore, the cells contain 47 chromosomes instead of 46. This disease cause grave damage of the intellect and is often associated with many fetal development aberrations.

When is the risk of the birth of a child with Down’s Syndrome increased?
Children with Down’s Syndrome can be born to any expectant mother. The risk grows with the increasing age of the expectant mother. At the age of 20, this risk is 1:1500; at 35, it grows to 1:360; and by 40, it is 1:100. The majority of these aberrations are not linked to family histories and occur completely at random – de novo.

What does the expression “Combined Test - Screening in the 1st Trimester mean”?
This is a test which combines screening of the expectant mother’s blood with the scanning of specific ultrasound details of the fetus (“NT” – Nuchal Translucency thickness, “NB” – the presence of nasal bones). The combination of these two methods enables the detection of more than 85% of fetuses with Down’s Syndrome. Traditional screening (2nd Trimester), carried out in the 16th week of pregnancy – the so-called Triple Test – manages to identify only 65 – 70 % of children suffering from this syndrome.
What are the advantages of Combined Screening?
It is currently the most effective system for identifying Down’s Syndrome within the framework of one trimester. The Integrated Test is absolutely the most advanced way of screening, whose integral components are the Combined Test and the Triple Test in the second trimester.
- High sensitivity to the discovery of greater malformations of the fetus and many other genetic syndromes
- Minimal risk
- Precise determination of the duration of the pregnancy
- Diagnosis of multiple pregnancies

Just what do the blood tests involve?
In the 10th–13th (ideally, 10+0 to 11+3) weeks of pregnancy, we check the maternal blood for substances which are called PAPP-A, and free-beta hCG. These are formed in the placenta and enter the mother’s blood. In pregnancies carrying Down’s Syndrome, the levels of these materials are abnormal.

What does the Combined Test –1st Trimester involve?
The Combined Test is done in the 11th – 14th weeks of pregnancy. With the aid of ultrasound, the accumulation of sub-dermal fluids in the nape of the neck is checked. This layer of fluids shows up as brightness under ultrasound imaging. The presence of a greater quantity of fluid in this area is often associated with chromosomal aberration of the fetus – e.g. with Down’s Syndrome.

What does the Nuchal Translucency – NT Test involve?
The Nuchal Translucency Test is done in the 11th – 14th weeks of pregnancy. With the aid of ultrasound, the accumulation of sub-dermal fluids in the nape of the neck is checked. This layer of fluids shows up as brightness under ultrasound imaging. The presence of a greater quantity of fluid in this area is often associated with chromosomal aberration of the fetus – e.g. with Down’s Syndrome.

What does the Nasal Bone - NB Test involve?
The Nasal Bone measurement is also performed between the 11th – 14th weeks of pregnancy. The nasal bone can be depicted under higher magnifications of the fetal profile. The absence of nasal bone in this period can signal affliction with Down’s Syndrome.

What does measurement of the so-called FMF angle mean?
Here, it means the measuring of the angle of the line formed by the upper jaw of the fetus to the tangent of the edge of the frontal bone. For fetuses with Down’s Syndrome, this angle is greater than under normal physiological conditions.

What does the Ultrasound DopplerScan of the so-called Tricuspid Regurgitation – TR involve?
This involves the evaluation of blood flow across the tricuspid heart valve. For a fetus with Down’s Syndrome, or in the case of certain other cardiac anomalies, a backward return pulse wave is apparent.

What does the Ultrasound DopplerScan of the so-called Ductus venosus – DV involve?
This involves the evaluation of the pulse curves in the minor capillaries. In fetuses with Down’s Syndrome, this curve is also abnormal.

Calculation of the risks of chromosomal aberration
In this calculation, we combine the known risk given by the age of the expectant mother, the thickness of the Nuchal Translucency (NT), the presence or absence of the Nasal Bone (NB) and the level of biochemical markers in the maternal blood. The result is a number, which evaluates the risk-factor of the birth of a child with Down’s Syndrome.

If the test results are negative ...
If the calculated risk factor is less than 1:100, then the risk of the birth of a child With Down’s Syndrome is low. It is important to be aware that; low risk is not equivalent to the expression, no risk. Even after a negative result, it would be appropriate to also undergo the so-called Triple test and Ultrasound Screening between the 18th – 22nd weeks of pregnancy oriented on the eventual determination of the presence/absence of fetal development aberrations.

If the test results are positive ...
If the subsequent results of the tests are greater than 1:100, this means the higher probability of the birth of a child with Down’s Syndrome. This of course does not mean the child has Down’s Syndrome. Should the expectant mother wish to eliminate the 100% risk of this syndrome; it is possible to perform genetic testing of the cells in the amniotic fluid, or Chorionic Villus Sampling (CVS) or a non-invasive test.

Is the Combined Test in the first trimester covered by Health Insurance?
This treatment is considered to be “above-standard”, and is not covered by Health Insurance. They do cover treatment performed in the second trimester of pregnancy – the Triple Test and Ultrasound Scan performed between the 18th and 22nd weeks of gravidity. The price of the Combined Test is 1,400,- CZK.

Ultrasound and Biochemical Treatment Quality in the Prenatal Diagnostics Centre
The Ultrasound marker screening (NT, NB, FMF, TR, DV) is performed in the Centre, is based on King’s College Hospital, London (Fetal Medicine Foundation) methodology. The precision of our measurements are regularly verified by an audit of our results. The quality of the biochemical assessments is continuously verified by the UKNEQAS (Great Britain) external quality control system.

Is it essential after undergoing the Combined Test with a negative outcome, to also undergo the so-called Triple Test blood tests in the second trimester?
It would be appropriate to complement the investigative treatment of the 1st trimester by the so-called Triple Test in the 2nd trimester. This is the essence of the so-called Integrated Test, which has the highest percentage of detecting Down’s Syndrome with the lowest percentage of so-called “False Positivity” - 94 %. Abnormal levels, discovered in the blood serum of the pregnant person in the form of the Triple Test may signalise the presence of other pathological states (e.g. neural tube defects).
**Basic Information:**

The Integrated Test establishes the individual’s risk of Down’s Syndrome and other serious fetal aberrations from the results of the Combined Test and Triple Test. This is the most sensitive—-with the highest possible probability of enabling the diagnosis of fetal aberration. On the other hand, the test has the lowest known “False Positivity”.

This means that the percentage of expectant mothers, who are unnecessarily stressed, is very low. An important aspect of the low percentage of “False Positivity” is the fact that a very low percentage of these women must undergo invasive diagnostic procedures (i.e. CVS, Amniocentesis).

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**Practical Approach to Undergoing the Test**

- **Determination of the results of the Combined Test.** If negative, then the pregnancy continues into the 2nd trimester, when we recommend undergoing the Triple Test. The point being to ensure the greatest possible sensitivity and the lowest possible false positives.
- **In the case of a Positive result of the Combined Test,** further potential diagnostic approaches will be explained by the attendant doctor—in most cases, CVS or amniocentesis (fetal Karyotyping).
- **In the second trimester, ideally between the 15th – 17th weeks,** the attending gynaecologist will perform the blood sampling for the so-called Triple Test. This can be done in the patient’s own gynaecologist’s or G.P.’s surgery. During the 2nd trimester, further biochemical markers including AFP, which is the unique biochemical marker for NTD (Neural Tube Defects) will be tested for. It is not possible to biochemically test for Neural Tube Defects in the 1st trimester.
- **Explanation and hand-over of the Integrated Test results.** (evaluation is provided by the ALPHA system). Provided that the results are negative, then the expectant mother has undergone the most sensitive test from the point-of-view of the prediction of fetal aberrations. In the case of a positive result, consultations upon further approaches are once again made with the gynaecologist concerned—or even with the doctor from the Prenatal Diagnostics Centre.
- **The Ultrasound Scan Check-up is performed,** approximately, in the 20th week of gravidity. This check-up is performed on the basis of indications by the attendant gynaecologist. Check-ups can be ordered over the telephone, on the same numbers as for the Combined Test: (+420 606 780 317, +420 577 645 172) and once again, these are performed in the Prenatal Diagnostics Centre.

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**Evaluation of the Integrated Test, just like the Ultrasound Scan in the 20th week, is covered by Health Insurance.**

**Screening Protocols**

Our screening protocols are based upon the experience of one of the most renowned workplaces of this type in Great Britain, (The Wolfson Institute Of Preventive Medicine, London, Prof. Sir Nicholas Wald), USA (Brown University, Providence, Prof. Jacob Canick) as well as the experience of our Prague-based colleagues in GENNET s.r.o., which is the largest screening centre in the Czech Republic. All of our staff have undergone specialist work placements at these institutions.

**Screening Organisation**

The actual organisation of the screening is based upon cooperation between The PREDIKO Centre and the laboratories of IMALAB (www.imalab.cz). In the Prenatal Diagnostics and Genetics, we perform Ultrasound Scanning and genetic consultations. The Centre is audited for measuring the US marker in the 1stTrimester by the Fetal Medicine Foundation London (Prof. Kypros Nicolaides). Biochemical screening is performed by IMALAB laboratories, which are registered in the Register of Laboratories Performing Screening, are submitted to external quality controls in the Czech Republic as well as in Great Britain.
Amniocentesis–Establishing the Karyotype from the Amniotic Fluid

Amniocentesis is a procedure which involves the introduction of thin needles through the abdominal wall and into the amniotic sac. Thereby, we acquire a small amount of amniotic fluid, which is very quickly replaced. Fetal cells are to be found in this amniotic fluid, which are then possible to cultivate in a special medium. In each of these cells, the fetal genetic information is stored in special structures, called chromosomes. A healthy individual or fetus has 46 chromosomes. After special coloring we are able to track their number and structure whether the genetic information of the fetus (its karyotype) is normal. Among the most common genetic abnormalities that can be found in the fetal karyotype is the trisomy of the 21st chromosome—so-called Down’s Syndrome. Sampling of the amniotic fluid is performed between the 16th and 20th weeks of pregnancy and the results are available within 3 weeks.

CVS –Establishing Karyotype from Chorionic Villus Sampling

CVS is a procedure which involves the introduction of very thin needles into the so-called Chorionic Villus, which is flesh that serves as the basis for the future placenta. Sampling of the Chorionic Villus and the cultivation of cells for the establishment of karyotype is usually performed between the 12th and 14th weeks of pregnancy. In this way, it is possible to confirm or refute the doctor’s suspicions in the case of a positive Combined Test—and frequently serves to eliminate suspicion of Down’s Syndrome. Results are available within 2 weeks.

FISH Diagnostics (Fluorescence In Situ Hybridisation)

Apart from the above-mentioned “normal” procedures, our Centre, in conjunction with the Imalab laboratories, also perform so-called FISH diagnostics, which stands out for the rapidity with which it reveals eventual fetal developmental aberrations in the prenatal phase. This method enables one to know the results of screening for the presence of certain aberrations within 48 hours of sampling of the amniotic fluid or biopsy of the Chorionic Villus. Thereby, to the maximum possible extent, it eliminates the stress factor when waiting for the results of the screening performed. Fluorescence In Situ Hybridisation (FISH) is a suitable method for rapid diagnosis of the most frequently occurring aneuploidy and enables immediate management of an affected pregnancy.

Basic Overview of Quick Diagnostic Tests in collaboration with IMALAB, Ltd:

• Rapid screening test for the most frequent chromosomal aberrations - Exclusion of Down’s, Patau and Edwards Syndromes - The reliable FISH Method.

Results are known within 2 days of amniotic fluid sampling or Chorionic Villus biopsy.

• Establishment of the gender of the fetus from the amniotic fluid.
• Establishment of gonosomal aberrations (Turner’s Syndrome, Klinefelter’s Syndrome, Gonosomal Mosaics)

In emergencies and in case of recommendation by a doctor, the FISH test is covered by insurance companies. Otherwise, patients have to cover these costs themselves.
Ultrasound in the 1st trimester of pregnancy
- Ideal time is between 11th - 14th weeks of pregnancy
- Fetal Biometry is measured - mainly CRL: the Crown-Rump Distance
- Specific ultrasound markers for detection of genetic syndromes are:
  - NT - height of Nuchal Translucency
  - NB - presence and length of a Nasal Bone
  - TR - Tricuspid Regurgitation (detection of reverse blood flow across the tricuspid heart valve)
  - FMF (Frontomaxillary Facial Angle) - the angle of the line formed by the upper jaw of the foetus to the tangent of the edge of the frontal bone
  - DV - Doppler examination of the Venous Duct
- Other anatomical signs, basic cardiac morphology, heart rate, movement of the fetus, fetal membranes, etc. are monitored
- In the case of multiple pregnancy it is possible to determine whether foetuses have a joint or separate placenta

Ultrasound in the 2nd trimester of pregnancy
- Ideal time is between 18th - 22th weeks of pregnancy
- Fetal Biometry is carried out. Basic dimensions for determination of gestational age of the fetus are: BPD, HC, AC, FL
- Certain organs are measured in order to determine the risk of some developmental defects (eg. Nuchal Fold, Cerebellum Width, length of a Nasal Bone, Renal Pelvic Width, etc.)
- Basic anatomy of fetal organs is evaluated
- Basic anatomy of the heart is evaluated - the so-called fetal echo-cardiography
- Indirect signs of foetus are monitored: the nature of the placenta, position of the fetus, the amount of amniotic fluid, fetal mobility, etc.

3D/4D ultrasound
Due to the three-dimensional ultrasound the doctors have the opportunity to get a very detailed and virtual image of fetal organs at all stages of pregnancy.
The 3D ultrasound image can be simply described as an image given by a very accurate and rapid processing of data from the three examined levels. Four-dimensional ultrasound (4D) is three-dimensional display in real time. This achieves high resolution of the resulting shots.

Spatial perception, the choice of a certain display level and high-magnification ability enable more targeted diagnosis of certain developmental defects or anomalies. On the other hand, there is a real chance to quickly verify and often exclude so-called „suspicious” findings. These findings are particularly cleft defects which can be easily confirmed and more accurate diagnosis can be accomplished. These cleft defects can occur not only in the face, but also in the abdominal wall and mainly in the spinal area. For an expectant mother a three-dimensional image of the foetus, is an incomparably greater visual experience than the conventional ultrasound image which works on the basis of the „tiered gray“ principle, and is often difficult to understand for parents.

Under ideal conditions a pregnant woman can watch movements of the foetus, its facial expressions, gestures, yawning and even laughter. 3D images can be recorded on DVD discs and photographs can be taken if desired.

**Ideal time for 3D ultrasound is between 20th – 30th weeks of pregnancy.** The examination takes about 10 minutes. The display is dependent on the position of the foetus.

**Prenatal cardiology**

The fetal echocardiography, carried out by ultrasound specialist at 20 weeks of pregnancy, is a part of the screening for congenital defects, suspected congenital defects or heart rhythm disorders are subsequently examined by pediatric cardiologist in a specialized centre who is experienced in screening of congenital heart defects at birth, and knows well the anatomy of both a healthy and diseased heart. They also know the treatment options and do further observations of the patients.

The examination is carried out on pregnant women without prior preparation, between 18 to 22 weeks of pregnancy. The examination is noninvasive, the transabdominal approach is used (through the abdomen of pregnant women) - this is actually a 3D/4D ultrasound device.

**Our center provides genetic consultations in the following areas:**

- Genetic consultations for married couples with a high risk of congenital developmental defects.
- Genetic consultations for dysfertile couples
- Consultations for women with proven risk factors in the periconceptional or prenatal period

A specific feature of a genetic disease is the tendency to occur in the family repeatedly. An important component of genetic consultations is not only the original patient, but also their present and future family members.

This prevention precedes manifestation of diseases and disorders with a hereditary component. It is often of crucial importance when dealing with various disorders of fertility and reproduction. These risks can be reduced significantly.

Not only detailed health status examinations of patients (personal history) but also genealogical studies and possible genetic risks are parts of the genetic consultations, and then suitable health care services are provided.
• Screening in the 1st and 2nd trimester of pregnancy (combined and integrated test)
• Consultative ultrasound for suspected congenital defects or in case of high risk for severe fetal genetic disease
• Genetic consultations in case of a biochemical screening in the first or second trimester of pregnancy with a suggestion for further approaches
• Invasive prenatal diagnostic procedures: Amniotic Fluid Sampling (AMC), Chorionic Biopsy (CVS), Fetal blood sampling (KC)
• Non-invasive prenatal diagnosis of chromosomal aberrations - MaterniT21PLUS
• Genetic consultations in cases of infertility
• Genetic consultations for women with proven risk factors in the periconceptional or prenatal period
• 3D/4D ultrasound of the foetus
• Prenatal cardiology - specialized examinations performed by child’s cardiologist
• Performance Fetal Medicine: amnio drainage, amnioinfusion, Percutaneous procedures for obstruction of hollow systems, etc.

It is required to make an appointment in advance before being examined at the Prediko Centre