

# PRENATAL DIAGNOSIS: A SOCIAL PROBLEM

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Pregnancy is a happy moment in a woman's life. However, various maternal and/or fetal factors may put the future mother in a stressful, worrying situation.

Statistical data indicate that 10.7 million children aged below 5 die every year in the world. Statistics also reveal that out of all deaths registered in this population category, 4 million children, i.e. almost half of all recorded deaths, die in the first month of life. There are also 3.3 million stillbirths (intrauterine fetal death). Romania is no exception. With 23 deaths in 1000 live births, our country is ranked third in Europe. Over 30% of these events are caused by embryo-fetal diseases that could have been detected and treated prenatally.

The current situation proves that the creation and development of maternal-fetal medicine as a new clinical subspecialty focusing on mother and fetus in the perinatal period is an absolute must.

Specialists in maternal-fetal medicine require training and experience in order to be able to make an early and complete diagnosis and to find the most appropriate therapeutic procedures for mother, fetus and newborn during pregnancy or immediately after birth.

Specialists in maternal-fetal medicine have advanced knowledge of the obstetrical, medical, genetic and surgical complications associated with pregnancy and of the effects that these might have on both mother and fetus. Such specialists may use various investigation methods and/or the expertise of specialists in neonatology, genetics, biology, pediatric

surgery, cardiology, pediatrics, psychology, who are all part of the team required in such a vast medical field.

Obstetrics might be the only area in which ultrasound offers such enormous satisfactions. Here, the joy of discovering a new world, which is neither Christopher Columbus's "New World", nor a new planet, is incomparable. This discovery is related to the beginnings of life. Currently available investigation methods such as abdominal ultrasound, transvaginal ultrasound, 2D, 3D or 4D investigations, pulse Doppler, color Doppler, Power Doppler or M module enabled the study of various aspects of fetal physiology and physiopathology. Thus, the concept of fetal health became palpable reality and opened the path to invasive investigations involving medical genetics.

The value and safety of using the ultrasound technique generated a long list of indications in pregnant patients.

**Table 1.**

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Estimation of gestational age
Evaluation of fetal growth
Vaginal bleeding of unknown cause in pregnancy
Determination of fetal presentation
Suspected multiple pregnancy
Associated with amniocentesis or Chorionic villus sampling
Discrepancy between uterus size and amenorrhoea
Clinical detection of pelvic masses
Suspected hydatidiform mole
Associated with cerclage
Suspected ectopic pregnancy
Associated with special procedures
Suspected pregnancy loss
Suspected uterine anomaly
Fetal biophysical profile (after the 28 <sup>th</sup> week)
Monitoring intrapartum events (e.g. version / removal of second fetus, manual removal of placenta)
Suspected hydramnios or oligohydramnios
Suspected premature detachment of a normally situated placenta
Abnormal alpha-fetoprotein values for gestational age
Follow-up or detection of fetal anomalies
History of congenital anomalies
Serial evaluations of fetal growth in multiple pregnancies
Estimation of gestational age on first appointment

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The list in Table 1 clearly shows which pregnant patients are not eligible for ultrasound screening. A young (but not very young) and healthy patient who is able to provide exact anamnestic data regarding the last menstruation, schedules for antenatal visits, shows no pathological changes on objective examination, has no history of hereditary or collateral obstetrical events and no pathological laboratory values is not a candidate for ultrasound screening. Focus should be placed on the patient's need of professional healthcare for a successful pregnancy and not on finding arguments in favor of using routine ultrasound in all patients. Routine obstetric ultrasounds have become a social experience and expectation in today's society and are atypically attractive for a medical procedure. Indeed, the first trimester of pregnancy is characterized by a dynamic, rapid evolution of the embryo, which is crucial in the development of the pregnancy. The rapid development of the embryo causes ultrasound images to constantly change. Therefore, only periodic and frequent examinations provide early and exact monitoring. Besides highly efficient ultrasound examinations, which are now able to detect fetal or embryonic disorders as accurately as the direct examination of the newborn, medical genetics is also a vital tool since it allows disorders with major consequences on the newborn's quality of life to be tested and diagnosed. Currently there are exact indications for the use of invasive procedures in prenatal diagnosis (see Table 2).

**Table 2.**

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Advanced maternal age
Fetal pathological findings on ultrasound
Increased nuchal translucency
cystic hygroma
fetal heart abnormalities
Positive maternal serologic screening
History of fetuses with congenital anomalies
Chromosomal rearrangements in one of the parents
Increased risk of monogenic disease or X-linked transmission
Administration of teratogenic drugs (valproic acid, carbamazepine, gestational or insulin dependent diabetes).

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An invasive diagnosis is based on obtaining sample tissue or cells from the placenta, fetus or amniotic fluid by puncturing the pregnant uterus under ultrasound guidance. Fetal material may be obtained using the following invasive methods:

1. **Amniocentesis**, introduced in medical practice in 1960, may be used in fetuses of 15-24 gestational weeks. This period is suitable for carrying out the procedure and growing fetal cells in culture as there is a low percentage of cell culture failure. Early

amniocentesis performed between 12 -14 gestational weeks has also been described although the extraction of amniotic fluid may be problematic.

2. **Chorionic villus sampling** may be carried out between 10 - 14 gestational weeks. A transabdominal or transcervical approach is used to obtain chorionic villus from the placenta. Since this procedure can be done sooner than amniocentesis, it allows the early detection of chromosomal anomalies. The risk of contamination with maternal cells is of 1-2% as compared with 0.37% in amniocentesis while false positive results occur in 0.8-2% of confined placenta mosaic cases.

Prenatal invasive diagnostic methods are accompanied by a high rate of miscarriages. In addition, chorionic villus sampling carries an increased risk of limb reduction defects. Therefore, the benefit/risk ratio must be considered in such cases. It must not be forgotten that an abnormal karyotype is present in 60% of miscarriages happening before the 8<sup>th</sup> week and in 25% of miscarriages between the 8<sup>th</sup> and 12<sup>th</sup> week. Almost all anomalies are associated with a high risk of miscarriage with incidences depending on the type of chromosomal aberration and chromosome pair involved. Recent studies established that the risk of chromosomal anomalies is higher after the threshold age of 37. Developments in ultrasound contributed to defining and selecting pregnancies at high risk of developing chromosomal anomalies. Furthermore, the association of several screening methods increases the diagnosis rate of fetal anomalies. Studies published by Nicolaides revealed that measurements of nuchal translucency, PAPP-A and beta hCG in the first trimester of pregnancy were associated with a 90% rate of trisomy 21 detection, at a 5% rate of false positive results. The same screening test was associated with a 90% rate of trisomy 18 and 13 detection at a 1% rate of false positive results. The measurement of alpha-fetoprotein, estriol and beta hCG in the second trimester of pregnancy represents another screening method. Maternal serology (triple test, double test) and ultrasound are worldwide methods of non-invasive prenatal diagnostic. Such tests only detect epiphenomena associated with chromosomal aneuploidy; they must be carried out within a limited time interval and have reduced sensibility and sensitivity. Therefore, two new strategies for the non-invasive detection of fetal anomalies were suggested: analysis of fetal cells and of free fetal DNA in maternal blood. Fetal cells were detected in the maternal body as early as 1983, when George Schmorl observed trophoblastic cells in the lungs of 17 women who had died from preeclampsia. Half a

century later, Kleinbauer et al showed the presence of fetal cells from the erythrocytic line in maternal blood. Current studies on fetal cells in maternal blood use fetal erythroblasts as the source of genetic material in prenatal diagnosis. The greatest disadvantage of this method is represented by the low number of fetal cells – one cell is found in 1 ml of maternal blood, therefore a million maternal cells must be analyzed in order to detect one fetal cell.

New developments in prenatal diagnosis opened in 1994 after the discovery of free fetal DNA by Lo et al, who demonstrated the presence of Y chromosome sequences in the circulation of pregnant women with male fetuses. Rh and sex determination are currently used in clinical practice.

All these investigations require huge intellectual and financial efforts. In order to understand the need for these efforts I am presenting a particular case which proves that one may face complex questions in life:

“Alexandra, 30 and George, 35 are a couple. They both have university degrees. They had a daughter who died at the age of 13 from cystic fibrosis (genetic disease characterized by lack of lung development and digestion problems). They have always wanted to have a child, so they decided to try again. Alexandra got pregnant, but they both knew that they had a one in four risk of having another child with cystic fibrosis. They went to a perinatal medicine unit for ultrasounds, amniocentesis and genetic diagnosis.

The results showed that the fetus did not have cystic fibrosis, instead it had Down syndrome, another serious disorder (characterized by mental retardation) and heart problems. The couple decided to terminate the pregnancy. Six months later, the couple found that they could use in vitro fertilization. This time, preimplantation genetic diagnosis would be used”.

Preimplantation genetic diagnosis is a new concept in diagnosing hereditary genetic disorders that does not involve the therapeutic termination of the pregnancy. Coming back to our case, “major ethical problems were raised during the dialogue with our couple. They had to be informed before taking any therapeutic decision”. Providing information to patients should not be only an administrative procedure or a legal obligation for the physician. Patients must trust their physicians. Patients must be informed using language suitable to their level of understanding and by taking into account their idea of health or sickness. The information provided by the physician must be in accordance with the truth and adapted to each patient’s level of acceptance.

I strongly believe in and promote the role of the physician in pregnancy monitoring. Every intervention based on highly advanced technology must be performed sensibly and solely in cases that absolutely require it. The means offered by highly advanced technology must follow the identification of patient groups at risk, since most pregnant women can be monitored with non-invasive techniques.