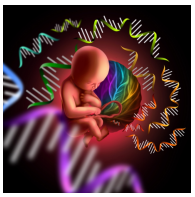
CLARA ANGELA FOUNDATION

Early invasive and non-invasive diagnostics to exclude chromosomal or genetic malformations in multiples



Dear mother-to-be,

Even in twin pregnancies, situations may arise in which genetic testing of the children during pregnancy seems useful.
At the beginning of the pregnancy, your gynecologist will consult with you to assess your personal risks and discuss the possibilities of genetic diagnostics and their consequences. Additional psychosocial and human genetic counseling may also be helpful.
The human genetic material, the genes, are distributed in the cell nucleus on a total of 46 chromosomes, 23 maternal and 23 paternal, two of which determine the sex of the child. During genetic examinations during pregnancy, initially only the number or larger microscopically visible structural defects of the chromosomes are recorded; this examination is called karyotyping. In addition, nowadays it is also possible to detect smaller structural defects of the chromosomes that cannot be seen with a microscope, up to single gene mutations of the DNA, by means of a microarray or by means of sequencing ("Next Generation Sequencing", NGS) as exome or even genome analysis. However, the latter methods are only reimbursed by health insurance companies in the case of special findings, such as evidence of developmental disorders or malformations, and should only be performed after a detailed genetic consultation. However, genetic disorders also leave sonographically conspicuous traces.

Invasive procedures
The performance of a genetic test requires that cells of the unborn child are available. These are present in the villi of the placenta, in the amniotic fluid or in the blood of the unborn child and must therefore be obtained by ultrasound-guided puncture of the placenta (chorionic villus sampling), the amniotic cavity (amniocentesis) or the umbilical cord vein (fetal blood collection), i.e. by an invasive procedure.

Non-invasive prenatal diagnostics in multiples
For several years, it has also been possible to test for trisomy 13, 18, and 21, maldistribution of sex chromosomes, and the child's blood group antigen in the freely circulating fetal DNA that passes from fetal placental villi into maternal blood in a maternal blood sample. This test is called NIPT (non-invasive prenatal testing) and gives good results in ruling out trisomy 21 and trisomy 18 in one or both children, even in twin pregnancies. NIPT is not currently recommended for higher-order multiple pregnancies.

Decision-making process in multiples
The most common reason to consider an invasive examination (right column image) is an ultrasound diagnosis of developmental abnormalities or malformations. In early pregnancy, this can also be a thickened nuchal translucency or, in twins, a severe size discrepancy. Targeted genetic testing may also be useful in cases of familial risk. Even if the risk of numerical malformations of chromosome 13 (Pateau),

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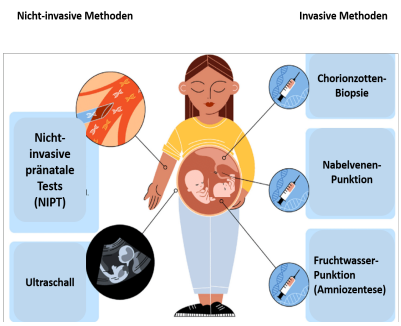

18 (Edwards) or 21 (Down syndrome) is increased with increasing maternal age compared to younger mothers, age alone is not a reason to immediately perform invasive diagnostics. There are now better criteria for determining the individual risk of fetal trisomies. These include the first trimester ultrasound examination with early exclusion of malformations and nuchal translucency measurement between 12+0 and 13+6 SSW, which - depending on the extent of the examination and the experience of the examiner - has very high detection rates. The result should be the basis of individual counseling on the pros and cons of invasive prenatal diagnostics; non-invasive prenatal testing (NIPT) can then also be used as an additive test (left column image).

The disadvantage of invasive prenatal diagnostics is the risk of miscarriage before viability; other complications are extremely rare. The procedure-related miscarriage risk of a chorionic villus sampling performed between 10+0 and 14+0 SSW and an amniocentesis performed at 14+0 SSW at the earliest are comparable and are reported to be 0.2% or 1: 500 in singletons, i.e., miscarriage can be expected in approximately 500 procedures. The experience and practice of the doctors performing the procedure is very important. Unfortunately, only a few specialists still have sufficient experience and puncture numbers to be able to guarantee this. In the case of multiples, the procedure-related risk of miscarriage in twins is reported to be between 1% and 3%. Therefore, it is even more important to first exhaust the possibilities of non-invasive diagnostics. Here, the chorionicity (see special information sheet), conspicuous findings in the children, location of placenta and the visibility conditions influence the decision as to which intervention is preferable for one or more children. These alternatives should be discussed with you in detail.

In your decision for or against invasive diagnostics, the resulting consequences for you are of utmost importance. In the event of severe disease in a multiple, abortion of the affected child may be performed. This is called selective fetocide. The associated risk of miscarriage increases significantly with gestational age; therefore, this procedure should be performed before 14 weeks of gestation, if possible, and chorionic villus sampling should be the method of first choice. Amniocentesis can be performed only after 14+0 weeks, and the availability of a reliable result can then take until the 17th week.

A detailed early ultrasound examination with documentation of the placental chorionicity and amnionicity as well as the position of the children and its placentas should always be performed beforehand and form the basis of the decision-making process. All this should be discussed with the specialists who will be responsible for you and perform the procedures.

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