Cytogenetic background of fetal minor and major ultrasound anomalies in pregnancy

Ph.D. Theses

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Budapest
2005
Introduction

The prenatal screening, diagnostics and possible decreasing of the incidence of the abnormalities is a very important part of the health service. A significant measure of the efficiency of the Hungarian prenatal care system and the genetic counseling is the fact that without counseling the rate of the anomalies at birth would be 2-3%, while this rate is only 0.4-0.6% as a result of the successful prenatal care.

The intrauterine screening and diagnostic methods, the ultrasound screening during the pregnancy, the cytogenetic and molecular genetic examinations in the genetic centers made the early, intrauterine diagnosis of the chromosomal abnormalities possible. In case of prenatally diagnosed severe abnormalities the pregnancy could be terminated at the parents’ request. By means of the early, intrauterine diagnosis of the curable or treatable abnormalities, their effect on the perinatal mortality and morbidity can be reduced. The genetic centers by their extensive and complex activities and their role in the prenatal diagnostics can significantly influence the perinatal outcome of the pregnancies.

The chromosomal abnormalities account for a considerable part of the anomalies of the intrauterine fetus. Chromosomal abnormalities are the numerical (aneuploidies) and structural anomalies, which can be demonstrated by special methods and microscopic examination. The numerical and structural anomalies can be duplications/trisomies, deletions/monosomies and other rearrangements on the chromosomes. The balanced chromosomal reorganizations will not cause anomalies, but in the offspring unbalanced rearrangements might occur.

The autosomal trisomies and unbalanced rearrangements might cause severe multiple malformation syndromes and mental retardation. The rate of the intrauterine deaths is high. They cause mainly severe diseases, in some cases they are associated with anomalies which are incompatible with the postnatal life. In cases of the numerical anomalies of the sex chromosomes (aneuploidy) the perinatal mortality is not increasing significantly, except monosomy X. The ratio of the chromosome abnormalities is 60% in cases of early miscarriages, 6% in cases of 16 to 20 weeks gestation abortions, and 4-5% in cases of stillbirths.
Currently, non-invasive intrauterine screening for chromosome abnormalities is not available, so ultrasound examinations play an important role during pregnancy, by drawing the attention to the suspect of a possible abnormality.

Besides the age of the father and/or the mother, a history of aneuploidy, and biochemical parameters, positive ultrasound findings - which could be major structural abnormalities, or minor ultrasound markers - can be an indicator for chromosome analysis.

In many cases of ultrasound findings the literature data is conflicting, very often there are inconsistent statements in the reports. The respective authors take different views about the various ultrasound findings.
Aims of the study

The Genetic Counseling at the I. Department of Obstetrics and Gynecology of the Semmelweis University works as a center. All the obstetrical institutes, departments and genetic counseling departments send pregnant women, patients to our center from all parts of the country, in order to have a medical consultation. Many patients arrive to our department within the scope of the progressive health care, but also many patients call on our genetic counseling on their own initiative. Currently we perform about 10 thousand of counseling yearly at our Department.

At the genetic counseling - in addition to other situations - we often meet positive ultrasound findings of the intrauterine fetus. These anomalies might be as follows:

- anomalies detected at another department by ultrasonography, and confirmed by the genetic ultrasound examination of our Genetic Center
- positive ultrasound findings in cases of pregnant women who were examined by the routine ultrasound screening of our Department
- anomalies detected by our ultrasound screening in cases of patients who were sent to our Genetic Center for various other reasons (e.g.: abnormal biochemical parameters)
- positive findings of the fetal echocardiography, performed owing to other maternal or fetal reasons.

In many cases of positive ultrasound findings the literature data is conflicting, very frequently there are inconsistent statements in the studies. The respective authors take different views about the various ultrasound findings.

The increasing demand for the invasive procedures, the concerns of the pregnant women led me to examine the various ultrasound findings, which are those, where the risk of the chromosomal abnormalities is so high that it makes the intrauterine karyotyping justified, either in itself or associated with another anomaly. We also have to consider the risks of fetal loss of the invasive procedures, which are currently 0.5% in case of genetic amniocentesis (GAC) and 1.7% in case of chorionic villus sampling (CVS) in our Department.
In order to answer these questions, I set myself the task of examining the following factors:

1. Which are the minor and major anomalies, where the risk of the chromosome abnormalities is higher than 1%, and the chromosome analysis of the intrauterine fetus is recommended?

2. In cases of the various positive ultrasound findings, how it influences the risk of the chromosome abnormalities, if the anomaly occurs in itself or is associated with other positive ultrasound findings?

3. In cases of the positive ultrasound findings occurring at various bilateral anatomical features, how the unilateral or bilateral form of the anomalies influence the incidence of the chromosomal abnormalities?

4. How is the ratio of the trisomies and other chromosomal abnormalities distributed at the various positive ultrasound findings?

5. In cases of the anomalies with subcutaneous edema, how the risk of the chromosomal abnormalities is changing, if we separately examine the nuchal edema, cystic hygroma, non-immune hydrops cases, and when the non-immune hydrops occurs associated with the cystic hygroma?

6. Considering the cranial and cerebral anomalies, what is the genetic risk of the ventriculomegaly and the choroid plexus cyst?

7. What is the genetic risk of the anomalies of the heart and the large blood vessels, and the presence of the echogenic intracardiac focus?

8. Does the fetal pyelectasis in itself, and the case of a unilateral anomaly justify the invasive procedure?

9. How the anomalies of the abdominal wall and the abdomen increase the risk of the chromosomal abnormalities? Does the echogenic bowel in association with other anomalies or without any other abnormalities justify the invasive procedure?

10. To what extent the shortened long bones increase the risk of the chromosomal abnormalities?

11. Do the polyhydramnios and oligohydramnios in themselves or only in association with other anomalies justify the invasive procedure?
Materials and methods

We have processed the results of chromosome analysis performed following positive ultrasound findings during a 10-year period (1990-2000) in the 1st Department of Obstetrics and Gynecology of the Semmelweis University Medical School. We have karyotyped pregnancies with positive ultrasound findings for subcutaneous edema (non-immune hydrops, cystic hygroma, nuchal edema).

We examined cerebral anomalies (ventricular dilatation, choroid plexus cyst, other cerebral and cranial abnormalities), abnormalities of the heart and thorax (echogenic intracardiac focus, ventricular septum defect and other anomalies), pyelectasis, malformations of the abdominal wall and the abdomen (omphalocele, gastrochisis, duodenal atresia, echogenic bowel), abnormalities of the extremities, and anomalies of the umbilical cord and amniotic fluid (oligohydramnios, polyhydramnios).

The ultrasound examinations were performed in the Ultrasonography Laboratory of the I. Department of Obstetrics and Gynecology, using ATL Ultramark4 and Ultramark 9 (Ultramark 4 and 9, Advanced Laboratories Technology, Bothwell, WA, 3.5 MHz curvi linear transducer). The examinations were carried out on the basis of the professional protocols of the Hungarian Association on Ultrasonography in Obstetrics and Gynecology.

In cases with positive ultrasound findings the couple was given full information about the risk of the chromosome abnormalities. Following the counseling - with full knowledge of the risk of the invasive intervention - the couple decided to undergo the examination.

The majority of the invasive interventions carried out for chromosome analysis were ultrasound guided transabdominal genetic amniocentesis (GAC), which were performed between 15 and 21 weeks of pregnancy. Previous to the procedure we performed a detailed, full ultrasound examination (Hitachi EUB 405). We determined the exact gestational age, compared to the first day of the menstruation and the measured biometrical data. We also determined the position of the fetus and placenta, and if enough amniotic fluid is present, and then indicated the exact place of the amniocentesis. We avoided the transplacental immission if it was possible, and also the originating spot of the umbilical cord. Following the desinfection of the operative field, we performed
the centesis of the amniotic cavity under continuous ultrasound control. In each case we obtained 8 to 10 ml of amniotic fluid.

The minority of the chromosome analyses was carried out by chorionic villus sampling (CVS), which were performed in the first trimester between 10 and 13 weeks of pregnancy, or in the second trimester between 18 and 23 weeks gestation. CVS was performed when the size of the pregnancy or some other reason made the genetic amniocentesis impossible. Similarly to the genetic amniocentesis, during the studied period each case was performed by transabdominal immission.

The samples from the amniotic fluid and chorionic villi were cytogenetically processed in the Cytogenetic Laboratory of the I. Department of Obstetrics and Gynecology. We examined the amniotic fluid samples after cell culturing and the chorionic villus samples without culturing (utilizing the direct mitotic activity) or after culturing.

By arresting the mitotic cell division in the metaphases, microscopic examination and karyotyping of the chromosomes becomes possible. In some cases, the demonstration of numerical chromosome abnormalities was confirmed by molecular genetic examination, fluorescent PCR (F-PCR) technique in the Molecular Genetic Laboratory of our Department.

During the statistical analysis of the data we used the computer data base of the Genetic Center. In all cases of positive ultrasound findings we examined separately those which were associated with other fetal anomalies, polyhydramnios or oligohydramnios. If there was the possibility of a bilateral anomaly, we examined separately the unilateral and the bilateral abnormalities.

In cases of the various anomalies we examined the sensitivity, the specificity, the false-negative rate, the false-positive rate, the likelihood-ratio (LR), the positive predictive value, the negative predictive value. In all cases we carried out detailed statistical analyses, we applied the chi-squared ($\chi^2$) test at the significance test.
Results

During the examined ten-year period, we carried out intrauterine chromosome analysis in 9766 cases, and in 1907 cases because of positive ultrasound findings in the embryo/fetus. The invasive intervention was genetic amniocentesis in 1619 cases, and chorionic villus sampling in 288 cases. Chromosome analysis (karyotyping) demonstrated chromosome abnormalities in 103 cases (5.4%). During the examination period of the cases of karyotyping owing to other indications (maternal age, biochemical parameters, positive anamnensis, maternal concerns) we performed 7859 karyotyping, and we found 254 cases of abnormal karyotypes (3.23%)

In cases with subcutaneous edema we detected abnormal karyotype in 8.3% of cases with nuchal edema in the 1st trimester, and 5.5% in the 2nd trimester, in 48.1% of cases with cystic hygroma, in 20% of cases with non-immune hydrops, and in 53.9% of cases with non-immune hydrops and cystic hygroma altogether.

In cases of cranial and cerebral anomalies the incidence rates of the chromosome abnormalities were 6.3% of cases with ventricular dilatation, 3.6% of cases with choroid plexus cyst, and 15.9% of cases with other cranial anomalies. Ventricular dilatation (ventriculomegaly) in association with other positive ultrasound findings was accompanied with chromosome abnormality in 8.4% of cases, while isolated ventriculomegaly was found in only 3.7% of cases. We also found a higher rate of occurrence in cases of bilateral malformations (8.6%) as opposed to unilateral malformation (4.6%). In cases with choroid plexus cysts we found abnormal karyotypes in almost the same proportion of cases with other associated ultrasound findings (3.9%), without findings (3.3%), with unilateral malformations (3.3%), and with bilateral malformations (3.9%). In cases of other cranial malformations (fossa posterior cyst, dilatation of the 3rd-4th ventricle, and deformed cranium) we found abnormal karyotypes in 15.9%.

In cases of cardiac and thoracic anomalies the findings of isolated echogenic intracardiac focus and ventricular septal defect (VSD) were not
associated with chromosome abnormality, but these findings in association with other ultrasound malformations had an abnormal incidence rate of 7.9%, and 26.7%, respectively. The total risk for chromosome aneuploidy was 4.7% in case of echogenic intracardiac focus and 22.2% in cases of VSD. In cases with other cardiac or outflow tract anomalies, the rate of abnormal karyotype was 18.2%.

In cases of diaphragmatic hernia, we found no chromosome abnormalities. Altogether we performed 7 karyotyping because of hernia diaphragmatica, and there was no abnormal karyotype detected.

In cases of isolated hydrothorax (showing no other signs of hydrops), we detected chromosome abnormalities characteristic of non-immune hydrops in proportion and division. We carried out 6 karyotyping owing to isolated hydrothorax, and we found 2 cases of abnormal karyotypes (33.3%)

In cases with abnormalities of kidneys the incidence of chromosome abnormalities was 1% of cases with isolated, unilateral pyelectasis. In cases of bilateral pyelectasis or pyelectasis in association with other findings, the rate was 3%. The total risk was 2.3%.

Regarding the more uncommon abnormalities of the abdominal wall and the abdomen, the association with chromosomal abnormalities was 9.5% of omphaloceles, and 11.8% of duodenal atresias. In cases with the more frequently occurring echogenic bowel, the incidence rate of abnormal karyotype was 5.7%. Pregnancies with echogenic bowel in association with other ultrasound findings demonstrated chromosome abnormalities in 8.6%, however no abnormal karyotypes were detected in cases with isolated echogenic bowel.

In cases with abnormalities of extremities in cases with short femur and humerus, the rate of abnormal karyotype was 16%. The rate of abnormal karyotypes was 15.8% in cases of other abnormalities, and without other positive ultrasound findings this rate was 16.7%.

Considering other anomalies of the extremities, we performed karyotyping in 12 cases. There were mainly deformities of the lower limbs, and
in the examined cases there were no chromosomal abnormalities in the background of the deformities.

*In cases of abnormalities of umbilical cord and amniotic fluid* we performed chromosome analysis in 6 cases of singular umbilical artery. In 4 cases of the 6 the arteria umbilicalis singularis was associated with other anomalies, and in there were 2 isolated cases. We found one case of chromosome abnormality (16.7%). In this case there were other ultrasound findings associated with the singular umbilical artery.

In cases with isolated polyhydramnios, the rate of chromosome abnormalities was 0.3%. In cases of polyhydramnios associated with other ultrasound findings, the rate of chromosome abnormalities was 5.9%. In cases with polyhydramnios the total risk was 3.5%.

In cases of oligohydramnios associated with other anomalies, the rate of chromosome abnormality was 8.9%, but chromosome abnormalities were also found in cases of isolated oligohydramnios (4.5%), the total risk was 7.7%.
Findings

In the study we examined which positive ultrasound findings indicate the intrauterine karyotyping. According to the processed data, chromosome analysis is recommended in the following instances of positive ultrasound findings:

1. We specified the positive ultrasound findings where the incidence rate of the chromosomal abnormalities is higher, than 1%. These anomalies are discussed in detail as follows.

2. We established during our examinations, that in cases of certain ultrasound findings the opinion of the genetic counseling is determined by the fact whether the anomaly occurs in itself or in association with other findings.

3. In cases of various bilateral anatomical features we established, that the risk of the chromosomal abnormalities is different in the cases of unilateral and bilateral anomalies.

4. Examining the distribution of the trisomies and other chromosomal abnormalities we established, that from the anomalies with subcutaneous edema the nuchal edema and the cystic hygroma increase the risk of trisomy 21 and trisomy 18, beside the monosomy X. In cases of non-immune hydrops we determined monosomy X, while in cases of non-immune hydrops and cystic hygroma occurring together we detected trisomy 18 and monosomy X. Considering cranial and cerebral anomalies, in cases of ventriculomegaly the incidence rate of the trisomies (trisomies 21, 18 and 13) and the other chromosomal abnormalities (monosomy X, 47,XXY karyotype) were almost the same. In case of choroid plexus cyst mainly the risk of the trisomy 18 and monosomy X increased, but there were also trisomy 21 and 47, XXY karyotypes detectable. In cases of the cardiac and large blood vessels abnormalities the echogenic intracardiac focus increased the risk of the trisomy 21, and in cases of ventricular septal defect there were trisomy 18 and trisomy 13 detectable. Considering the renal anomalies, the fetal pyelectasis increased the risk of monosomy X, trisomy 21 and trisomy 18. Regarding the abnormalities of the abdominal wall and abdomen, in cases of omphalocele there were trisomies 18 and 13 detectable, while in cases of duodenal atresia the risk of the trisomy 21 was higher. In cases of echogenic bowel the risk of the trisomies 21 and 18 was higher. Considering the abnormalities of the
extremities, in cases of shortened femur and humerus increased the risk of trisomies 18 and 21, and monosomy X from the aneuploidies.

5. In cases of abnormalities with subcutaneous edema we established, that it is very important to distinguish the various positive ultrasound findings according to the proper definitions. It is important to mark out the cystic hygroma from the nuchal edema, in cases of non-immune hydrops we have to examine separately the cases associated with cystic hygroma and the non-associated cases. If we can give the correct definitions of the positive ultrasound findings, in case of nuchal edema, in the first and second trimester there are lower risks than in the literature data, so we can avoid the unjustified alarming in the course of the genetic counseling. It is very important to give the degree of the risk to the parents. According to our studies, in cases of nuchal edema (nuchal translucency) measured in the first trimester the risk is 8.3%, while in cases of nuchal edema (nuchal thickening) in the second trimester it is 5.5%. The risk justifies the invasive procedure.

In other cases of subcutaneous edema we detected abnormal karyotypes in higher ratio. In cases of cystic hygroma the incidence rate of the chromosomal abnormalities was 48.2%, in cases of cystic hygroma and non-immune hydrops occurring together this rate was 53.9%, and in cases of non-immune hydrops it was 20%. The high risk in all cases gives reason for the invasive procedure.

6. We established that in cases of ventriculomegaly the karyotyping is reasonable (chromosomal abnormalities were detected in 6.3%). We also established, that karyotyping is justified in both cases of unilateral and bilateral abnormalities (risk of chromosomal abnormalities is 4.6% in cases of unilateral anomalies, 8.6% in cases of bilateral abnormalities). We detected abnormal karyotypes in cases associated with other malformations in 8.4%, and in 3.7% without other anomalies.

According to the examinations, it could be stated that in cases of choroid plexus cyst the karyotyping is reasonable, we detected abnormal karyotypes in 3.6%. On the basis of our examinations, karyotyping is justified in both cases of unilateral and bilateral abnormalities; the incidence rate of the chromosomal abnormalities was 3.3% in cases of unilateral, and 3.9% in cases of bilateral anomalies. It can be also established, that karyotyping is recommended in isolated cases and in cases associated with other anomalies,
we detected abnormal karyotypes in isolated cases in 3.6%, and in associated cases in 3.9%.

7. From the cardiac findings, the echogenic intracardiac focus occurs also in normal pregnancies, which might not indicate the incidence of any other abnormal factor, if there is no chromosomal abnormality verifiable. According to our examinations we only detected chromosomal abnormalities in those cases, where the echogenic intracardiac focus was associated with other positive ultrasound findings (7.9%). The total risk was 4.7%, which was calculated considering the isolated and associated cases together. With regard to this high total risk, karyotyping can be recommended also in isolated cases (echogenic intracardiac focus without other anomalies).

In our experiments we detected chromosomal abnormalities in 26.7% in cases of ventricular septum defect associated with other malformations. In isolated cases there were less karyotypings performed, and we did not detect any chromosomal abnormalities. The total risk (isolated and associated cases) was 22.2%. On the basis of the higher total risk, karyotyping is recommended in cases of ventricular septum defect.

8. From the renal anomalies, the pyelectasis justifies karyotyping only in bilateral and associated cases, since the risk of unilateral and isolated cases was not higher than 1%. If the pyelectasis was associated with other anomalies, the incidence rate of the chromosomal abnormalities was 3%, in isolated cases it was 1%. In unilateral cases the incidence rate of the abnormal karyotypes was 1%, in bilateral anomalies it was 3%.

9. From the abnormalities of the abdominal wall and abdomen, in cases of omphalocele we detected abnormal karyotypes in 9.5%. The risk of the chromosomal abnormalities was 7.1% in isolated cases, and in cases of findings associated with other ultrasound abnormalities it was 14.3%. Relying upon these findings (the high incidence rate of the associated chromosomal abnormalities) the omphalocele definitely justifies the karyotyping.

The high incidence rate of the chromosome abnormalities in case of the positive ultrasound findings of duodenal atresia definitely gives reasons for the karyotyping. In the course of the karyotyping in cases of duodenal atresia we detected abnormal karyotypes in 11.8%.

In cases of echogenic bowel we detected chromosomal abnormalities in 5.7%. All chromosomal abnormalities were found in those cases where the
anomaly was associated with other ultrasound findings (8.6%). Although in our studies we could not detect chromosomal abnormalities in the isolated cases, if we calculate the total risk (isolated and associated cases), it is so high (5.7%) that even in isolated cases the karyotyping is recommended. In cases of echogenic bowel the Toxoplasmosis and CMV immunological tests should be also performed in addition to the karyotyping.

10. From the abnormalities of the extremities, the shortened femur and humerus justify the invasive procedure (16%). The incidence rate of the anomalies associated with other findings was 15.8%, in isolated cases this rate was 16.7%.

11. In cases of polyhydramnios we detected chromosomal abnormalities in 3.5%. In our studies we established that the polyhydramnios justifies the invasive procedure only in cases associated with other findings. In isolated cases of polyhydramnios the risk of the chromosomal abnormalities is lower than 1% (0.3%). In cases of polyhydramnios detailed ultrasound examination and echocardiography is recommended, because in association with other anomalies chromosome analysis is reasonable (5.9%). In cases with polyhydramnios, a parallel examination of maternal carbohydrate metabolism is recommended.

In cases of oligohydramnios, chromosome analysis is reasonable even without other findings. In our studies we detected chromosomal abnormalities in 4.6% in isolated cases oligohydramnios, while in the associated cases the risk of the abnormal karyotypes was 8.9%. The total risk (calculated from the isolated and associated cases together) was 7.7%. Before performing the examination the possibility of rupture of the membranes must be eliminated, and, along with the careful renal examination of the fetus, an echocardiographic examination must be performed to exclude possible associated cardiac malformations. Amniocentesis should be performed only in the presence of a certain amount of amniotic fluid.
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