Chapter

The Risk of Chromosomal Abnormalities in Cases of Minor and Major Fetal Anomalies in the Second Trimester

Artúr Beke and Aténé Simonyi

Abstract

Currently, noninvasive intrauterine screening for most chromosome abnormalities is available, but ultrasound examinations also play an important role during pregnancy, by drawing the attention to the suspect of a possible abnormality. Fetal ultrasound disorders can be classified into two major groups: (1) Major abnormalities are actually diagnosed malformations that are often associated with certain chromosome abnormalities but may be associated with other disorders (multiplex malformation) and may occur as isolated disorders (e.g., cardiac disorders, duodenal atresia, omphalocele, cystic hygroma (CH)). (2) Minor anomalies ("soft markers") are not abnormal in themselves but are mild abnormalities that may occur in normal pregnancy but also increase the risk of certain chromosome aberrations. The minor anomalies in the second trimester include thickened nuchal fold (NF), mild ventriculomegaly, pyelectasis, hyperechogenic bowels, hyperechogenic papillary muscle, and shorter long bones. Plexus choroid cyst which is classified as a minor marker does not increase the risk of Down syndrome but increases the risk of trisomy 18 (Edwards syndrome). We want to emphasize the importance of screening of minor and major ultrasound abnormalities in detecting chromosomal abnormalities in the second trimester.

Keywords: obstetric genetics, prenatal diagnosis, chromosomal abnormalities, prenatal ultrasound, fetal anomalies

1. Introduction

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 of examination. The numerical and structural anomalies can be duplications/trisomies, deletions/monosomies, and other rearrangements on the chromosomes.

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.

Besides the age, a history of aneuploidy, and noninvasive tests, positive ultrasound findings—which could be major structural abnormalities or minor ultrasound markers—can be an indicator for chromosome analysis [1].

2. Abnormalities with subcutaneous edema

As the first-trimester nuchal edemas (nuchal translucency, NT), the second-trimester nuchal edemas (nuchal thickening, nuchal fold, NF) also elevate the risk of chromosome abnormalities. It is important to distinguish nuchal edema and cystic hygroma (CH), and in the case of nonimmune hydrops (NH), it is also important to discuss cases with or without cystic hygroma separately.

Abnormalities with subcutaneous edema (nonimmune hydrops (NH), cystic hygroma, nuchal edema) increase the risk of chromosome abnormalities. They may warn of a possible intrauterine infection; in the case of nonimmune hydrops, for example, parvovirus B19 infection may occur. They may also be indicative of other pathologies accompanied with fetal anemia, including thalassemia, twin-to-twin transfusion, and disorders of fetal circulation and abnormal anatomy of the fetal heart.

2.1 Nuchal fold (nuchal thickening) in the second trimester

In the second trimester, we examine the thickened nuchal fold (nuchal thickening, NF) in the horizontal section, level with the cerebellum and also containing the cavum septum pellucidum and the cisterna magna. This method, in contrast to the one used in the first trimester, measures the thickness of the soft tissue from the external aspect of the skin to the external aspect of the bone. Authors suggest 5 mm as a cutoff value [2, 3]. A large nuchal translucency detected in the first trimester is a non-specific malformation, and in most cases it resolves during the second trimester of the pregnancy, although it might persist in certain cases to show a picture of nuchal thickening. It indicates an increased risk of trisomy 21 (Down syndrome) [4].

Benacerraf et al. were the first in drawing the attention to the fact that the nuchal fold or nuchal thickening (≥6 mm) observed during the ultrasound examination in the second trimester increases the risk of Down syndrome [4].

Numerous authors carried out similar examinations, subsequently demonstrating different results. Gray and Crane [3] tried to determine the proper cutoff values of nuchal thickening. They formulated two groups according to the size of the pregnancy, putting the values measured in weeks 14–18 to the first group and the data of weeks 19–24 to the second group. Considering the examinations, the suggested cutoff value in the first group (weeks 14–18) is ≥5 mm, and in the second group (weeks 19–24), it is ≥6 mm [5]. In their investigations, Gray and Crane [3] detected pathological karyotypes in 12 out of 47 cases (25.53%). Analyzing 23 cases, DeVore and Alfi found pathological karyotypes in 9 cases (39.13%) [6].

Other authors detected pathological karyotypes in 10% of second-trimester nuchal edema. Grandjean and Sarramon [7] processed the data of 3308 ultrasound examinations, with the help of 12 centers, and they found nuchal thickening in 38% of the cases of trisomy 21. According to the records of 12 centers, they performed karyotyping of 295 pregnancies in the second trimester with nuchal thickening. They found abnormal chromosomes in 22 cases (7.46%), 17 of these were trisomy 21 (5.76%) [7]. Gonen et al. [8] carried out karyotyping in 573 cases because of positive ultrasound findings during ultrasound examinations in the second trimester. There were 38 chromosome analyses carried out due to nuchal thickenings; in one case they found an abnormal karyotype (2.63%) [8]. Zimmer et al. discussed their cases of early second-trimester nuchal edema in 43 out of 1254 cases (3.43%); they detected pathological karyotypes, trisomy 21 being the chief cause in 27 cases, while other pathological karyotypes were blamed in 16 cases [9].

Beke et al. [10] showed a value within 10% in the case of nuchal fold (thickening) measured in the second trimester. A total of 254 cases of chromosomal examination was performed for second-trimester nuchal edema, and in 14 cases, an abnormal karyotype was detected (5.51%). With the highest frequency, monosomy X occurred (nine cases, 3.54%), while in three cases trisomy 21, in 1-1 cases trisomy 18 (Edwards syndrome), and another chromosome abnormality were detected [10].

2.2 Cystic hygroma

Cystic hygroma is observable in the first and second trimesters. It can be differentiated from nuchal translucency and nuchal thickening by the clearly isolated fluid space and the typical medial line septation shown on ultrasound examination [11, 12]. Cystic hygroma often persists and is often associated with aneuploidy (mainly monosomy X), other abnormalities, and fetal loss [12].

In the case of cystic hygroma, the risk of the chromosome abnormality is even higher than in cases of nuchal thickening. Bronshtein et al. found chromosome anomalies in 6 of 106 nonseptated cases (5.66%), whereas the risk of the chromosome abnormality in the 25 septated cases was 72% [12].

Nadel et al. [13] examined in separate groups those cases where the cystic hygroma occurred by itself (isolated) and those where it was a part of the hydrops phenomenon. In cases of individually occurring 26 hygromas, there were chromosome abnormalities in 12 cases (46.15%), while in hydrops-associated cases (37 cases), they found 31 chromosome anomalies (83.78%) [13]. Due to cystic hygroma, Gonen et al. detected 15 cases of pathological (abnormal) karyotype in 182 cases (8.24%) [8]. Sohn and Gast [14] found 20 cases of abnormal karyotype of the 57 cystic hygroma cases (35.09%). There were 11 cases of monosomy X (Turner syndrome), 5 cases of trisomy 21, and 4 cases of trisomy 18 [14]. Taipale et al. carried out karyotyping in 76 cases of cystic hygroma, and they found chromosome abnormalities in 18 cases (23.68%), monosomy X in 5 cases, trisomy 21 in 7 cases, and trisomy 13 (Patau syndrome) and trisomy 18 in 6 cases [15].

Beke et al. [10] had a similar result. In terms of isolated cystic hygroma, fetal chromosome examinations were performed in 27 cases, and in 13 cases abnormal karyotypes were detected (48.15%). When cystic hygroma was associated with hydrops, a total of 13 cases was investigated, and 7 cases of chromosomal abnormalities (53.85%) were detected [10].

In the first and early second trimesters, Rosati and Guariglia [16] examined the volume of cystic hygromas by volumetric calculations. They also analyzed the proportion of associated chromosomal abnormalities, and in 8 of 14 septated cases, they detected pathological karyotypes (57.14%), whereas four pathological karyotypes (21.05%) were seen in the 19 nonseptated cases. In summary, the 12 patients with chromosomal abnormalities (36.36%) were divided as follows: trisomy 21 in 6 patients, monosomy X in 4 cases, and trisomy 18 and 13 in 1 case each [16]. Examining the septated and nonseptated cases together, Tanriverdi et al. found 13 pathological karyotypes (56.52%) among the 23 karyotyped patients [17]. Donnenfeld et al. applied karyotyping and fluorescent in situ hybridization (FISH) in the chromosomal investigation of the cells in the sample obtained from the fluid of the cystic hygroma and could justify monosomy X in 86% [18].

Examining a total of 218 fetuses with subcutaneous edema, Gezer et al. [19] found that nuchal fold, cystic hygroma, and nonimmune hydrops could be significant markers for abnormal chromosome numbers. Of these 218 cases, 71 (32.57%) were diagnosed with abnormal karyotype. The percentage breakdown

in 71 cases was as follows: 37% monosomy X, 44% trisomy 21, 15% trisomy 18, and 4% trisomy 13 [19].

2.3 Nonimmune hydrops

Similarly to cystic hygroma, nonimmune hydrops can be observed both in the first and second trimesters and is often associated with aneuploidy (monosomy X or trisomy 21) and fetal loss [13].

Nicolaides et al. studied 37 cases in 1986 and demonstrated 12 cases of chromosome anomalies (32.43%) [20]. Gembruch et al. found 17 abnormal karyotypes examining 45 hydrops cases (37.78%), 10 cases of monosomy X (1 mosaic form), 6 cases of trisomy 21, and 1 case of trisomy 18 [21].

Boyd and Keeling [22] and Anandakumar et al. [23] found X-monosomies in 50% of the demonstrated chromosome abnormalities. Boyd and Keeling [22] found 11 X-monosomies of the 22 cases of chromosome anomalies of the 72 nonimmune hydrops cases (30.56%), while Anandakumar et al. [23] carried out karyotyping in cases of 100 hydrops-affected fetuses and demonstrated 5 cases of X-monosomies of 10 abnormal cases (10%).

Schwanitz et al. examined in separate groups the nonimmune hydrops cases associated with cystic hygroma and the individually occurring ones. When it was associated with cystic hygroma, abnormal karyotypes were demonstrated in 54.39%; without cystic hygroma this rate was 27.69% [24].

Has carried out investigations into nonimmune hydrops in the first trimester and found 9 pathological karyotypes (47.37%) out of 19 cases [25].

In the case of nonimmune hydrops, Beke et al. found chromosomal abnormalities in 4 out of 20 cases (20%), in each case monosomy X [10].

3. Cerebral and cranial anomalies

In the case of ventriculomegaly, a greater than normal amount of liquor expands the ventricular system. Cerebrospinal fluid may be overproduced, impaired, or obstructed. Increased pressure leads to thinning of the brain, creating hydrocephalus internus. Hydrocephalus externus is referred to as the proliferation of liquor in the subarachnoid space. Ultrasound first shows the expansion of the posterior horn of the side chamber. In cases of choroid plexus cyst and other cranial malformations, the risk of chromosomal abnormalities is also elevated.

3.1 Ventriculomegaly

In cases of cerebral anomalies, we define ventricular dilatation (ventriculomegaly) as a lateral ventricle with a diameter ≥ 10 mm. The ventricle of normal male fetuses is mildly wider (average 6.4 mm) than of the ventricle of normal female fetuses (average 5.8 mm) [26]. Ventriculomegaly increases the incidence rate of aneuploidy (trisomy 21 and other aneuploidies) [27, 28].

Several authors were examining ventriculomegaly as one possible marker of the fetal chromosome abnormalities in the second trimester. Nicolaides et al. carried out karyotyping in 9 cases because of fetal ventriculomegaly, examining this among other anomalies, and they found chromosome abnormalities in 2 cases (22.22%) [20]. Following this, Mahony et al. [28] found 1 case of 20 ventriculomegalies (5%); Bromley et al. [27] observed 5 cases of chromosome anomalies examining 44 cases of ventriculomegaly (11.36%). The study of Gonen et al. [8] also extended to more anomalies; as a part of it, they carried out karyotyping in 25 cases of

ventriculomegalies and found no abnormal karyotypes. Terry et al. [29] detected abnormal chromosomes in 3 cases of the 25 examined fetuses (12%).

Beke et al. [30] found different karyotypes in 26 (6.25%) out of the 416 examined fetuses. If ventriculomegaly was isolated (191 cases), the rate of the chromosome abnormality was 3.7% (7 cases). In four cases, trisomy 21 was detected, in two cases monosomy X, and in one case trisomy 18. Lateral ventricular dilation (ventriculomegaly) was associated with other ultrasound findings in 225 cases, and in 19 of these, there were chromosome abnormalities detected (8.4%). The distribution of pathological (abnormal) karyotypes was as follows: 4-4 cases of monosomy X and 47, XXY karyotype (Klinefelter syndrome), 3-3 cases of trisomy 21 and trisomy 18, and 1-1 case of trisomy 13, 47,XXX, 47,XYY, 49,XXXY karyotypes and triploidy were detected. We found a higher rate in cases of bilateral anomaly (ventriculomegaly) (8.6%) than in unilateral cases (4.6%) [30].

3.2 Choroid plexus cysts

According to the data of more authors, the choroid plexus cysts (CPC) mainly increase the risk for trisomy 18 [31, 32]. According to certain studies, the risk level does not depend on whether the anomaly is unilateral or bilateral, but other studies show that the larger the anomaly (>10 mm), the higher the risk [33, 34]. Certain authors suggest the 2–2.5 mm cutoff value [35], while others determined the 5 mm limiting value [33]. The cysts resolve practically every time, so the absence of the anomaly on a repeated ultrasound examination does not indicate a decrease in the risk [36].

Chudleigh et al. were the first who described cysts in the fetal choroid plexus [37]. Nicolaides et al. were the first who drew attention to the connection between the positive ultrasound finding of choroid plexus cysts and chromosome abnormalities, through a study including a small number of cases [20]. Thereafter, more authors demonstrated that fetal choroid plexus cysts mainly increase the risk of trisomy 18 and, to a lesser degree, the risk of trisomy 21.

Achiron et al. demonstrated 2 trisomy 18 cases from chromosome analysis of 30 CPC cases (6.67%); in 1 case the CPC was associated with other ultrasound anomalies [38]. Platt et al. found 4 cases of chromosome abnormalities from 62 cases (6.45%), in 3 cases it was trisomy 18, and in 1 case it was trisomy 21 [39]. Nadel et al. demonstrated 12 cases (5.13%) of abnormal chromosomes from a larger number of cases (234 cases), 11 of which were trisomy 18 (4.7%) and 1 case of triploidy, but from 234 cases there were 220 cases of isolated CPC, and in these cases they did not detect any chromosome abnormalities [40].

Walkinshaw et al. demonstrated 4 cases (2.63%) of chromosome anomalies out of 152 isolated CPC cases, 3 cases trisomy 18 (1.97%) and 1 case trisomy 21 [33]. Nava et al. found eight chromosome abnormalities in 176 cases (4.55%), 4 cases of trisomy 18 (2.27%), 2 cases of trisomy 21 (1.14%), 1 case of 47, XXY karyotype, and 1 case of another chromosome anomaly [41]. From the trisomy 18 cases, there was one case of isolated choroid plexus cyst, while in three cases the abnormality was associated with other ultrasound findings. Gonen et al. in 1995 demonstrated no abnormalities in the course of intrauterine karyotyping of 108 CPC cases [8].

Gray et al. performed karyotyping in 208 cases, and they detected abnormal karyotypes in 7 cases; each case was trisomy 18 (3.37%) [34]. Bakos et al. found 3 abnormal karyotypes out of 108 examined cases (2.78), 1 case was trisomy 18, and 1 case was trisomy 13 and one inversion of chromosome 9 [42].

Chitty et al. [43] with a larger number of cases found chromosome abnormalities in 14 cases (2.13%). They examined separately the isolated cases and the cases associated with other ultrasound anomalies. In 603 cases, the choroid plexus cyst

was not associated with other ultrasound abnormalities, and in 3 cases (0.5%), they found abnormal karyotypes (each was trisomy 18); in 55 cases the abnormality was associated with other ultrasound findings, and in 11 cases (20%), they detected abnormal karyotypes (in 9 cases trisomy 18, in one case trisomy 21, and in 1 case 47,XXX karyotype) [43]. With a similarly large number of cases, Ghidini et al. examined the incidence of chromosome abnormalities in cases of choroid plexus cysts, they only examined the isolated cases (765 cases), and they found abnormal karyotypes (trisomy 18) in 13 cases (1.7%) [44].

Coco et al. [45] in 2004 examined separately the isolated cases and those associated with other abnormalities, the cases associated with minor and major ultrasound anomalies. The rate of abnormal karyotypes was 0.55% in total. In isolated cases (311 cases) and in associated cases with minor anomalies (43 cases), they did not find any abnormal karyotypes. In the two detected cases of trisomy 18, the choroid plexus cyst was associated with major anomalies (16.67% from 12 cases) [45]. Sahinoglu et al. [46] performed karyotyping in 109 cases due to choroid plexus cyst, 3.67% of the patients had an abnormal karyotype, in 102 cases, it was isolated anomaly, and in 3 cases they found chromosome abnormalities (2.94%). In seven cases, the choroid plexus cysts were associated with other ultrasound anomalies, and they found chromosome abnormality in one case (14.29%); in all the detected four cases, the abnormal karyotype was trisomy 18.

According to a 2008 study, of the 435 cases identified by CPC, 390 undertook karyotyping. Of these, anomalies were found in 14 fetuses (3.59%), with the highest frequency being trisomy 18 (6 cases, 1.54%); in 1 case trisomy 21 (1, 0.26%) and 1 case trisomy 9 (0.26%) were detected. The incidence of monosomy X was 0.77% (3 cases). In one case, 47, XXY karyotype (0.26%) and in two cases other chromosomal abnormalities (0.51%) were confirmed (46,XX/46,XY and 46,XY/47,XXY/47,XYY mosaicism). Of the cases studied, other ultrasound abnormalities associated with the plexus cyst were found in 178 pregnancies, and 7 abnormal karyotypes were found (3.93%), 5 cases of trisomy 18, and 2 cases of monosomy X. Choroid plexus cyst occurred as an isolated anomaly in 212 pregnancies (it was not associated with any other fetal ultrasound findings (anomalies) and/or poly/oligohydramnios), and 7 chromosome abnormalities (3.3%) were found, one of which was trisomy 18, 1 case trisomy 21, 1 case trisomy 9, 1 case monosomy X, and 1 case 47,XXY karyotype. The incidence of chromosome abnormalities was also similar in the case of unilateral and bilateral CPC; chromosome abnormalities were detected in the case of unilateral (3.3%) and in the case of bilateral anomalies (3.9%) [47].

3.3 Other cranial and cerebral anomalies

Other cranial and cerebral anomalies (holoprosencephaly, agenesis or dysgenesis of the corpus callosum, Dandy-Walker malformation, and cleft lip or palate) according to observations increase the risk of chromosome abnormalities, but they do not increase the risk of trisomy 21 [48]. A strawberry-shaped head mainly increases the risk of trisomy 18 [49].

Benacerraf et al. reported five cases already in 1984, where they found intrauterine cleft lip and palate and holoprosencephaly during the ultrasound examinations, and the chromosome analysis verified trisomy 13 in two cases (33.33%) [50].

Both Parant et al. [51] and later Tongsong et al. [52] reported 12 cases where they diagnosed intrauterine holoprosencephaly. The karyotyping in Parant et al. [51]'s study verified trisomy 13 in four cases (33.33%); in Tongsong et al. [52]'s study, there were three cases of trisomies found (25%); in two cases it was trisomy 13 (16.67%), and in one case it was trisomy 18 (8.33%). Bullen et al. reported in their

study (2001) 68 cases of holoprosencephaly, they made karyotyping in 52 cases, where they found an abnormal karyotype in 38% (from 20 cases in 15 cases it was trisomy 13, in 2 cases trisomy 18, and in 3 cases other chromosome anomalies, from which in 2 cases they recognized the deletion of the long arm of chromosome 13) [53]. Studying the etiology of the holoprosencephaly, besides the maternal diabetes and trisomy 13, there are also monogenic types [54].

In cases of cleft lip and/or palate, Perrotin et al. [55] demonstrated in their study that in those cases they examined, there were no chromosome anomalies provided the abnormality was isolated (14 cases), and when they detected it together with other positive ultrasound findings, the incidence rate of the chromosome abnormalities was high. In 26 cases, there were 15 chromosome anomalies (57.69%), in 8 cases trisomy 13, and in 5 cases trisomy 18 [55].

Aletebi and Fung [56] studied the abnormalities of the fossa posterior region, including the enlarged cisterna magna, the Dandy-Walker malformation, and the fossa posterior cyst. They found chromosome abnormalities (trisomy 18) in 1 of 15 cases (6.67%) [56].

Similarly, Beke et al. found in their study that the frequency of chromosome abnormalities was similar to other cranial abnormalities; with 44 fetuses being examined, they detected chromosome abnormalities in 7 cases (15.91%) [30].

The aim of Nazer Herrera et al. [57] was to estimate the prevalence of holoprosencephaly in relation to births. It turned out that this disorder occurred with low frequency in Chile, but it was associated with a high proportion of trisomy 13: occurring in 10.91% of the cases examined (6 out of 55 cases) [57].

In another study, this anatomical disorder and chromosome abnormalities were associated with a high proportion. According to a study in Japan, five out of seven holoprosencephaly cases (71.43%) showed the following differences: two children with trisomy 18, two children with trisomy 13, and one with 45,X karyotype [58].

4. Cardiac and thoracic abnormalities

The use of fetal echocardiography may further increase the importance of second-trimester ultrasound examinations for screening for chromosomal anomalies. This is particularly true in those cases where screening tests were not available in the first trimester or the pregnancy was only recognized later.

4.1 Echogenic intracardiac focus

In the fetal heart, the echogenic intracardiac focus is observable in 3–4% of normal pregnancies [59]; according to some studies, this rate might reach 10% in the Asian population [60]. Its incidence, by some authors, increases the risk of trisomy 21 [61–65] and, according to some studies, trisomy 13 [66]. According to some literature data, the risk is higher if the anomaly is observable in both ventricles [61].

Bromley et al. [61, 62] examined in their studies (reported in 1995 and 1998) the correlation between the chromosome anomalies and the echogenic intracardiac focus detected during the ultrasound examinations. In 1995 they studied 66 cases and found trisomy 21 in 4 cases (6.06%) [61]. Chromosome abnormalities were found in 14 cases (4.83%) with a higher number of cases (290). In 1998, they examined 290 pregnancies in two groups and detected chromosome abnormalities (mainly trisomy 21) in 6.4% (125 cases) in that group where the maternal age was ≥35 years, and in the age group under 35 years (165 cases), this rate was 3.64% [62]. Winter et al. demonstrated in their similar report 16 cases of trisomy 21 of the studied 163 cases (9.28%) [65].

In a 2005 publication, the echogenic papillary muscle showed abnormal karyotype only when it was associated with other anomalies (4.69%), not in isolated cases [30].

4.2 Ventricular septal defect and atrioventricular septal defect

Many authors investigated the correlation among the chromosome abnormalities and the ventricular septal defect (VSD) and the atrioventricular septal defect (AVSD). In some cases, the authors managed the cases discovered in the second trimester or later in pregnancy (third trimester) and the cases diagnosed after birth as aggregated data. Hajdu et al. studied 21 cases of AVSD and found chromosome anomalies in 9 cases (42.86%); 7 of these were trisomy 21, 1 case trisomy 18, and 1 case trisomy 22 [67].

Tennstedt et al. [68] analyzed all those cases where the fetopathological examination verified cardiac malformation, and there were ultrasound examinations and karyotyping during the pregnancy (altogether 129 cases). A total of 36 fetuses had VSD, and 21 fetuses had AVSD. In cases of VSD, there were 15 fetuses (41.67%) with detected chromosome anomalies (8 cases of trisomy 21, 4 cases of trisomy 18, 1 case of trisomy 13, 2 cases of other abnormalities). If AVSD occurred, the incidence rate of the chromosome anomalies was 61.9% (from 13 cases, 9 trisomy 21 and 3 trisomy 18, and in 1 case other anomaly) [68]. Delisle et al. [69] studied the incidence of the chromosome abnormalities in cases of AVSD detected by ultrasound examinations during pregnancy, and from the 38 cases, they found 22 (57.89%) with chromosome anomalies (19 cases of trisomy 21, 1 case of trisomy 18, 1 case of trisomy 13, and 1 case of other positive finding). Paladini et al. [70] reported a study about the risk of chromosome abnormalities in cases of all cardiac (heart and large blood vessels) anomalies. In case of ventricular septal defect, the incidence rate of the chromosome anomalies was 45.33% (34 of 75 cases), and in case of atrioventricular septal defect, this rate was 80% (32 of 40 cases) [70]. From the 34 VSD cases, there were 14 cases of trisomy 21 (18.67%), 16 cases of trisomy 18 (21.33%), 2 cases of monosomy X (2.67%), and 2 other anomalies detectable. The distribution of the 32 abnormal karyotypes in case of AVSD was the following: 26 cases of trisomy 21 (65%), 3 cases of trisomy 18 (7.5%), and 3 other anomalies.

In their work, Beke et al. found abnormalities in 4 out of 18 fetuses with VSD (22.22%), including 2 cases of trisomy 18 (11.11%) and 1 case of trisomy 13 (5.56%) as well as 1 case of another anomaly [30].

Hajdu et al. [71] later, in 2005 in the case of AVSD, the frequency of the abnormal karyotypes was 66.67%. They studied 39 cases of AVSD and found chromosome anomalies in 19 cases (66.67%); 19 of these were trisomy 21, 6 cases trisomy 18, and 1 case trisomy 22 [71].

A 2006 study dealt with the VSD-related clinical characteristics of the Moroccan pediatric population, among others. The 44 patients involved in the research were between 2 and 3 years old. Six of them (13.64%) had Down syndrome. VSD patients who were later subjected to surgical correction were more likely to be able to avoid irreversible pulmonary artery hypertension [72].

According to another, Chinese publication, the association of trisomy 21 is also high in the case of complete AVSD (CAVSD). In a group of 35 patients with this type of anatomical deviation, Zhong et al. performed chromosome tests in 15 cases. A total of 13 chromosome abnormalities (86.67%) have been reported, of which 11 patients with Down syndrome have been identified [73].

Relatively few studies deal with long-term follow-up of Fallot tetralogy cases. According to Shuhaiber et al., the prospects can be positive for those who are being treated surgically in the case of the disease. In their study, however, they also refer

to the related VSD and the high proportion of trisomy 21 (80.33%, according to their calculations) in their combined occurrence [74].

4.3 Other cardiac and large blood vessel abnormalities

In cases of other cardiac abnormalities and anomalies of the large blood vessels, the risk of chromosome abnormality is increased [75]. Paladini et al. [70] studied the incidence of the chromosome anomalies in cases of other cardiac and large blood vessel malformations. In the case of coarctation of the aorta, the incidence rate of abnormal chromosomes was 48.28%; in the case of double outlet right ventricle, it was 26.32%; in the case of hypoplastic left heart syndrome, it was 13.51%; in the case of truncus arteriosus, it was 33.33%; in the case of Fallot tetralogy, it was 45%; and in the case of atrial septal defect, there were no abnormal karyotypes found [70].

Other researchers also produced statistics for other heart disorders. Chromosome abnormalities were detected in six cases when investigating 33 fetuses [30].

4.4 Isolated hydrothorax

Only a few authors studied the isolated hydrothorax. Nicolaides carried out karyotyping in three cases because of isolated hydrothorax, in connection with an invasive intervention (blood gained by fetoscopy) performed due to other positive ultrasound findings, and found abnormal karyotype in one case [20]. Estoff et al. carried out karyotyping in 11 cases because of isolated hydrothorax, and in 1 case they found an abnormal karyotype (trisomy 21, 9.09%) [76]. In other studies, in two out of six (33.33%) cases, one case of trisomy 18 (16.67%) and one case of monosomy X (16.67%) associations were observed [30].

5. Abnormalities of the abdominal wall and abdomen

In the case of diaphragmatic hernia, abdominal organs appear in the chest due to a discontinuity in the compartment. About 90% of the lesion is on the left. The aperture of the compartment is not traceable; the abdominal organs of the fetus (liver, stomach, and intestines) appear in the chest, which dislocate the mediastinum and the heart. Chest space narrowing may lead to severe lung hypoplasia.

In cases of an omphalocele, organs (typically the intestines, stomach, and liver) protrude through the opening into the umbilical cord; the opening is in the center (median) of the abdominal wall, where the umbilical cord meets the abdomen.

Among the abdominal wall malformations, gastroschisis is a full-thickness defect of the abdominal wall, typically to the right of the umbilical cord, not including it. Through the open abdominal cavity, the small and large intestines protrude; there is no amnioperitoneal membrane covering the exposed organs.

During the ultrasound screening, the "double bubble" is a characteristic sign of duodenal atresia. The two "bubbles" are the distended stomach and dilated proximal duodenum.

Regarding anomalies of the abdominal wall and abdomen, the structural malformations associated with chromosome abnormalities are omphalocele and duodenal atresia. In cases with echogenic bowel—which is a marker and not necessarily abnormal in itself—the risk of trisomy 21 is higher [77–80]. The etiology of echogenic bowel could be other rare abnormalities (cystic fibrosis, atresia) in addition to the more frequent intrauterine infections [81].

5.1 Diaphragmatic hernia

Blancato et al. [82] demonstrated earlier (1992) by in situ hybridization the occurrence of tissue-specific mosaicism in some cases of diaphragmatic hernia. While during lymphocyte culturing there are no detectable anomalies (blood samples via cordocentesis or blood testing of the newborn), in cases of fibroblast samples (genetic amniocentesis and dermal biopsy), 12p isochromosome can be found. Donnenfeld et al. [83] carried out chromosome analysis in 15 cases of diaphragmatic hernia. In all cases they performed lymphocyte culturing (in 14 cases of fetal cordocentesis) in addition to the fibroblast tests. They found chromosome anomalies in seven cases (46.67%), of which there were three cases of trisomy 18, three cases of 12p mosaicism, and one case of other abnormality [83]. From the seven cases of anomalies, there were two with different results of the cells of different origins due to the mosaicism, and the 12p isochromosome was only detectable from the fibroblasts (amniocentesis and dermal biopsy) and not from the lymphocytes gained from the blood. In five cases, the examinations of the lymphocytes and the fibroblasts gave the same results (three cases of trisomy 18, one case of unbalanced translocation, and one case of 12p isochromosome). Huddy et al. studied 35 cases of diaphragmatic hernia, they examined the outcome of the pregnancy and the related abnormalities, and they found chromosome anomalies in 4 cases altogether (11.43%), of which 2 were trisomy 18 [84].

5.2 Omphalocele (exomphalos)

Many authors studied the abdominal malformations and the other anomalies associated with them. According to all data of the literature, the omphalocele (or exomphalos) is associated with chromosome abnormalities in high rates, mainly with trisomy 18, and in smaller proportion with trisomy 13.

Mann et al. in their study of obstetrical events associated with abdominal malformations reported 7 cases of chromosome abnormalities of 19 cases of omphalocele (36.84%) [85]. Rabe et al. processed the results of similar number of ultrasonographic screening during pregnancy, and in 17 omphalocele cases, they have found 6 chromosome anomalies (35.29%) [86]. Nicolaides et al. in 1986 with a smaller number of cases (8 chromosome abnormalities of 12 cases) [20] and later Gilbert and Nicolaides in 1987 with 19 chromosome anomalies of 35 cases demonstrated [87] that the omphalocele detected by ultrasonographic screening increases the risk of chromosome abnormalities.

Many other scientists verified the results of these studies. Nyberg et al. [88] demonstrated chromosome abnormalities in 10 of 26 cases (38.46%), Holzgreve et al. [89] in 5 of 10 cases (50%), Rizzo et al. [90] in 7 of 12 cases (58.33%), and Fogel et al. [91] in 5 of 37 cases. In their recent study with a higher number of cases, Nicolaides et al. detected abnormal karyotypes in 42 of 116 omphalocele cases (36.21%); 32 cases of these were trisomy 18 (27.59%) and in 7 cases trisomy 13 (6.03%) [92]. Snijders et al. [93] found in higher rate abnormal karyotype, mainly trisomy 18, in 12 of 18 cases (66.67%). The following studies demonstrated almost the same results, Dillon and Renwick [94] in 12 of 43 cases (27.91%), Axt et al. [95] in 7 of 26 cases (26.92%), and Rankin et al. [96] in 30 of 98 cases (30.61%), while Stoll et al. [97] have found abnormal karyotypes in 17 cases out of 58 cases (29.31%). The majority of the abnormal karyotypes were trisomy 18. Axt et al. found the risk of chromosome abnormalities four times higher when the liver was placed intracorporeally than when in the extracorporal placement [95]. Barisic et al. [98] processed the data of 19 European centers and described 34 abnormal karyotypes in total for 137 omphalocele cases (24.82%). Most of the chromosomal abnormalities were

trisomy 18 (21 cases, 15.33%); they described a lower rate of trisomy 13 (5 cases, 3.65%), one case of trisomy 21 and monosomy X, two cases of triploidy, and four cases of other chromosomal abnormalities. Salihu et al. [99] processed 29 cases, and 3 abnormal karyotypes were detected (10.34%); in all cases the liver was located intracorporeally.

In the study of Beke et al., out of 21 fetuses diagnosed with omphalocele, two cases (9.52%) were associated with different karyotypes, 1 case trisomy 18, and 1 case trisomy 13 [30].

5.3 Gastroschisis

Many investigators studied the gastroschisis cases in parallel with the omphalocele screenings, even though some of the studies were carried out with a smaller number of cases, so the results are not consistent. Rankin et al. found 1 case of chromosome abnormality in 133 gastroschisis cases (trisomy 13, 0.75%) [96]. Barisic et al. [98] also found abnormal karyotypes in 1.89% at a higher number of cases; they described chromosomal abnormalities in 2 out of the total 106 cases, of which 1 was trisomy 21 and the other was trisomy 13.

Other studies with a smaller number of cases did not indicate chromosome abnormalities; Mann et al. [85] studied 10 cases, Nicolaides et al. [20, 92] 3 and 26 cases, Dillon et al. [94] 56 cases, and Axt et al. [95] 18 cases, and they could not detect any abnormal karyotype. Stoll et al. [97] studied 47 cases of gastroschisis, while Salihu et al. [99] described 15 cases; in these cases there were no abnormal karyotypes detected.

Gastroschisis is often associated with other anomalies. Along with polyhydramnios, special attention should be paid to the ultrasound examination of the fetus. This was observed by Ozawa et al. [100] in a study involving the analysis of 52 fetuses. A quarter of them had trisomy (13 cases, 25%), particularly high rates of Edwards syndrome detected in 10 cases, while Patau syndrome in 2 cases and trisomy 21 in 1 case [100].

In contrast, Stoll et al. [101] diagnosed only one fetus with chromosome abnormality in the case of gastroschisis (trisomy 21) representing 1.16% of the patients studied. They also stated that the etiology of omphalocele and gastroschisis is unclear and their pathogenesis is controversial [101].

5.4 Duodenal atresia (duodenal obstruction)

The ultrasonographic mark of the duodenal obstruction is the "double bubble." The disease is not always detected intrauterine; therefore some investigators involved the subsequently proven, postnatal cases to their study. Studies demonstrated that it mainly increases the risk of trisomy 21. Nicolaides et al. studied 23 cases and found chromosome abnormalities in 10 cases (43.48%) [92]. Bailey et al. detected 15 cases of chromosome anomalies of the 138 cases (trisomy 21) (10.87%) [102]. This rate at Heydanus et al. was 7 abnormal karyotypes out of 29 cases (24.14%), 6 of which were trisomy 21 [103]. Lawrence et al. found 11 cases of chromosome anomalies of also 29 cases (37.93%), in 8 cases trisomy 21 [104]. Beke et al. found abnormalities in 2 out of 17 studied cases (11.76%), including a trisomy 21 [30].

5.5 Echogenic bowel

It is controversial in international literature whether the karyotyping is justified in cases of echogenic bowel. Nyberg et al. was the first to draw the attention to

the echogenic bowel increasing mainly the risk of trisomy 21 [105]. Subsequently Scioscia et al. reported 6 cases of chromosome abnormalities of 22 chromosome analyses associated with echogenic bowel (27.27%); in 5 cases trisomy 21 and in 1 case trisomy 18 were found [79]. Bromley et al. carried out 50 karyotyping associated with echogenic bowel and detected abnormal chromosomes in eight cases (16%), six cases of trisomy 21, one case of trisomy 13, and one case of monosomy X [77]. Sipes et al. studied seven cases and detected one case (14.3%) of trisomy 18 [81].

There were two greater studies fully investigating the expectable risk in association with echogenic bowel.

Slotnick and Abuhamad [106] separately screened the different measures of echogenity in their study published in Lancet, classifying them this way: grade1, mild increase of echogenity; grade2, moderate increase; and grade3, pronounced increase. They carried out altogether 145 karyotyping because of echogenic bowel and found abnormal karyotypes (all trisomy 21) in eight cases (5.5%). There were 6 cases of trisomy 21 of the 24 grade3 cases (25%), 2 positive cases of the 81 grade2 cases (2.47%), and no chromosome abnormalities of the 40 cases of grade1. They also studied the incidence of cystic fibrosis, they found 5 cases at grade3 and 2 cases at grade2, and they did not detect any cystic fibrosis at grade1 [106].

Strocker et al. [80] studied those cases separately, where the increasing bowel echogenity was associated with other malformations. They detected abnormal karyotypes in 15 cases of altogether 131 cases (11.45%). In 62 cases, the echogenic bowel was not associated with other positive ultrasonographic findings; in this group, there were 5 chromosome anomalies found, in 4 cases trisomy 21 (6.45%) and 47, XXY karyotype in 1 case. In the other group, there were 69 cases associated with other ultrasonographic findings; 10 of these cases carried chromosome abnormalities, 8 cases trisomy 21 (11.59), 1 case triploidy, and 1 case deletion X [80].

According to the observation of Beke et al., chromosome abnormalities were detected in only 3 out of 53 cases (5.66%), when the ultrasound image of the echogenic bowel was not isolated but associated with other defects [30].

5.6 Other abdominal malformations

Nicolaides et al. [92] also examined other abdominal malformations. In his study there were 24 cases of karyotyping due to lack of a visible stomach, and he found an abnormal karyotype in 18 cases (75%). In other 24 cases of chromosome analyses due to intestinal dilatation, there was 1 with abnormality (4.17%) [92].

6. Pyelectasis

Pyelectasis is the dilatation of only the renal pelvis and the calyces, in milder cases, while when the parenchyma is also affected by the longer lasting compression (becoming thinner), hydronephrosis develops. Obstructions of the urinary tract usually result in the dilatation of the proximal sections. Obstruction of the ureteropelvic junction is the main cause of hydronephrosis in the neonates.

According to some authors, an increase in the size of the renal pelvis elevates the risk of aneuploidies (mainly trisomy 21) [107–110]. We measure the renal pelvis in a horizontal section in the anteroposterior (AP) direction. We define renal pelvis dilatation (pyelectasis) as a pelvis with an AP dimension ≥5 mm. Hydronephrosis (a renal pelvis ≥10 mm) and enlarged, echogenic kidneys increase the risk of trisomy 13.

Benacerraf et al. [107] studied 210 cases of fetuses with pyelectasis. They found trisomy 21 in 7 of the 210 cases (3.33%). The suggested criteria for pyelectasis were the following cutoff values, ≥4 mm until week 20 and ≥5 mm in weeks 21–30, and after week 30 the limit should be ≥7 mm [107]. Corteville et al. studied 127 cases and detected chromosome abnormalities in 7 cases (5.51%), 4 of these were trisomy 21 (3.15%) [109]. They suggested that until week 33 the cutoff value should be ≥4 mm; after week 33 this limit would be ≥7 mm. Under comparable conditions (121 cases, similar cutoff values), Wickstrom et al. found chromosome anomalies in three cases (2.48%), two of which were trisomy 21 (1.65%) [111].

Nicolaides et al. reported in their study 35 abnormal karyotypes that are found in cases of 258 fetuses with pyelectasis (13.57%) [92]. Their recommended cutoff value was ≥5 mm as a criteria for pyelectasis. Chudleigh et al. carried out chromosome analysis using 5 mm cutoff value in 737 cases of fetal pyelectasis. Studying the results of the karyotyping, they found abnormal chromosomes in 12 cases (1.63%), and 6 of these were trisomy 21 (0.81%) [108]. Besides less number of cases, other scientists did not verify the higher rate of chromosome anomalies. Gonen et al. found no abnormal karyotypes in 58 cases of fetal pyelectasis [8].

Beke et al. [30] processed 302 cases, of which 7 (2.32%) were found to have abnormalities. Of these, 1-1 cases of trisomy 21 and trisomy 18, two cases of monosomy X, and three cases of other chromosome abnormalities were found [30].

According to the findings of a 2006 study, contrary to previous opinions that male fetuses had a higher rate of chromosome abnormalities associated with pyelectasis, they refuted this. According to this new article by Bronstein et al. [112], there is no significant difference between the sexes in the karyotype associated with the anatomical disorder. When investigating 672 cases, 35 (5.21%) cases of abnormal karyotype occurred [112].

Based on Coco's and Jeanty [113]'s findings, pyelectasis alone does not justify an amniocentesis if it is not associated with anatomical and other abnormalities. However, 3.01% of their cases were associated with chromosome abnormalities as well [113].

7. Abnormalities of the extremities

Measuring the length of fetal femur and more recently the humerus is part of the biometric test. Following the limbs of the fetus, the joints, the hands, and the feet and their deviations can be brought into the field of vision. Limb disorders may appear independently or as part of syndromes, causing extensive ossification anomalies. Most disorders can be rarely recognized prenatally.

7.1 Short femur and humerus

On the basis of several studies of cases with shortened long bones (femur and humerus), the incidence rate for the abnormal karyotypes is elevated. According to the literature, a shortened humerus is a more sensitive indicator. Mainly the risk of trisomy 21 increases [114–117].

Studying the long bones, the main ambition of the investigators was to determine the proper method to estimate the measure of the retardation in growth, which increases the risk of chromosome abnormalities. The two main methods are fundamentally different. Some investigators calculate with the observed/expected ratio (O/E ratio) and determine the proper cutoff value by expressing the quotient in percentile (≤0.91) [8, 115]. Other scientists calculate on the basis of the quotient of biparietal diameter (BPD) and femur length (FL) (BPD/FL) and consider abnormal the measure of >1.5 SD [114]. Calculating with both methods, most

investigators found significant differences between the fetal groups of normal chromosomes and those with chromosome abnormalities. According to some authors, the difference was not significant [118, 119].

Nyberg et al. [115] examined separately the parameters (O/E ratio) in the case of the humerus and femur and suggested the following cutoff values: humerus ≤0.89 and femur ≤0.91. If both the femur and the humerus are shortened according to the given cutoff values, the risk of trisomy 21 increased 11-fold [115].

Recent studies include both methods. In their report Snijders et al. draw the attention to the fact that although they found significant differences using both methods (O/E ratio, BPD/FL) between fetal groups of normal karyotype and trisomy 21, the screenings before week 18 of gestation are less suitable to predict trisomy 21 [116]. Vergani et al. [117] did not find a significant difference between measuring the O/E ratio and using the BPD/FL method; the difference reached the significance limit ($p = 0.04$). According to their report, the measurement of femur length is connected with the population, and each center should determine the cutoff values dependent on the population on their own [117].

According to a study, chromosome abnormalities occurred in 16% in cases of shortened tubular (long) bones, including 8% of trisomy 18 and 4-4% of monosomy X and trisomy 21 [30].

A Danish publication processed the data of 2718 fetuses detected with shortened femur between the gestational weeks of 17–22, of which 2.5% had chromosome abnormalities. In 11 cases, trisomy 21, in 3 cases trisomy 13, and in 8 cases trisomy 18 were found. Chromosome abnormalities were associated with a higher proportion of these anatomical disorders in the second trimester than the first trimester [120].

7.2 Other abnormalities of the extremities

Other malformations of the extremities increase the risk of trisomy 21 (clinodactyly, widened pelvic angle, sandal gap), trisomy 13 (postaxial polydactyly, clubbed or rocker-bottom feet), and trisomy 18 (clenched hands, overlapping digits, radial aplasia, limb shortening, clubbed feet) [48].

8. Conclusions

Ultrasound examinations play an important role during pregnancy, by drawing the attention to the suspect of a possible abnormality. The prenatal screening of minor ultrasound signs and major ultrasound anomalies and diagnostics is a very important part of the health service. The intrauterine screening and diagnostic methods, the ultrasound screening during the pregnancy, and the cytogenetic and molecular genetic examinations in the genetic centers made the early, intrauterine diagnosis of the chromosomal abnormalities possible.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Artúr Beke* and Aténé Simonyi
Department of Obstetrics and Gynaecology, Semmelweis University, Budapest, Hungary

*Address all correspondence to: beke.artur@med.semmelweis-univ.hu

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References

[1] Beke A. Ultrasound markers which indicate chromosome analysis. Ultrasound in Obstetrics & Gynecology. 2003;**3**:259-272

[2] Borrell A, Costa D, Martinez JM, Delgado RD, Casals E, Ojuel J, et al. Early midtrimester fetal nuchal thickness: Effectiveness as a marker of down syndrome. American Journal of Obstetrics and Gynecology. 1996;**175**:45-49

[3] Gray DL, Crane JP. Optimal nuchal skin-fold thresholds based on gestational age for prenatal detection of Down syndrome. American Journal of Obstetrics and Gynecology. 1994;**171**:1282-1286

[4] Benacerraf BR, Frigoletto FDJr, Laboda LA. Sonographic diagnosis of down syndrome in the second trimester. American Journal of Obstetrics and Gynecology. 1985;**153**:49-52

[5] Crane JP, Gray DL. Sonographically measured nuchal skinfold thickness as a screening tool for Down syndrome: Results of a prospective clinical trial. Obstetrics and Gynecology. 1991;**77**:533-536

[6] DeVore GR, Alfi O. The association between an abnormal nuchal skin fold, trisomy 21, and ultrasound abnormalities identified during the second trimester of pregnancy. Ultrasound in Obstetrics & Gynecology. 1993;**3**:387-394

[7] Grandjean H, Sarramon MF. Sonographic measurement of nuchal skinfold thickness for detection of Down syndrome in the second-trimester fetus: A multicenter prospective study. The AFDPHE study group. Association Francaise pour le Depistage et la prevention des Handicaps de l'Enfant. Obstet. Gynécologie. 1995;**85**:103-106

[8] Gonen R, Dar H, Degani S. The karyotype of fetuses with anomalies detected by second trimester ultrasonography. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 1995;**58**:153-155

[9] Zimmer EZ, Drugan A, Ofir C, Blazer S, Bronshtein M. Ultrasound imaging of fetal neck anomalies: Implications for the risk of aneuploidy and structural anomalies. Prenatal Diagnosis. 1997;**17**:1055-1058

[10] Beke A, Joo JG, Csaba A, Lazar L, Ban Z, Papp C, et al. Incidence of chromosomal abnormalities in presence of fetal subcutaneous oedema, nuchal oedema, cystic hygroma and non-immune hydrops. Fetal Diagnosis and Therapy. 2009;**25**:83-92

[11] Azar GB, Snijders RJ, Gosden C, Nicolaides KH. Fetal nuchal cystic hygromata: Associated malformations and chromosomal defects. Fetal Diagnosis and Therapy. 1991;**6**:46-57

[12] Bronshtein M, Bar-Hava I, Blumenfeld I, Bejar J, Toder V, Blumenfeld Z. The difference between septated and nonseptated nuchal cystic hygroma in the early second trimester. Obstetrics and Gynecology. 1993;**81**:683-687

[13] Nadel A, Bromley B, Benacerraf BR. Nuchal thickening or cystic hygromas in first- and early second-trimester fetuses: Prognosis and outcome. Obstetrics and Gynecology. 1993;**82**:43-48

[14] Sohn C, Gast AS. Hygroma colli (cervical neck edema) as an ultrasonographic parameter of fetal chromosome anomalies. Zentralblatt für Gynäkologie. 1997;**119**:232-236

[15] Taipale P, Hiilesmaa V, Salonen R, Ylostalo P. Increased nuchal

translucency as a marker for fetal chromosomal defects. The New England Journal of Medicine. 1997;**337**:1654-1658

[16] Rosati P, Guariglia L. Prognostic value of ultrasound findings of fetal cystic hygroma detected in early pregnancy by transvaginal sonography. Ultrasound in Obstetrics & Gynecology. 2000;**16**:245-250

[17] Tanriverdi HA, Hendrik HJ, Ertan AK, Axt R, Schmidt W. Hygroma colli cysticum: Prenatal diagnosis and prognosis. American Journal of Perinatology. 2001;**18**:415-420

[18] Donnenfeld AE, Lockwood D, Lamb AN. Prenatal diagnosis from cystic hygroma fluid: The value of fluorescence in situ hybridization. American Journal of Obstetrics and Gynecology. 2001;**185**:1004-1008

[19] Gezer C, Ekin A, Gezer NS, Ertas IE, Avci ME, Uyar I, et al. Prenatal karyotype results of fetuses with nuchal edema, cystic hygroma, and non-immune hydrops. Clinical and Experimental Obstetrics & Gynecology. 2015;**42**:586-589

[20] Nicolaides KH, Rodeck CH, Gosden CM. Rapid karyotyping in non-lethal fetal malformations. Lancet. 1986;**1**:283-287

[21] Gembruch U, Hansmann M, Bald R, Zerres K, Schwanitz G, Fodisch HJ. Prenatal diagnosis and management in fetuses with cystic hygromata colli. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 1988;**29**:241-255

[22] Boyd PA, Keeling JW. Fetal hydrops. Journal of Medical Genetics. 1992;**29**:91-97

[23] Anandakumar C, Biswas A, Wong YC, Chia D, Annapoorna V, Arulkumaran S, et al. Management of non-immune hydrops: 8 years' experience. Ultrasound in Obstetrics & Gynecology. 1996;**8**:196-200

[24] Schwanitz G, Zerres K, Gembruch U, Bald R, Hansmann M. Rate of chromosomal aberrations in prenatally detected hydrops fetalis and hygroma colli. Human Genetics. 1989;**84**:81-82

[25] Has R. Non-immune hydrops fetalis in the first trimester: A review of 30 cases. Clinical and Experimental Obstetrics & Gynecology. 2001;**28**:187-190

[26] Patel MD, Goldstein RB, Tung S, Filly RA. Fetal cerebral ventricular atrium: Difference in size according to sex. Radiology. 1995;**194**:713-715

[27] Bromley B, Frigoletto FDJr, Benacerraf BR. Mild fetal lateral cerebral ventriculomegaly: Clinical course and outcome. American Journal of Obstetrics and Gynecology. 1991;**164**:863-867

[28] Mahony BS, Nyberg DA, Hirsch JH, Petty CN, Hendricks SK, Mack LA. Mild idiopathic lateral cerebral ventricular dilatation in utero: Sonographic evaluation. Radiology. 1988;**169**:715-721

[29] Terry M, Calhoun BC, Walker W, Apodaca C, Martin L, Pierce B, et al. Aneuploidy and isolated mild ventriculomegaly. Attributable risk for isolated fetal marker. Fetal Diagnosis and Therapy. 2000;**15**:331-334

[30] Beke A, Papp C, Toth-Pal E, Mezei G, Oroszné NJ, Joo JG, et al. Trisomies and other chromosome abnormalities detected following positive sonographic findings. The Journal of Reproductive Medicine. 2005;**50**:675-691

[31] Ogle RF. Second trimester markers of aneuploidy. Baillière's Best Practice & Research. Clinical Obstetrics & Gynaecology. 2000;**14**:595-610

[32] Snijders RJ, Shawa L, Nicolaides KH. Fetal choroid plexus cysts and trisomy 18: Assessment of risk based on ultrasound findings and maternal age. Prenatal Diagnosis. 1994;**14**:1119-1127

[33] Walkinshaw S, Pilling D, Spriggs A. Isolated choroid plexus cysts—The need for routine offer of karyotyping. Prenatal Diagnosis. 1994;**14**:663-667

[34] Gray DL, Winborn RC, Suessen TL, Crane JP. Is genetic amniocentesis warranted when isolated choroid plexus cysts are found? Prenatal Diagnosis. 1996;**16**:983-990

[35] Turner SR, Samei E, Hertzberg BS, DeLong DM, Vargas-Voracek R, Singer A, et al. Sonography of fetal choroid plexus cysts: Detection depends on cyst size and gestational age. Journal of Ultrasound in Medicine. 2003;**22**:1219-1227

[36] Walkinshaw S. Fetal choroid plexus cysts: Are we there yet? Prenatal Diagnosis. 2000;**20**:657-662

[37] Chudleigh P, Pearce M, Campbell S. The prenatal diagnosis of transient cysts of the fetal choroid plexus. Prenatal Diagnosis. 1984;**4**:135-137

[38] Achiron R, Barkai G, Katznelson MB, Mashiach S. Fetal lateral ventricle choroid plexus cysts: The dilemma of amniocentesis. Obstetrics and Gynecology. 1991;**78**:815-818

[39] Platt LD, Carlson DE, Medearis AL, Walla CA. Fetal choroid plexus cysts in the second trimester of pregnancy: A cause for concern. American Journal of Obstetrics and Gynecology. 1991;**164**:1652-1655

[40] Nadel AS, Bromley BS, Frigoletto FD Jr, Estroff JA, Benacerraf BR. Isolated choroid plexus cysts in the second-trimester fetus: Is amniocentesis really indicated? Radiology. 1992;**185**:545-548

[41] Nava S, Godmilow L, Reeser S, LudomirskyA,DonnenfeldAE.Significance of sonographically detected second-trimester choroid plexus cysts: A series of 211 cases and a review of the literature. Ultrasound in Obstetrics & Gynecology. 1994;**4**:448-451

[42] Bakos O, Moen KS, Hansson S. Prenatal karyotyping of choroid plexus cysts. European Journal of Ultrasound. 1998;**8**:79-83

[43] Chitty LS, Chudleigh P, Wright E, Campbell S, Pembrey M. The significance of choroid plexus cysts in an unselected population: Results of a multicenter study. Ultrasound in Obstetrics & Gynecology. 1998;**12**:391-397

[44] Ghidini A, Strobelt N, Locatelli A, Mariani E, Piccoli MG, Vergani P. Isolated fetal choroid plexus cysts: Role of ultrasonography in establishment of the risk of trisomy 18. American Journal of Obstetrics and Gynecology. 2000;**182**:972-977

[45] Coco C, Jeanty P. Karyotyping of fetuses with isolated choroid plexus cysts is not justified in an unselected population. Journal of Ultrasound in Medicine. 2004;**23**:899-906

[46] Sahinoglu Z, Uludogan M, Sayar C, Turkover B, Toksoy G. Second trimester choroid plexus cysts and trisomy 18. International Journal of Gynaecology and Obstetrics. 2004;**85**:24-29

[47] Beke A, Barakonyi E, Belics Z, Joó JG, Csaba A, Papp C, et al. The risk of chromosome abnormalities in presence of bilateral or unilateral choroid plexus cysts (CPC). Fetal Diagnosis and Therapy. 2008;**23**:185-191

[48] Nyberg DA, Souter VL. Sonographic markers of fetal aneuploidy. Clinincs in Perinatology. 2000;**27**:761-789

[49] Hill LM. The sonographic detection of trisomies 13, 18, and 21. Clinical Obstetrics and Gynecology. 1996;**39**:831-850

[50] Benacerraf BR, Frigoletto FDJr, Bieber FR. The fetal face: Ultrasound examination. Radiology. 1984;**153**:495-497

[51] Parant O, Sarramon MF, Delisle MB, Fournie A. Prenatal diagnosis of holoprosencephaly. A series of twelve cases. Journal de Gynécologie, Obstétrique et Biologie de la Reproduction. 1997;**26**:687-696

[52] Tongsong T, Wanapirak C, Sirichotiyakul S, Siriangkul S. Prenatal sonographic diagnosis of holoprosencephaly. Journal of the Medical Association of Thailand. 1998;**81**:208-213

[53] Bullen PJ, Rankin JM, Robson SC. Investigation of the epidemiology and prenatal diagnosis of holoprosencephaly in the north of England. American Journal of Obstetrics and Gynecology. 2001;**184**:1256-1262

[54] Moog U, De Die-SmuldersCE,Schrander-StumpelCT, Engelen JJ, Hamers AJ, Frints S, et al. Holoprosencephaly: The Maastricht experience. Genetic Counseling. 2001;**12**:287-298

[55] Perrotin F, de Poncheville LM, Marret H, Paillet C, Lansac J, Body G. Chromosomal defects and associated malformations in fetal cleft lip with or without cleft palate. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2001;**99**:19-24

[56] Aletebi FA, Fung KFK. Neurodevelopmental outcome after antenatal diagnosis of posterior fossa abnormalities. Journal of Ultrasound in Medicine. 1999;**18**:683-689

[57] Nazer Herrera J, Cifuentes Ovalle L, Cortez López A. Frequency of holoprosencephaly in Chile. Revista Médica de Chile. 2015;**143**:874-879

[58] Hayashi Y, Suzumori N, Sugiura T, Sugiura-Ogasawara M. Prenatal findings of holoprosencephaly. Congenital Anomalies. 2015;**55**:161-163

[59] Levy DW, Mintz MC. The left ventricular echogenic focus: A normal finding. American Journal of Roentgenology. 1988;**150**:85-86

[60] Shipp TD, Bromley B, Lieberman E, Benacerraf BR. The frequency of the detection of fetal echogenic intracardiac foci with respect to maternal race. Ultrasound in Obstetrics & Gynecology. 2000;**15**:460-462

[61] Bromley B, Lieberman E, Laboda L, Benacerraf BR. Echogenic intracardiac focus: A sonographic sign for fetal Down syndrome. Obstetrics and Gynecology. 1995;**86**:998-1001

[62] Bromley B, Lieberman E, Shipp TD, Richardson M, Benacerraf BR. Significance of an echogenic intracardiac focus in fetuses at high and low risk for aneuploidy. Journal of Ultrasound in Medicine. 1998;**17**:127-131

[63] Huggon IC, Cook AC, Simpson JM, Smeeton NC, Sharland GK. Isolated echogenic foci in the fetal heart as marker of chromosomal abnormality. Ultrasound in Obstetrics & Gynecology. 2001;**17**:11-16

[64] Sepulveda W, Cullen S, Nicolaidis P, Hollingsworth J, Fisk NM. Echogenic foci in the fetal heart: A marker of chromosomal abnormality. British Journal of Obstetrics and Gynaecology. 1995;**102**:490-492

[65] Winter TC, Anderson AM, Cheng EY, Komarniski CA, Souter VL, Uhrich SB, et al. Echogenic intracardiac focus in 2nd-trimester fetuses with trisomy 21: Usefulness as a US marker. Radiology. 2000;**216**:450-456

[66] Lehman CD, Nyberg DA, Winter TC 3rd, Kapur RP, Resta RG, Luthy DA. Trisomy 13 syndrome: Prenatal US findings in a review of 33 cases. Radiology. 1995;**194**:217-222

[67] Hajdu J, Marton T, Cs P, Cesko I, Oroszne NJ, Papp Z. Prenatal diagnosis of atrioventricular septal defect and its prognostic significance. Orvosi Hetilap. 1998;**139**:23-26

[68] Tennstedt C, Chaoui R, Korner H, Dietel M. Spectrum of congenital heart defects and extracardiac malformations associated with chromosomal abnormalities: Results of a seven year necropsy study. Heart. 1999;**82**:34-39

[69] Delisle MF, Sandor GG, Tessier F, Farquharson DF. Outcome of fetuses diagnosed with atrioventricular septal defect. Obstetrics and Gynecology. 1999;**94**:763-767

[70] Paladini D, Russo M, Teodoro A, Pacileo G, Capozzi G, Martinelli P, et al. Prenatal diagnosis of congenital heart disease in the Naples area during the years 1994-1999—The experience of a joint fetal-pediatric cardiology unit. Prenatal Diagnosis. 2002;**22**:545-552

[71] Hajdu J, Beke A, Pete B, Oroszne NJ, Papp Z. Prenatal diagnosis of the atrioventricular septal defect and it's effect on the outcome of the pregnancies. Orvosi Hetilap. 2005;**146**(34):1775-1780

[72] Bendriss L, Sedrati M, Haddour L, Arharbi M. Ventricular septal defects: Anatomic, clinical, therapeutic and prognostic aspects. 44 cases. Presse Médicale. 2006;**35**(4 Pt 1):593-597

[73] Zhong P, Gu Y, Wang A, Sun X, Wang Y, Zhang X, et al. Complete atrioventricular septal defect: A clinicopathologic study of 35 cases. Zhonghua Bing Li Xue Za Zhi. 2016;**45**:107-110

[74] Shuhaiber JH, Robinson B, Gauvreau K, Breitbart R, Mayer JE, Del Nido PJ, et al. Outcome after repair of atrioventricular septal defect with tetralogy of Fallot. The Journal of Thoracic and Cardiovascular Surgery. 2012;**143**:338-343

[75] Paladini D, Tartaglione A, Agangi A, Teodoro A, Forleo F, Borghese A, et al. The association between congenital heart disease and down syndrome in prenatal life. Ultrasound in Obstetrics & Gynecology. 2000;**15**:104-108

[76] Estoff JA, Parad RB, Frigoletto FD Jr, Benacerraf R. The natural history of isolated fetal hydrothorax. Ultrasound in Obstetrics & Gynecology. 1992;**2**:162-165

[77] Bromley B, Doubilet P, Frigoletto FD Jr, Krauss C, Estroff JA, Benacerraf BR. Is fetal hyperechoic bowel on second-trimester sonogram an indication for amniocentesis? Obstetrics and Gynecology. 1994;**83**:647-651

[78] Nyberg DA, Dubinsky T, Resta RG, Mahony BS, Hickok DE, Luthy DA. Echogenic fetal bowel during the second trimester: Clinical importance. Radiology. 1993;**188**:527-531

[79] Scioscia AL, Pretorius DH, Budorick NE, Cahill TC, Axelrod FT, Leopold GR. Second-trimester echogenic bowel and chromosomal abnormalities. American Journal of Obstetrics and Gynecology. 1992;**167**:889-894

[80] Strocker AM, Snijders RJ, Carlson DE, Greene N, Gregory KD, Walla CA, et al. Fetal echogenic bowel:

Parameters to be considered in differential diagnosis. Ultrasound in Obstetrics & Gynecology. 2000;**16**:519-523

[81] Sipes SL, Weiner CP, Wenstrom KD, Williamson RA, Grant SS, Mueller GM. Fetal echogenic bowel on ultrasound: Is there clinical significance? Fetal Diagnosis and Therapy. 1994;**9**:38-43

[82] Blancato JK, Hunt M, George J, Katz J, Meck JM. Prenatal diagnosis of tetrasomy 12p by in situ hybridization: Varying levels of mosaicism in different fetal tissues. Prenatal Diagnosis. 1992;**12**:979-983

[83] Donnenfeld AE, Campbell TJ, Byers J, Librizzi RJ, Weiner S. Tissue-specific mosaicism among fetuses with prenatally diagnosed diaphragmatic hernia. American Journal of Obstetrics and Gynecology. 1993;**169**:1017-1021

[84] Huddy CL, Boyd PA, Wilkinson AR, Chamberlain P. Congenital diaphragmatic hernia: Prenatal diagnosis, outcome and continuing morbidity in survivors. British Journal of Obstetrics and Gynaecology. 1999;**106**:1192-1196

[85] Mann L, Ferguson-Smith MA, Desai M, Gibson AA, Raine PA. Prenatal assessment of anterior abdominal wall defects and their prognosis. Prenatal Diagnosis. 1984;**4**:427-435

[86] Rabe D, Hendrik HJ, Leucht W, Roth H, Walter C, Schmidt W. Ventral abdominal wall defects—Antenatal diagnosis, course of pregnancy and post partum therapy. Geburtshilfe und Frauenheilkunde. 1985;**45**:176-182

[87] Gilbert WM, Nicolaides KH. Fetal omphalocele: Associated malformations and chromosomal defects. Obstetrics and Gynecology. 1987;**70**:633-635

[88] Nyberg DA, Fitzsimmons J, Mack LA, Hughes M, Pretorius DH, Hickok D, et al. Chromosomal abnormalities in fetuses with omphalocele. Significance of omphalocele contents. Journal of Ultrasound in Medicine. 1989;**8**:299-308

[89] Holzgreve W, Miny P, Gerlach B, Westendorp A, Ahlert D, Horst J. Benefits of placental biopsies for rapid karyotyping in the second and third trimesters (late chorionic villus sampling) in high-risk pregnancies. American Journal of Obstetrics and Gynecology. 1990;**162**:1188-1192

[90] Rizzo N, Pittalis MC, Pilu G, Orsini LF, Perolo A, Bovicelli L. Prenatal karyotyping in malformed foetuses. Prenatal Diagnosis. 1990;**10**:17-23

[91] Fogel M, Copel JA, Cullen MT, Hobbins JC, Kleinman CS. Congenital heart disease and fetal thoracoabdominal anomalies: Associations in utero and the importance of cytogenetic analysis. American Journal of Perinatology. 1991;**8**:411-416

[92] Nicolaides KH, Snijders RJ, Cheng HH, Gosden C. Fetal gastro-intestinal and abdominal wall defects: Associated malformations and chromosomal abnormalities. Fetal Diagnosis and Therapy. 1992;**7**:102-115

[93] Snijders RJ, Brizot ML, Faria M, Nicolaides KH. Fetal exomphalos at 11 to 14 weeks of gestation. Journal of Ultrasound in Medicine. 1995;**14**:569-574

[94] Dillon E, Renwick M. The antenatal diagnosis and management of abdominal wall defects: The northern region experience. Clinical Radiology. 1995;**50**:855-859

[95] Axt R, Quijano F, Boos R, Hendrik HJ, Jessberger HJ, Schwaiger C, et al. Omphalocele and gastroschisis: Prenatal diagnosis and peripartal management. A case analysis of the years 1989-1997 at the Department of

Obstetrics and Gynecology, University of Homburg/Saar. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 1999;**87**:47-54

[96] Rankin J, Dillon E, Wright C. Congenital anterior abdominal wall defects in the north of England, 1986-1996: Occurrence and outcome. Prenatal Diagnosis. 1999;**19**:662-668

[97] Stoll C, Alembik Y, Dott B, Roth MP. Risk factors in congenital abdominal wall defects (omphalocele and gastroschisis): A study in a series of 265,858 consecutive births. Annales de Génétique. 2001;**44**:201-208

[98] Barisic I, Clementi M, Hausler M, Gjergja R, Kern J, Stoll C, et al., Euroscan Study Group. Evaluation of prenatal ultrasound diagnosis of fetal abdominal wall defects by 19 European registries. Ultrasound in Obstetrics & Gynecology. 2001;**18**:309-316

[99] Salihu HM, Boos R, Schmidt W. Omphalocele and gastrochisis. Journal of Obstetrics and Gynaecology. 2002;**22**:489-492

[100] Ozawa K, Ishikawa H, Maruyama Y, Nagata T, Nagase H, Itani Y, et al. Congenital omphalocele and polyhydramnios: A study of 52 cases. Fetal Diagnosis and Therapy. 2011;**30**:184-188

[101] Stoll C, Alembik Y, Dott B, Roth MP. Omphalocele and gastroschisis and associated malformations. American Journal of Medical Genetics. Part A. 2008;**146A**:1280-1285

[102] Bailey PV, Tracy TFJr, Connors RH, Mooney DP, Lewis JE, Weber TR. Congenital duodenal obstruction: A 32-year review. Journal of Pediatric Surgery. 1993;**28**:92-95

[103] Heydanus R, Spaargaren MC, Wladimiroff JW. Prenatal ultrasonic diagnosis of obstructive bowel disease: A retrospective analysis. Prenatal Diagnosis. 1994;**14**:1035-1041

[104] Lawrence MJ, Ford WD, Furness ME, Hayward T, Wilson T. Congenital duodenal obstruction: Early antenatal ultrasound diagnosis. Pediatric Surgery International. 2000;**16**:342-345

[105] Nyberg DA, Resta RG, Luthy DA, Hickok DE, Mahony BS, Hirsch JH. Prenatal sonographic findings of down syndrome, review of 94 cases. Obstetrics and Gynecology. 1990;**76**:370-377

[106] Slotnick RN, Abuhamad AZ. Prognostic implications of fetal echogenic bowel. Lancet. 1996;**347**:85-87

[107] Benacerraf BR, Mandell J, Estroff JA, Harlow BL, Frigoletto FD. Fetal pyelectasis: A possible association with Down syndrome. Obstetrics and Gynecology. 1990;**76**:58-60

[108] Chudleigh PM, Chitty L, Pembrey M, Campbell S. The association of aneuploidy and mild fetal pyelectasis in an unselected population: The results of a multicenter study. Ultrasound in Obstetrics & Gynecology. 2001;**17**:197-202

[109] Corteville JE, Dicke JM, Crane JP. Fetal pyelectasis and down syndrome: Is genetic amniocentesis warranted? Obstetrics and Gynecology. 1992;**79**:770-772

[110] Wilson RD, Lynch S, Lessoway VA. Fetal pyelectasis: Comparison of postnatal renal pathology with unilateral and bilateral pyelectasis. Prenatal Diagnosis. 1997;**17**:451-455

[111] Wickstrom E, Maizels M, Sabbagha RE, Tamura RK, Cohen LC, Pergament E. Isolated fetal pyelectasis:

Assessment of risk for postnatal uropathy and down syndrome. Ultrasound in Obstetrics & Gynecology. 1996;**8**:236-240

[112] Bronstein E, Barnhard Y, Donnenfeld A, Ferber A, Divon MY. Fetal pyelectasis: Does fetal gender modify the risk of major trisomies? Obstetrics and Gynecology. 2006;**107**:877-879

[113] Coco C, Jeanty P. Isolated fetal pyelectasis and chromosomal abnormalities. American Journal of Obstetrics and Gynecology. 2005;**93**:732-738

[114] Johnson MP, Michaelson JE, Barr M Jr, Treadwell MC, Hume RF Jr, Dombrowski MP, et al. Combining humerus and femur length for improved ultrasonographic identification of pregnancies at increased risk for trisomy 21. American Journal of Obstetrics and Gynecology. 1995;**172**:1229-1235

[115] Nyberg DA, Resta RG, Luthy DA, Hickok DE, Williams MA. Humerus and femur length shortening in the detection of Down's syndrome. American Journal of Obstetrics and Gynecology. 1993;**168**:534-538

[116] Snijders RJ, Platt LD, Greene N, Carlson D, Krakow D, Gregory K, et al. Femur length and trisomy 21: Impact of gestational age on screening efficiency. Ultrasound in Obstetrics & Gynecology. 2000;**16**:142-145

[117] Vergani P, Locatelli A, Piccoli MG, Mariani E, Strobelt N, Pezzullo JC, et al. Critical reappraisal of the utility of sonographic fetal femur length in the prediction of trisomy 21. Prenatal Diagnosis. 2000;**20**:210-214

[118] Perrella R, Duerinckx AJ, Grant EG, Tessler F, Tabsh K, Crandall BF. Second-trimester sonographic diagnosis of down syndrome: Role of femur-length shortening and nuchal-fold thickening. AJR. American Journal of Roentgenology. 1988;**151**:981-985

[119] LaFollette L, Filly R, Anderson R, Golbus MS. Fetal femur length to detect trisomy 21. A reappraisal. Journal of Ultrasound in Medicine. 1989;**8**:657-660

[120] Mathiesen JM, Aksglaede L, Skibsted L, Petersen OB, Tabor A, Danish Fetal Medicine Study Group. Outcome of fetuses with short femur length detected at second-trimester anomaly scan: A national survey. Ultrasound in Obstetrics & Gynecology. 2014;**44**:160-165