

# Association between selected structural defects and chromosomal abnormalities

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## ABSTRACT

**Objective.** To determine the association between some major structural abnormalities detected prenatally by ultrasound and chromosomal abnormalities. **Material and methods.** The present study was a retrospective, transversal study. We analyzed case records of patients during the fetal follow-up at the Department of Maternal Fetal Medicine from January 1994 to May 2010 to identify fetal patients with a diagnosis of holoprosencephaly, diaphragmatic hernia, omphalocele, cystic hygroma, hydrops and cardiac defects. We analyzed patients who had a prenatal invasive diagnosis procedure to obtain the odds ratio (OR) for some major isolated anomalies and their different combinations with respect to chromosomal abnormalities. **Results.** We examined 280 patients with ultrasonographic markers for chromosomal alteration, 197 met inclusion criteria, from which 88 had chromosomal abnormalities. The most frequent diagnosis was trisomy 18 (31.8%), which was followed by trisomy 21 (21.6%), trisomy 13 (21.6%), Turner syndrome (monosomy X) (14.8%) and other chromosomal abnormalities (10.2%). Among the fetuses with nonisolated holoprosencephaly, we obtained an OR of 4.9 95% CI (0.99-24.2) for aneuploidy. Associated omphalocele had an OR of 7.63 95% CI (2.07-46.75),  $p < 0.01$ . Interestingly, 62% of aneuploidy cases had associated cardiac defects [OR = 7.7 95% CI (1.4-41.7)]. In addition, associated cystic hygroma had an OR of 2.5 95% CI (0.59-10.91). Heart defects were the most common defects in fetuses with trisomy 18 (57.1%), when they were associated with facial cleft, we had an OR of 11.08 95% CI (2.99-41.11),  $p < 0.0001$ . Statistical potency was calculated for each analyzed defect and it was over 80% for all of them but diaphragmatic hernia. **Conclusions.** The association of 2 or more structural defects increased the probability of a fetus to be a carrier of a chromosomal disorder; however this was not statistically significant except for associated omphalocele. Heart defects showed the greatest association with all chromosomal abnormalities. The most important

## Asociación entre defectos estructurales seleccionados y anomalías cromosómicas

## RESUMEN

**Objetivo.** Determinar la asociación entre algunos defectos estructurales mayores detectados prenatalmente por ultrasonido y anomalías cromosómicas. **Material y métodos.** El diseño del estudio fue transversal retrospectivo. Se analizaron expedientes de pacientes que tuvieron seguimiento en el Departamento de Medicina Fetal de enero de 1994 hasta mayo 2010 para identificar fetos con diagnósticos de holoprosencefalia, hernia diafragmática, hígroma quístico, hidrops y defectos cardíacos. Se analizaron los pacientes que contaban con un procedimiento de diagnóstico prenatal invasivo con la finalidad de obtener la razón de momios (OR) para algunos defectos mayores aislados y sus diferentes combinaciones con respecto a anomalías cromosómicas. **Resultados.** Se examinaron 280 casos con marcadores ultrasonográficos para cromosomopatía, 197 cumplieron los criterios de inclusión; de éstos, 88 tenían anomalías cromosómicas. El diagnóstico más frecuente fue trisomía 18 (31.8%), seguida por trisomía 21 (21.6%), trisomía 13 (21.6%), síndrome de Turner (monosomía del X) (14.8%) y otras anomalías cromosómicas (10.2%). Entre los fetos con holoprosencefalia asociada se obtuvo un OR de 4.9 95% IC (0.99-24.2) para aneuploidía. El omfalocele asociado tuvo un OR de 7.63 95% IC (2.07-46.75),  $p < 0.01$ . De manera interesante, 62% de los casos de aneuploidía estuvo asociado con defectos cardíacos [OR = 7.7 IC (1.4-41.7)]. Además, el hígroma quístico asociado tuvo un OR de 2.5 95% IC (0.59-10.91). El defecto más común en fetos con trisomía 18 fue la cardiopatía (57.1%), cuando éstos se asociaron con defecto facial se obtuvo un OR de 11.08 95% IC (2.99-41.11),  $p < 0.0001$ . Se calculó la potencia estadística para cada defecto analizado y fue mayor a 80% en todos ellos excepto para la hernia diafragmática. **Conclusiones.** La asociación de dos o más defectos estructurales incrementó la probabilidad de

association was among heart defect, facial cleft and trisomy 13.

**Key words.** Prenatal diagnosis. Fetal structural defects. Chromosomal abnormalities. Holoprosencephaly. Cystic hygroma. Hydrops. Heart defect. Diaphragmatic hernia.

## INTRODUCTION

Major birth defects occur in approximately 3-5% of live births worldwide. Outcomes depend on whether the defects are isolated or associated with additional structural defects and chromosomal abnormalities. These findings are quite diverse, and range from isolated defects that were repaired at birth, to associated defects that were incompatible with life or associated with high rates of disability and mortality.<sup>1</sup>

The vast majority of fetuses with chromosomal defects have abnormalities that may be recognized in a detailed ultrasound examination.<sup>1</sup>

The aneuploidies of greater significance in newborns are trisomy 13, 18 and 21. Trisomy 21, which is the most frequent autosomal aneuploidy, is the leading cause of mental retardation in children. Trisomy 21 occurs in approximately 1 per 660 live births, and the incidence increases with increasing maternal age. Ultrasound findings reported for trisomy 21 include a tendency to brachycephaly, mild ventriculomegaly, nasal hypoplasia, nuchal edema, heart defects (mainly septal atrioventricular defects), duodenal atresia, echogenic bowel, mild hydronephrosis, shortening of femur and humerus, sandal gap and fifth finger clinodactyly.<sup>1</sup>

The phenotypic manifestations of trisomy 18 constitute a syndrome that is characterized by multiple congenital anomalies. At least one hundred defects are known to be associated with trisomy 18, and the main defects are lip and/or cleft palate, esophageal atresia, heart defects, diaphragmatic hernia, omphalocele, spina bifida, urogenital defects, single umbilical artery, shortening of limbs, and postural abnormalities of hands and feet.<sup>2,3</sup>

The phenotypic expression of trisomy 13 includes facial, skeletal, central nervous system, cardiovascular, genitourinary (mostly renal) and gastrointestinal abnormalities. An additional finding on trisomy 13 is postaxial polydactyly. Trisomy 13 is associated with almost a 100% of perinatal mortality.<sup>2,4</sup>

*que un feto fuera portador de un desorden cromosómico; sin embargo, esto no fue estadísticamente significativo excepto para el onfalocele asociado. Los defectos cardíacos mostraron la mayor asociación con todas las anomalías cromosómicas. La asociación más importante fue entre defecto cardíaco asociado a defecto facial y trisomía 13.*

**Palabras clave.** Diagnóstico prenatal. Defectos estructurales fetales. Cromosomopatías. Holoprosencefalia. Higroma quístico. Hidrops. Cardiopatía. Hernia diafragmática.

Prenatal ultrasounds can detect one or more abnormalities in approximately 90% of fetuses with trisomy 13, 80% of fetuses with trisomy 18 and over 50% of fetuses with trisomy 21.<sup>1-4</sup>

In other way, the overall incidence of chromosomal abnormalities in fetal holoprosencephaly is 30%, and the most common chromosomal abnormalities are trisomy 13 (75%) and trisomy 18 (8%).<sup>5</sup> The incidence of chromosomal abnormalities increases the risk of holoprosencephaly and extrafacial defects.<sup>2</sup>

Diaphragmatic hernia is presented as an isolated defect and 62% of all cases have a normal phenotype. About 25% of cases are associated with a chromosomal abnormality (commonly trisomy 18), and 25 to 55% are associated with major defects, such as cardiovascular defects, facial defects, gastrointestinal and omphalocele, renal anomalies and neural tube defects.<sup>6</sup> Diaphragmatic hernia is associated with approximately 10% of trisomy 18 cases, 6% of trisomy 13 cases and 2% of triploids.<sup>7</sup>

Cystic hygroma is generated by multiple etiologies, including chromosomal abnormalities such as Turner syndrome and multiple genetic syndromes. Hygromas are associated with up to 70% of fetuses with Turner syndrome, which is the leading cause of cystic hygroma in the second trimester.<sup>8</sup>

Although there is a huge number of publications about the association between multiple structural defects and aneuploidy, there is not much information about the association between aneuploidies and isolated and associated structural defects reporting odds ratios and confidence intervals.

The aim of the current study was to determine the association between selected major structural defects (isolated and associated) that were detected prenatally by ultrasound and the presence of chromosomal abnormalities.

## MATERIAL AND METHODS

We conducted a retrolective, transversal study of singleton pregnant patients and diagnosis of at least one of the following structural defects on the mor-

phologic ultrasound scan: holoprosencephaly, heart defects, cystic hygroma, hydrops and diaphragmatic hernia, confirmed at birth by autopsy. In newborns who survived, holoprosencephaly was confirmed by nuclear magnetic resonance and in those cases with heart defects an echocardiogram was performed. All neonates undergone a detailed postnatal physical evaluation by the geneticist. Cases were recruited between 15.5 weeks and 38.6 weeks of gestation. Gestational age was determined according to a first trimester ultrasound scan (crown-rump lenght), or a reliable last menstrual period. Files of patients without complete information or born else were excluded.

Ultrasound was performed by experienced medical specialists in maternal fetal medicine in detecting structural defects. We used a Voluson 730 Expert (GE Medical Systems, WI, USA) ultrasound machine equipped with convex transducers of 2-6 and 4-8 MHz. All cases with structural defects were evaluated according to the protocols of clinical management of the Instituto Nacional de Perinatología, and discussed at multidisciplinary meetings (i.e., Departments of Perinatal Genetics, Neonatology, Perinatal Cardiology, Perinatal Neurology, and Maternal Fetal Medicine). The purpose of these meetings is to establish a consensus diagnosis, to propose prenatal diagnosis procedures (amniocentesis for cytogenetic studies), and to plan follow-up strategies. All of these patients were offered an invasive prenatal diagnosis procedure after they had a fetus with at least another structural defect related to chromosomal abnormality. The amniocentesis was always performed by ultrasound guidance to avoid the placenta and the fetus, obtaining a 20 mL sample for cytogenetic analysis. The samples were analyzed in the Genetic Department.

Demographic data, and reports of ultrasound scans and cytogenetic analysis were obtained from medical records.

We used descriptive statistics to analyze demographic variables. We also calculated the OR for

aneuploidy of all major isolated abnormalities and their different combinations in our group of patients. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS 14.0, SPSS Inc., Chicago, IL, USA) and MedCalc 8.0 (MedCalc Software, Broekstraat, Belgium).

## RESULTS

One hundred ninety-seven patients met the inclusion criteria, and eighty-eight had chromosomal abnormalities from January 1994 to May 2010. The mean of the maternal age of patients with fetal abnormal karyotype was 31 years (16-44 years). The most frequent diagnosis was trisomy 18, which was observed in 28 patients (31.8%). We also observed trisomy 21 in 19 cases (21.6%), trisomy 13 in 19 cases (21.6%), Turner syndrome in 13 cases (14.8%) and 9 cases of other abnormalities (10.2%) (e.g., complex chromosomal rearrangements and triploidy) (Table 1).

### Holoprosencephaly

We gathered 30 cases with holoprosencephaly, which presented as associated with other defects in 11/30 cases, and as an isolated defect in 19/30 cases (14/19 not associated with aneuploidies, and 5/19 associated with trisomy 13). A heart defect was present in all 11 cases where holoprosencephaly was associated with other defects, and 7 of these were cases of trisomy 13 (OR = 4.9; 95% CI 0.9-24.2) (Table 2).

### Omphalocele

We found 42 cases with omphalocele, which presented as an isolated defect in 26 cases, and associated with other defects in 16/42. Interestingly, only 3/26 fetuses with isolated omphalocele showed chromosomal abnormality. Six cases involving omphalocele and at least another major structural

Table 1. Demographic characteristics of the major chromosomal abnormalities.

Variable	Trisomy 18 (n = 28)	Trisomy 21 (n = 19)	Trisomy 13 (n = 19)	45X (n = 13)	Others (n = 9)
Maternal age (years)	34 (16-44)	34 (18-44)	26 (16-36)	27 (17-38)	31 (21-41)
Gestational age at diagnosis (weeks)	26.4 (15-38)	27.2 (16.4-38.0)	28.4 (15.5-34.6)	21.1 (16.6-30.2)	25.3 (20.2-32.1)
Gestational age at birth (weeks)	31.0 (24-41.5)	30.4 (20.1-40.0)	35.3 (30.2 - 41)	29 (20 - 38.6)	27.6 (23.1-35.1)
Birth weight (grams), range	1,252 (450-3,510)	1,638 (830-3,870)	2,084 (1,290-3,510)	1,516 (370-3,000)	1,488 (390-2,560)
Mortality	100% a month	73.7%	100%	83%	77.7%

Table 2. Isolated or associated fetal defects and its association with normal and abnormal karyotype.

Fetal defect (n = 197)	Associated or isolated	Abnormal karyotype	Normal karyotype	P	OR	(IC 95%)
Holoprosencephaly (n = 30)	Associated (n = 11) Isolated (n = 19)	7 5	4 14	0.104	4.9	(0.99-24.2)
Omphalocele (n = 42)	Associated (n = 16) Isolated (n = 26)	9 3	7 23	< 0.01	7.63	(2.07-48.7)
Diaphragmatic hernia (n = 17)	Associated (n = 8) Isolated (n = 9)	5 5	3 4	0.839	1.33	(0.19-9.31)
Fetal hydrops (n = 48)	Associated (n = 25) Isolated (n = 23)	11 6	14 17	0.32	2.22	(0.65-7.54)
Cystic hygroma (n = 36)	Associated (n = 25) Isolated (n = 11)	17 5	8 6	0.364	2.5	(0.59-10.9)
Heart defect (n = 92)	Associated (n = 52) Isolated (n = 40)	29 19	23 21	0.564	1.39	(0.60-3.18)

defect had trisomy 18 and three had trisomy 13. In the group of fetuses with an associated defect, a heart defect (11/16) was the most common defect observed (68.7%, OR = 7.7; 95% CI 1.4-41.7). We found a significative OR when omphalocele was associated with other defects (OR 7.6; 95% CI 2.07-46.75),  $p < 0.01$ .

### Diaphragmatic hernia

We found 17 cases involving diaphragmatic hernia: it presented as an isolated defect in 9 cases, whereas it was associated with one or more defects in 8 cases. Among the cases where the diaphragmatic hernia presented in isolation, 3 cases were diagnosed as trisomy 18, 2 cases as trisomy 13 and the remaining 4 were not associated with abnormal chromosomes. In cases where the diaphragmatic hernia was associated with other defects, 6 cases involved a heart defect. Interestingly, 4 of these 6 cases had trisomy 18, whereas the other 2 were not associated with abnormal chromosomes. Two cases of diaphragmatic hernia were associated with hydrops, and one of the two fetuses had trisomy 18. In cases where diaphragmatic hernia was associated with heart defects in chromosomally normal fetuses, the diagnosis was Pentalogy of Cantrell.

### Fetal hydrops

We found 48 cases involving fetal hydrops, 25/48 occurred as associated with other anomalies, while 23/48 occurred as isolated hydrops. Interestingly, 6 of the cases of isolated fetal hydrops had trisomy 21,

whereas the remainder were not associated with abnormal chromosomes. Among the 25 cases where fetal hydrops was associated with other defects, we observed cystic hygroma, heart defect, omphalocele and diaphragmatic hernia. In this group we found 11 fetuses with abnormal chromosomes. The presence of hydrops and cystic hygroma was associated with the highest incidence of chromosomal abnormalities in the group. Indeed, all fetuses with hydrops and cystic hygroma had chromosomal abnormalities, and the most prevalent abnormality was Turner syndrome (7/11), there were 2/11 with trisomy 21 and 2/11 with trisomy 18.

### Cystic hygroma

We found 36 cases of cystic hygroma: 11 cases occurred in isolation, and 25 cases were associated with other defects. Of the 11 isolated cases, 5 were diagnosed with Turner syndrome, and 6 were not associated with any chromosomal disorder. In the group associated with other defects 17/25 had abnormal chromosomes. The main associated defects were hydrops and heart disease, which occurred in 16/17 and 10/17 cases respectively. Furthermore the most frequent diagnosis was Turner syndrome 11/17. Other diagnoses were trisomy 21, 13 and 18.

### Heart defect

We found 92 cases involving heart defects, 40/92 were isolated defects. Nineteen cases with an isolated heart defect had chromosomal abnormalities: 9 cases of trisomy 18, 6 cases of trisomy 21, 1 case of

trisomy 13 and 3 cases of another chromosomal disorder. In the group of associated defects 52/92, the most frequent defects were holoprosencephaly, hydrops and omphalocele. In this group 29/52 had chromosomal abnormalities. There were 12 cases of trisomy 13, 12 of trisomy 18, 3 of Turner syndrome and 2 of trisomy 21. The highest percentage of chromosomal abnormalities was present when heart defects were associated with holoprosencephaly (7/11 cases). But we found a statistically significant association between heart defect and facial cleft with trisomy 13 (9/23 cases) OR 11.08 95% CI (2.99-41.11),  $p < 0.0001$ .

## DISCUSSION

The most common aneuploidy reported in the literature is trisomy 21, which is followed by trisomy 18 and trisomy 13. In the present study, we found more cases of trisomy 18, which was followed by trisomy 21 and trisomy 13. We probably observed more cases of trisomy 18 because we selected fetuses that were prenatally diagnosed with structural defects, and trisomy 18 is most commonly associated with a variable spectrum of major structural defects, while half of cases of trisomy 21 may go unnoticed during prenatal diagnoses because it has a lower association with major defects compared with trisomy 18.

Some series have shown that fetuses with trisomy 18 have at least one major defect in 90% of cases, whereas trisomy 13 and trisomy 21 have at least one major defect in 75-80% and 50% of cases, respectively.<sup>9</sup>

In the present study, we found that the most common abnormality was a heart defect, which was found in 44.2% of the cases. In addition, 56.5% of the cases involving heart defects were associated with another major defect. The karyotype in 50% of the cases revealed chromosomal abnormalities.

The chromosomal abnormalities most commonly present in fetuses with heart defects were trisomy 18, trisomy 13 and trisomy 21. Unlike trisomy 13 and 18, where the majority of defects were shown to be associated with other defects, there was a predominance of isolated defects in cases of trisomy 21 (e.g., 75% for heart defects). Heart defects have been reported in almost half (47%) of fetuses with trisomy 18.<sup>1,3,10</sup> This finding was consistent with the present study, which found that 50% of trisomy 18 cases were associated with heart defects, and 57.1% of the fetuses with trisomy 18 had an additional associated defect.

Blazer, *et al.*,<sup>11</sup> reported that the prevalence of omphalocele and chromosomal abnormalities depen-

ded on the gestational age during which the scan was made, which is why the published prevalence of this association varies between 20 and 50%. We found a frequency of 26.1%, and trisomy 18 was the most common chromosomal disorder, which coincided with previous studies. Blazer, *et al.*,<sup>11</sup> reported that 58% of fetuses with omphalocele also had another associated structural anomaly most frequently cardiac anomalies. None of the cases with isolated omphalocele in the Blazer, *et al.*, study had aneuploidies. Our results were very similar to the results of Blazer, *et al.*, as nearly half the cases (48.1%) of omphalocele were associated with another structural anomaly. In fetuses with trisomy 18, heart defects were the most frequent, and cystic hygroma was the second most common defect found in this group. In cases with isolated omphalocele, a chromosomal disorder was only diagnosed in 11.5% of cases. Conversely, chromosomal abnormalities were diagnosed in 50% of cases where omphalocele was associated with another defect.

We found that holoprosencephaly was associated with chromosomal abnormality in 40% of cases, all of which were fetuses diagnosed with trisomy 13. This finding was consistent with reports in the literature showing a frequency of 40 to 50%.<sup>4,12,16</sup> When isolated and associated cases were analyzed separately, however, we found that only 63.6% of fetuses who had other associated defects were diagnosed with trisomy 13. In addition, all holoprosencephaly cases associated with a heart defect were diagnosed with trisomy 13. Limm, *et al.*,<sup>12</sup> examined 13 fetuses with holoprosencephaly and reported a much higher incidence of chromosomal abnormalities (i.e., 92.3%).

Nonimmune hydrops is related to chromosomal abnormalities in about 10 to 15% of cases, including trisomy 21, trisomy 18, trisomy 13, trisomy 16, Turner syndrome, and triploids, being trisomy 21 and Turner syndrome the most frequent.<sup>13,14</sup> In the present study, just over one third of all hydrops cases were associated with abnormal chromosomes (predominantly trisomy 21 and Turner syndrome, 44.4% in both cases).

Hydrops commonly occurs secondary to heart disease in fetuses with abnormal karyotype. Rotmensch<sup>14</sup> examined 187 fetuses of all gestational ages with trisomy 21 and reported that cystic hygroma was the most common defect. Interestingly, when he only examined fetuses between 14 and 23 weeks, the most consistent findings were hydrops and cardiac defects. Sepúlveda, *et al.*<sup>15</sup> reported cystic hygroma in 88% and hydrops in 37.5% of trisomy 21 cases.

In addition, Farina<sup>8</sup> reported 30 cases of trisomy 21 and found cystic hygroma in 30%, hydrops in 16.6% and cardiac defects.<sup>13</sup> Similarly, the present study found that fetal hydrops (27.5%), cardiac defects (27.5%) and cystic hygroma (10%) were common in fetuses with trisomy 21.

Previous studies<sup>17</sup> have reported that approximately 50% of cystic hygromas are associated with chromosomal abnormalities. Similarly, we found that 61.1% of cystic hygromas were associated with chromosomal abnormalities. The most frequent abnormality associated with cystic hygroma was Turner syndrome, which was followed by trisomy 21, trisomy 18 and trisomy 13.

We did not prove statistical association in our study but OR for associated omphalocele and OR for fetal heart defect and facial cleft with chromosomal abnormality. The wide range of the confidence intervals may be due to lack of sample size. However we calculated the statistical potency of the obtained sample size for each fetal defect and except for diaphragmatic hernia all of them were over 80%.

All the patients carrying a fetus with major structural defect are candidates to an integral diagnostic approach<sup>18,19</sup> and we must offer them a prenatal cytogenetic diagnosis as a first step; however, the patient will not accept the procedure in several occasions due to her fear to the pregnancy loss and hence we miss the opportunity to obtain the prenatal karyotype. We know that not all fetuses with a major structural defect will have a chromosomal anomaly; but we also know that the normal karyotype is the essential result we need before we start looking for a monogenic disease which is less frequent and more expensive to detect.

Most of these defects might be detected during first trimester of pregnancy; nevertheless, in our country the first trimester screening does not work properly and a lot of them will not be detected until the second or third trimester or even at birth. For the aforementioned, some defects will be found lately. In spite of this, the diagnosis is important because we need to plan the correct neonatal treatment in case a lethal chromosomal abnormality is excluded. On the other hand, when we have a fetus with a lethal defect the parents might have the possibility to make a decision about interrupting the pregnancy. The correct and definitive diagnosis of the current fetus will give the genetist the opportunity to offer an adequate counseling for future pregnancies. Unfortunately, in our country, a lot of pregnancies are interrupted taking into account only the ultraso-

nographic findings and without a definitive and complete diagnosis.

We conclude that all the patients who have a fetus with a major structural defect, as those included in this study, which have a high association with chromosomal defects, are candidates to an invasive procedure in order to determine their karyotype and whether they are related to another defect.

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