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Prognostic Factors and Pregnancy Outcomes in Fetuses Diagnosed with Cystic Hygroma During the First Trimester

Birinci Trimesterde Kistik Higroma Tanısı Alan Fetüslerde Prognostik Faktörler ve Gebelik Sonuçları

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Prognostic Factors and Pregnancy Outcomes in Fetuses Diagnosed with Cystic Hygroma During the First Trimester

ABSTRACT

Objective: To evaluate the genetic, sonographic, and clinical characteristics of fetuses diagnosed with cystic hygroma in the first trimester and to identify prognostic factors influencing pregnancy outcomes.

Material and Method: This retrospective study included 84 pregnancies diagnosed with fetal cystic hygroma during the first trimester between January 2023 and June 2025 at a tertiary center. Demographic data, ultrasound findings, and results of invasive genetic testing were analyzed. Cases were compared according to the presence or absence of chromosomal abnormalities to assess clinical and perinatal outcomes.

Results: A total of 84 patients prenatally diagnosed as cystic hygroma were analyzed. Chromosomal abnormalities were identified in 33 cases (39.3%), including trisomy 21 (n=13), monosomy X (n=10), trisomy 18 (n=6), trisomy 13 (n=3), and mosaicism (n=1). Major fetal anomalies were detected in 24 cases (28.6%), most commonly cardiac defects (n=19, 22.6%). Hydrops fetalis was present in 25 fetuses (29.8%). Compared with the normal karyotype group, patients with chromosomal abnormalities had higher maternal age ($p=0.037$), greater NT thickness ($p=0.008$), and increased rates of hydrops ($p=0.003$), intrauterine fetal death ($p=0.030$), and termination of pregnancy ($p<0.001$).

Conclusion: First-trimester cystic hygroma is strongly associated with chromosomal abnormalities and adverse perinatal outcomes. Increased maternal age, greater NT thickness, and hydrops fetalis are significant predictors of poor prognosis. Early diagnosis and detailed sonographic and genetic evaluation are essential for accurate assessment of pregnancy outcome and appropriate counseling of affected families.

Keywords: Cystic hygroma, Chromosomal disorders, First trimester, Non-immune hydrops fetalis.

Birinci Trimesterde Kistik Higroma Tanısı Alan Fetüslerde Prognostik Faktörler ve Gebelik Sonuçları

ÖZ

Amaç: Birinci trimesterde kistik higroma tanısı alan fetüslerin genetik, sonografik ve klinik özelliklerini değerlendirmek, gebelik sonuçlarını etkileyen prognostik faktörleri belirlemek.

Gereç ve Yöntem: Bu retrospektif çalışmaya, Ocak 2023 ile Haziran 2025 tarihleri arasında üçüncü basamak bir merkezde birinci trimesterde fetal kistik higroma tanısı alan 84 gebelik dahil edildi. Demografik veriler, ultrason bulguları ve invaziv genetik test sonuçları analiz edildi. Klinik ve perinatal sonuçları değerlendirmek amacıyla vakalar kromozomal anomali varlığına göre karşılaştırıldı.

Bulgular: Prenatal olarak kistik higroma tanısı alan toplam 84 hasta incelendi. Olguların 33'ünde (%39,3) kromozomal anomali tespit edildi; trizomi 21 (n=13), monosomi X (n=10), trizomi 18 (n=6), trizomi 13 (n=3) ve mozaiklik (n=1) mevcuttu. Yirmi dört olguda (%28,6) majör fetal anomaliler saptandı ve en sık görülen kardiyak defektlerdi (n=19, %22,6). Hidrops fetalis 25 fetüste (%29,8) mevcuttu. Normal karyotip grubuyla karşılaştırıldığında, kromozomal anomalisi olan hastalarda maternal yaş ($p=0.037$), NT kalınlığı ($p=0.008$), hidrops ($p=0.003$), intrauterin fetal ölüm ($p=0.030$) ve gebelik terminasyonu ($p<0.001$) oranları daha yüksekti.

Sonuç: Birinci trimester kistik higroma olguları, kromozomal anomaliler ve olumsuz perinatal sonuçlarla ilişkilidir. Artmış maternal yaş, artmış NT kalınlığı ve hidrops kötü prognozun önemli belirteçleridir. Erken tanı ile ayrıntılı sonografik ve genetik değerlendirme, gebelik sonucunun doğru şekilde öngörülmesi ve etkilenen ailelere uygun danışmanlık verilmesi açısından kritik öneme sahiptir.

Anahtar kelimeler: Birinci trimester, kistik higroma, kromozomal bozukluklar, non-immün hidrops fetalis.

Introduction

Fetal cystic hygroma is a congenital lymphatic malformation characterized by multiloculated fluid-filled cavities, most often located in the posterior cervical region. It results from abnormal development or obstruction of the lymphatic system, leading to localized fluid accumulation and, in severe cases, generalized fetal edema or hydrops fetalis. The reported incidence ranges from approximately 1 in 6,000 to 1 in 15,000 live births, though it is more frequently detected in the first trimester due to advances in early prenatal imaging. According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), cystic hygroma should be differentiated from simple nuchal translucency (NT) thickening by its characteristic septations and bilateral extension along the fetal neck.

The etiology of cystic hygroma is heterogeneous, encompassing both chromosomal and structural abnormalities. Chromosomal aneuploidies, particularly Turner syndrome (45, X0), trisomy 21, trisomy 18, and trisomy 13, are strongly associated with increased NT and cystic hygroma. Additionally, a proportion of cases occur in euploid fetuses, in whom the condition may be transient or related to cardiac or lymphatic developmental anomalies. The detection of septations, increased lesion thickness, or associated soft markers has been shown to significantly increase the likelihood of underlying genetic or major structural pathology (1).

The development of nonimmune hydrops fetalis represents one of the most serious complications of fetal cystic hygroma, reflecting cardiac decompensation and impaired lymphatic drainage. This condition carries a poor prognosis with high rates of intrauterine demise or termination of pregnancy. Although some euploid cases may resolve spontaneously, the majority of affected pregnancies result in adverse outcomes (2).

Given these considerations, early identification of cystic hygroma during the first trimester and prompt evaluation for chromosomal and structural anomalies are crucial for accurate counseling and management. The present study aims to retrospectively analyze the genetic, sonographic, and clinical characteristics of first-trimester cystic hygroma cases diagnosed at a tertiary perinatology center and to identify prognostic factors influencing pregnancy outcomes.

Material and Method

This study was designed retrospectively and conducted at the Perinatology Clinic of the Department of Obstetrics and Gynecology, Ankara Bilkent City Hospital, between January 2023 and June 2025. Cases that were diagnosed with cystic hygroma or referred to our clinic with this diagnosis during the study period were included. The diagnosis of cystic hygroma was confirmed in each case through sonographic examination by maternal–fetal medicine specialists, NT measurements, presence of hydrops fetalis, and any accompanying soft markers or major anomalies were documented.

All patients received genetic counseling that included information on both non-invasive prenatal testing (NIPT) and invasive diagnostic procedures. The screening nature of NIPT and the definitive diagnostic value of invasive tests were explained, and testing decisions were made based on informed patient preference. The patients who underwent an invasive diagnostic test were eventually included in the study. Informed consent forms were obtained from both the patient and her partner prior to the invasive procedure.

Demographic characteristics, ultrasound findings, NT measurements, results of invasive diagnostic tests, pregnancy outcomes, and, where applicable, delivery details such as gestational age at birth, birth weight, Apgar scores, cord blood gas pH, and base excess were retrieved from the hospital information system and recorded retrospectively by the investigators.

Statistical analyses were performed to assess the associations between antenatal cystic hygroma diagnosis and maternal demographic characteristics, ultrasound findings, procedural

variables (gestational age at invasive testing), karyotype results, and pregnancy outcomes. Cases with soft markers were categorized as having one, two, or three or more markers, and the specific types of soft markers were recorded. Major fetal anomalies, most commonly cardiac defects, were documented. Cases with fetal growth restriction during pregnancy follow-up were also noted.

Patients diagnosed with chromosomal abnormalities following invasive testing were statistically compared with those having normal karyotypes in terms of maternal age, gravidity, parity, number of abortions and living children, NT values, presence of soft markers, hydrops fetalis, cardiac and major anomalies, termination rates, and intrauterine fetal death.

For patients who delivered in our hospital, gestational age at birth, birth weight, cord blood gas, and base excess values were analyzed; however, due to the limited number of births in the chromosomally abnormal group, statistical comparisons between groups were not feasible.

The sample size of the study was determined based on the total number of pregnancies diagnosed with fetal cystic hygroma during the first trimester at our tertiary referral center within the predefined study period. All eligible cases that met the inclusion criteria and had complete clinical, sonographic, and genetic data were consecutively included to minimize selection bias and maximize statistical power.

Patients whose ultrasound findings did not confirm cystic hygroma, those who declined invasive testing, or those with inaccessible hospital records were excluded from the study.

This study was conducted in accordance with the ethical principles outlined in the 2024 revision of the Declaration of Helsinki and approved by the Ethics Committee of the University of Health Sciences, Ankara Bilkent City Hospital (approval ID: TABED 2-25-1633). Informed consent for the use of clinical data in academic studies is obtained from all patients upon admission to our clinic, and the patients who do not give consent are excluded.

Statistical analyses were conducted to test the hypothesis that first-trimester fetal cystic hygroma is associated with chromosomal abnormalities and adverse pregnancy outcomes, and to identify prognostic factors influencing these outcomes. Continuous variables were initially assessed for normality using visual inspection of histograms and the Kolmogorov–Smirnov test.

For comparisons between two independent groups (normal versus abnormal karyotype), normally distributed continuous variables were analyzed using the Student's *t*-test, assuming independence of observations and homogeneity of variances. When normal distribution assumptions were not met, the Mann–Whitney *U* test was applied to compare median values between groups. Categorical variables were compared using the chi-square (χ^2) test, provided that expected cell counts were sufficient; otherwise, appropriate exact tests were considered.

All statistical tests were two-tailed, and a p value <0.05 was considered indicative of statistical significance. Descriptive statistics were presented as mean ± standard deviation for normally distributed variables, median with interquartile range for non-normally distributed variables, and frequency with percentage for categorical data. Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results

A total of 84 patients diagnosed with cystic hygroma between January 2023 and June 2025 at the Perinatology Clinic of Ankara Bilkent City Hospital were included in the study. The demographic and clinical characteristics of these patients are presented in Table I. The mean maternal age was 30.67 years.

Table I. Demographic and Clinical Features of Cystic Hygroma Cases

Demographic features	Mean & Median	SD & Min-Max
Maternal age (years)*	30.67	5.43
Gravida**	2	1-10
Parity**	0	0-4
Abortus**	0	0-6
Live children**	1	0-4
Clinical features	**Frequency**	**Percentage (%)**
Soft marker	38	45.2
Major fetal anomaly	24	28.5
Associated cardiac anomaly	19	22.6
Hydrops	25	29.7
Fetal growth restriction	5	5.9
Termination of pregnancy	31	36.9
Intrauterine fetal death	8	9.2

*: mean, standard deviation (SD) **: median, min-max

Soft markers were detected in 38 cases. Among these, 33 patients had a single soft marker, 3 had two, and 2 had three or more. The most frequent findings were nasal bone aplasia/hypoplasia in 12 patients (14.3%), echogenic cardiac focus in 7 (8.3%), echogenic bowel in 7 (8.3%), single umbilical artery in 5 (5.9%), ventriculomegaly in 3 (3.5%), renal pelviectasis in 3 (3.5%), choroid plexus cyst in 2 (2.4%), sandal gap in 1 (1.2%), and aberrant right subclavian artery (ARSA) in 1 (1.2%).

Detailed ultrasound examinations revealed major fetal anomalies in 24 cases, of which 19 involved cardiac anomalies either alone or in combination with other defects. The most frequent cardiac anomalies were ventricular septal defect (VSD; n=6), atrioventricular septal defect (AVSD; n=3), and hypoplastic left heart syndrome (n=3). Other observed anomalies included tetralogy of Fallot (TOF; n=2), aortic stenosis (AS; n=2), transposition of the great arteries (TGA; n=1), and double outlet right ventricle (DORV; n=1). Additional non-cardiac anomalies comprised holoprosencephaly (n=2), skeletal anomalies (n=2), encephalocele (n=1), pentalogy of Cantrell (n=1), agenesis of the corpus callosum (n=1), cleft palate (n=1), and agenesis of the ductus venosus (n=1). Hydrops fetalis was identified in 25 patients.

Thirty-one pregnancies were terminated at parental request due to the presence of major fetal anomalies, chromosomal abnormalities, or both. Eight pregnancies ended in intrauterine fetal demise. Among patients who continued antenatal follow-up at our clinic, five developed fetal growth restriction (FGR) and one developed late-onset preeclampsia. Twenty patients delivered live infants at our institution.

Chorionic villus sampling (CVS) was performed in 71 patients, while 13 underwent amniocentesis (A/S) as they opted for invasive testing at a later gestational age. Karyotype analysis revealed chromosomal abnormalities in 33 patients. This group included trisomy 21 in 13 cases, trisomy 18 in 6, trisomy 13 in 3, and monosomy X (45, X0) in 10. One patient was diagnosed with 69, XXX/46, XX mosaicism (Table II).

Table II. Karyotype Analysis Results of Cystic Hygroma Cases

Karyotype analysis	Frequency	Percentage (%)
Normal karyotype	51	60.7
Trisomy 21	13	15.5
Trisomy 18	6	7.1
Trisomy 13	3	3.6
45, X0	10	11.9
69 XXX, 46 XX	1	1.2

Comparison between patients with normal and abnormal karyotypes showed that maternal age was significantly higher in the chromosomally abnormal group (p=0.037) (Table III). Gravidity, parity, and number of living children did not differ significantly; however, the number of abortions was higher in the abnormal karyotype group (p=0.004). No statistically significant differences were observed between the two groups regarding the presence of soft markers, major fetal anomalies, or cardiac defects (p=1.00, 0.83, and 0.77, respectively). NT measurements and the incidence of hydrops fetalis were significantly higher in the chromosomally abnormal group (p=0.008 and p=0.003, respectively). Termination of pregnancy and intrauterine fetal death rates were also higher in this group (p<0.001 and p=0.03, respectively).

Table III. Comparison of Demographic and Clinical Features between Genetically Normal and Abnormal Cystic Hygroma Cases

	Normal Karyotype	Abnormal Karyotype	*p value*
Maternal age (years)*	30 (7)	31.5 (11.5)	*0.037*
Gravida**	2 (2)	2 (2)	*0.079*
Parity**	1 (2)	1 (2)	*0.37*
Abortus**	0 (0)	1 (1)	*0.004*
Live children**	1 (1)	1 (2)	*0.27*
Gestational week at invasive prenatal testing**	13 (2)	13.1 (1.55)	*0.81*
NT**	5.1 (2.70)	6.1 (2.05)	*0.008*
Soft marker***	23 (45.1)	15 (45.4)	*1.00*
Major fetal anomaly***	15 (29.8)	9 (27.3)	*0.83*
Associated cardiac anomaly***	11 (21.6)	8 (24.2)	*0.77*
Hydrops***	9 (17.9)	16 (48.5)	*0.003*
Termination of pregnancy***	9 (17.9)	22(66.7)	*<0.001*
Intrauterine fetal death***	3 (5.9)	5(15.2)	*0.03*

*: mean, standard deviation (SD) **: median, interquartile range (IQR) ***: number, percentage NT: Nuchal translucency

Twenty-two of 84 patients (26,1%) delivered live infants at our hospital: Eighteen (21,4%) with normal karyotypes, and four (4,7%) with chromosomal abnormalities. Among the normal karyotype group, the median gestational age at delivery was 37.1 weeks, the median birth weight was 2915 g, and the median 1- and 5-minute Apgar scores were 7 and 9, respectively. Median cord blood pH was 7.34, and median base excess was −2.55. One neonate with TGA, VSD, and FGR died at one hour post-delivery, and one patient was delivered at 35 weeks due to preeclampsia. In the chromosomally abnormal group, the median gestational age was 38.0 weeks, the median birth weight was 3210 g, and the median 1- and 5-minute Apgar scores were 7 and 9, respectively. Median cord blood pH was 7.28, and median base excess was −3.00.

Discussion

Cystic hygroma is predominantly diagnosed during the first trimester, allowing early counseling and diagnostic evaluation. Since the majority of patients underwent CVS following diagnosis, 39 % of fetuses exhibited abnormal karyotypes, a proportion that falls within the range reported in previous systematic reviews, highlighting the strong association between cystic hygroma and underlying genetic defects.

A substantial proportion of the cohort also presented with major structural anomalies, most commonly of cardiac origin. Since almost all cases were diagnosed in early gestation, and a considerable proportion of these pregnancies ended in termination or intrauterine fetal death at early weeks, it is possible that some fetal anomalies were not fully identified and may therefore be underestimated. Still, the high rate of associated anomalies further underlines the need for comprehensive ultrasonographic assessment and detailed fetal echocardiography in such cases.

When patients with normal and abnormal karyotypes were compared, those with chromosomal abnormalities had significantly higher maternal age and number of previous abortions. In addition, NT measurements and the incidence of hydrops fetalis were all markedly higher in the abnormal karyotype group. These findings suggest that advanced maternal age, increased NT thickness, and the presence of hydrops may serve as predictive indicators of chromosomal abnormality in fetuses with cystic hygroma. Although only a small number of patients with chromosomal abnormalities reached delivery, their perinatal outcomes appeared less favorable compared with those of the normal karyotype group, reflecting the adverse prognostic impact of genetic abnormalities and associated structural defects on fetal survival.

Recent evidence supports our findings regarding the close association between cystic hygroma, chromosomal abnormalities, and adverse perinatal outcomes. The large meta-analysis by Wang et al. reported that nearly two-thirds of cystic hygroma cases were associated with chromosomal defects, predominantly Turner syndrome and trisomies 21, 18, and 13 (3). Similarly, Zheng et al. demonstrated a strong correlation between increased NT, cystic hygroma, and chromosomal abnormalities, reinforcing the diagnostic value of NT measurements in early pregnancy (4). The high frequency of abnormal karyotypes in our cohort,

especially in those with greater NT thickness, further supports this relationship.

A three-decade retrospective series using 3D/4D ultrasonography identified cardiac anomalies as the most frequent coexisting defect(5). The predominance of cardiac malformations in our cohort is consistent with many previous studies and aligns with long-standing observations that lymphatic and cardiovascular developmental pathways are closely interconnected (6, 7).

A recent study reported spontaneous fetal demise or termination in up to 70 % of cases, which seems comparable to the high early loss rates in our cohort (8). Consequently, the true incidence of major fetal anomalies may be underestimated, as early pregnancy loss precludes complete morphologic assessment.

The predominance of invasive testing through chorionic villus sampling in our population mirrors the findings of Morgan et al., who observed that women confronted with an abnormal early ultrasound finding are more likely to choose early diagnostic procedures (9). Early CVS not only enables prompt karyotypic confirmation but also facilitates informed decision-making before viability. Furthermore, a study reported that cystic hygroma identified at smaller crown–rump lengths (<45 mm) had a substantially lower rate of chromosomal abnormalities and a higher proportion of normal neonatal outcomes compared with lesions detected later in the first trimester (10).

Comparative analyses in our study revealed that chromosomally abnormal cases were associated with higher maternal age, increased NT measurements, and greater prevalence of hydrops fetalis. Similar trends were reported by recent studies, which emphasized that the presence of hydrops is a key prognostic indicator and correlates strongly with abnormal karyotypes and poor fetal survival (11, 12). The greater number of previous abortions among women in the abnormal karyotype group in our study may also reflect an underlying predisposition to chromosomal nondisjunction events.

The spectrum of chromosomal abnormalities in our series closely resembles that described by a systematic review of 45, X fetuses with cystic hygroma. This review noted that although some Turner cases may survive into the second trimester or even to live birth, overall survival remains extremely limited, particularly in the presence of hydrops (13).

A study demonstrated that more than two-thirds of septated cystic hygroma cases resulted in termination or intrauterine fetal death. However, surviving fetuses were mostly found to have a normal postnatal neurologic outcome (14).

Interestingly, while many studies once considered cystic hygroma an almost uniformly lethal condition, more recent reports suggest a small subset of euploid fetuses may have favorable outcomes. A cohort study described euploid cystic hygromas with spontaneous resolution and healthy neonatal outcomes, proposing that these cases might represent a benign variant of transient lymphatic obstruction (15). Peek et al. similarly showed that resolution during the second trimester significantly improved survival rates (16).

NIPT may be considered as an initial screening tool; however, its clinical utility is limited in pregnancies complicated by cystic hygroma. Given the high rate of chromosomal abnormalities observed in our cohort, including sex chromosome aneuploidies and mosaicism, a low-risk NIPT result would not reliably exclude clinically significant genetic abnormalities. The findings of a recent study demonstrated that fetuses with cystic hygroma and low-risk NIPT results still carried a substantial risk of pathogenic chromosomal findings, supporting the need for invasive diagnostic testing in this high-risk group. The study also emphasized that NT thickness and the persistence or resolution of cystic hygroma are strong predictors of pregnancy outcome. They reported markedly better survival rates when the hygroma regressed by the second trimester, while persistent lesions and increased NT values were linked to chromosomal abnormalities and fetal loss (17).

Our findings also correspond with the study, which analyzed 93 cases and identified chromosomal anomalies as the dominant determinant of outcome, followed by the presence of hydrops and major malformations (18). Similarly, another study found that the prognostic factors of the fetal cystic hygroma are chromosome abnormalities, hydrops fetalis, septations, or the thickness of the cystic hygroma (19).

This study provides a comprehensive evaluation of fetuses diagnosed with cystic hygroma in the first trimester, emphasizing the strong association between increased NT, hydrops, and chromosomal abnormalities with adverse pregnancy outcomes. Our findings suggest that pregnancies with chromosomal or major structural anomalies end in fetal loss or termination, and that cardiac anomalies constitute the most frequent structural defects accompanying this condition. These results may indicate the importance of early sonographic assessment and invasive or non-invasive genetic testing in refining prognosis and guiding parental counseling.

A major strength of this study is its relatively large single-center cohort, with all cases evaluated by experienced maternal–fetal medicine specialists using standardized sonographic and genetic protocols. However, its retrospective design, the limited number of live births in the abnormal karyotype group, and the inability to systematically confirm postnatal outcomes represent notable limitations. Additionally, since many affected pregnancies end early, some structural anomalies might remain undetected, potentially underestimating the true prevalence of associated malformations. Future multicenter prospective studies integrating genomic technologies and long-term neonatal follow-up could provide deeper insights into the natural history and prognostic stratification of fetal cystic hygroma.

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