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Typical Morphological Features on Prenatal Ultrasound of Fetuses With Trisomy 13 (Patau's Syndrome)

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Abstract

Background: Trisomy 13 (Patau's syndrome) is a devastating chromosomal abnormality with a poor prognosis. Fetal ultrasound is an effective screening method for early detection of trisomy 13. This study aimed to describe the typical morphological features detected on prenatal ultrasound in fetuses with trisomy 13 at Vietnam National Hospital of Obstetrics and Gynecology from 2012 to 2021.

Methods: This was a retrospective, descriptive cross-sectional study of 50 fetuses with trisomy 13, compared to 4,166 normal fetuses. Maternal age and medical history were collected. Fetal ultrasound was performed in the first and second trimesters, and major structural abnormalities were recorded. The data were analyzed using descriptive statistics.

Results: Trisomy 13 was detected in 98% of fetuses on ultrasound in the first and second trimesters. Of the 23 fetuses examined in the first trimester, 18 had increased nuchal translucency (NT $\geq$ 3 mm). The major structural abnormalities detected in fetuses with trisomy 13 included facial malformations (53.85%), brain anomalies (26.92%), heart defects (26.92%), abdominal wall abnormalities (23.08%), and kidney anomalies (26.92%). Nine cases of trisomy 13 (18%) were not detected on ultrasound.

Conclusions: Increased NT and major structural abnormalities are suggestive signs for early screening of trisomy 13 by ultrasound. The combination of fetal ultrasound with other prenatal screening methods provides good results for the early detection of fetal abnormalities. This study provides important information on the typical morphological features detected on prenatal ultrasound in fetuses with trisomy 13, which can aid in counseling and decision-making for affected families.

Keywords: Patau's syndrome; Trisomy 13; Prenatal ultrasound; Prenatal screening; Chromosomal abnormalities; Aneuploidies; Fetal abnormalities; Prenatal diagnosis

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Introduction

Patau's syndrome (trisomy 13) was first described by Patau et al in 1960 [1]. This is a chromosomal abnormality, which is caused by an extra copy of chromosome 13 in cells of body. Trisomy 13 is the third most common chromosomal aneuploidy in live-born infants with a frequency of 1/5,000 - 1/10,000 live births [2, 3]. It is characterized by many serious abnormalities, including central nervous system abnormalities, facial abnormalities, heart defects, genitourinary abnormalities, limb abnormalities, and others [4, 5]. Trisomy 13 often leads to miscarriage, stillbirth, or infant death shortly after birth. About 90% of babies with trisomy 13 dead within the first year, and very rarely do they live to adulthood [3, 6].

Because of the very poor prognosis of Patau's syndrome, early prenatal diagnosis is important, helping to make choices regarding the continuation of pregnancy and avoid unnecessary interventions for pregnant patients. Unlike trisomy 21 and trisomy 18, screening for maternal serum biochemistry seems to be not significant for trisomy 13 [7]. Ultrasound is one of the simple and effective prenatal screening tools helping detect fetuses at high risk for trisomy 13 [4, 5, 8]. Ultrasound has been reported to detect more than 90% of fetuses with trisomy 13 [9, 10]. Many typical morphological abnormalities representing fetuses with trisomy 13 were detected on ultrasound. Common abnormalities on ultrasound in trisomy 13 include: holoprosencephaly, ventriculomegaly, microcephaly, cyclopia, nasal proboscis, heart defects, cleft lip, cleft palate, limbs abnormalities, umbilical hernia, genitourinary malformations, increased nuchal translucency (NT), and others [4, 11, 12].

Because of the low frequency of trisomy 13, the number of reports of fetuses with trisomy 13 is still very modest, both in the world and in Vietnam. To our knowledge, in Vietnam, no author has reported on the morphological characteristics of fe-

tuses with trisomy 13 on ultrasound. Therefore, we carried out the study with the objective of describing the typical abnormal morphological features detected on ultrasound of fetuses with trisomy 13 at Vietnam National Hospital of Obstetrics and Gynecology from 2012 to 2021.

Materials and Methods

Research subjects

The research subjects consisted of fetuses diagnosed with trisomy 13 at the Vietnam National Hospital of Obstetrics and Gynecology between 2012 and 2021. Selection criteria included a single pregnancy, a live fetus, and confirmation of trisomy 13 through one or more methods such as karyotyping, quantitative fluorescence PCR (QF-PCR), or prenatal BoBs (BACs-on-Beads) from amniotic cells. The fetuses underwent morphological ultrasound prior to amniocentesis and had complete research profile information. Exclusion criteria included fetal death at the time of ultrasound, multiple pregnancies, and a lack of fetal morphological ultrasound results. The research sample was selected through convenience sampling, and 50 fetuses with trisomy 13 were included in the study.

Research methods

This study employed a retrospective case-control study design to compare morphological abnormalities in fetuses with trisomy 13 to 4,166 fetuses without aneuploidy. The data were collected at the Vietnam National Hospital of Obstetrics and Gynecology (which is the leading referral center in Vietnam with more than 1,000 beds and approximately 4,000 pregnant patients seen per day) from 2012 to 2021 and were entered, managed, and analyzed using the statistical software SPSS 20. The tests used in the research included Chi-squared test, Fisher's exact test, and *t*-test.

Research ethics

The study was permitted by the leadership of the Vietnam Central Obstetrics and Gynecology Hospital, and the Ethics Committee of the National Hospital of Obstetrics and Gynecology. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Comparison of characteristics between trisomy 13 and normal cases in prenatal screening

The study included 50 fetuses with trisomy 13, with maternal ages ranging from 19 to 44 years old and an average age of 31.49 years old. Among them, 20 were elderly pregnant patients (35 years old or older), accounting for 40% of the sample (Table 1).

Regarding gestational age, the minimum and maximum ages at which morphological abnormalities were detected were 11 weeks and 1 day and 24 weeks and 5 days, respectively. Most fetuses with trisomy 13 were detected in the first and second trimesters, with only one being detected in the third trimester. The sample included 23 first pregnancies, 26 second pregnancies, and only one third pregnancy, accounting for 46%, 52%, and 2% of the total, respectively.

None of pregnant patients in trisomy 13 group had been pregnant with trisomy before or had personal history of chronic diseases (chronic hypertension, diabetes, systemic lupus erythematosus).

Reasons for amniocentesis

Table 2 presents the causes leading to indications for amniocentesis in fetuses with trisomy 13. Among cases with morphological abnormalities detected on ultrasound, the most common causes leading to amniocentesis were abnormalities on ultrasound combined with a high-risk non-invasive prenatal testing (NIPT) result for aneuploidies (two cases), followed by abnormalities on ultrasound combined with a high-risk double test/triple test result for aneuploidies (10 cases) and maternal age ≥ 35 years old (six cases). In cases where no morphological abnormalities were detected on ultrasound, a high-risk NIPT result for aneuploidies was the most common cause leading to amniocentesis (nine cases), followed by a high-risk double test/triple test result for aneuploidies (two cases) and maternal age ≥ 35 years old (six cases). Overall, this table suggests that abnormalities detected on ultrasound and high-risk results from NIPT or maternal age were the most common causes leading to amniocentesis in fetuses with trisomy 13.

Characteristics of karyotype result

Table 3 provides information on the karyotype results of the study participants. The data show that the majority of cases (94%) had pure trisomy 13, while only a small proportion had mosaicism (2%) or translocation (4%). Overall, the total number of cases included in the analysis was 50, representing 100% of the study population. These findings suggest that pure trisomy 13 is the most common form of the disease in the study population.

Morphological features on ultrasound

The P-value for the increased NT in the trisomy 13 group compared to the normal group is < 0.0001, which indicates a statistically significant difference between the two groups. Specifically, 78.26% of fetuses with trisomy 13 had an NT measurement ≥ 3 mm, while only 3.25% of normal fetuses had an NT measurement ≥ 3 mm. This suggests that increased NT

Table 1. Comparison of Characteristics Between Trisomy 13 and Normal Cases in Prenatal Screening

Characteristics	Trisomy 13 (n = 50)	Normal (n = 4,166)	P
Maternal age			
Mean age	31.49 years	29.88 years	0.093
Age range	19 - 44 years	15 - 55 years	
≥ 35 years old	20 (40%)	1,075 (25.8%)	0.059
< 35 years old	30 (60%)	3,091 (74.2%)	
Gestational age			
Mean age	16 weeks and 1 day	17 weeks and 3 days	0.091
Age range	11 weeks and 1 day - 24 weeks and 5 days	11 week and 0 day - 23 weeks 3 days	
First pregnancy	23 (46%)	1,230 (29.5%)	0.062
Second pregnancy	26 (52%)	2,936 (70.5%)	
Third pregnancy	1 (2%)	0 (0%)	
History of pregnancy with trisomy			
Trisomy 21	0 (0%)	33 (0.79%)	0.511
Trisomy 18	0 (0%)	3 (0.07%)	
Trisomy 13	0 (0%)	0 (0%)	
No	50 (100%)	4,130 (99.14%)	
Personal history of chronic hypertension			
Yes	0 (0%)	4 (0.1%)	0.82
No	50 (100%)	4,162 (99.9%)	
Personal history of diabetes			
Type 1	0 (0%)	1 (0.02%)	0.968
Type 2	0 (0%)	4 (0.1%)	
No	50 (100%)	4,161 (99.88%)	
Personal history of the systemic lupus erythematosus			
Yes	0 (0%)	2 (0.05%)	0.872
No	50 (100%)	4,164 (99.95%)	

measurement in the first trimester may be indicative of trisomy 13. However, it is important to note that increased NT measurement can also be associated with other chromosomal abnormalities, as well as non-genetic factors such as maternal age, obesity, and infections. Therefore, further testing and evaluation would be necessary to confirm a diagnosis of trisomy 13 (Table 4).

Of the fetuses with trisomy 13, 4.35% had tricuspid valve

Table 2. Causes Leading to Indications for Amniocentesis in Fetuses With Trisomy 13

Causes leading to amniocentesis	n
Cases of morphological abnormalities detected on ultrasound	41
Combined with a high-risk NIPT result for aneuploidies	2
Combined with a high-risk double test/triple test result for aneuploidies	10
Combined with maternal age ≥ 35 years old	6
Based only on abnormalities on ultrasound	23
Cases that were not detected morphological abnormalities on ultrasound	9
A high-risk NIPT result for aneuploidies	2
A high-risk double test/triple test result for aneuploidies	6
Based only on the maternal age ≥ 35 years old	1

NIPT: non-invasive prenatal testing.

Table 3. Karyotype Results

Disease form	n	%
Pure trisomy 13	47	94%
Mosaicism	1	2%
Translocation	2	4%
Total	50	100%

regurgitation, which is significantly higher compared to normal group with the P-value of < 0.0001.

We looked at other markers of fetal well-being in the first trimester: absent nasal bone and holoprosencephaly, but did not find any trisomy 13 fetus having these markers.

Based on Table 5, it seems that out of the 26 ultrasound fetuses in the second trimester, 23 fetuses have pure trisomy 13, while the remaining three fetuses have either mosaic or translocation trisomy 13. In terms of facial malformations, more than half of the fetuses (53.85%) have cleft lip or palate, absent nasal bone, cyclopia, or nasal proboscis. Seven fetuses (26.92%) have brain anomalies such as holoprosencephaly, ventriculomegaly, and enlarged cisterna magna, while the same number of fetuses have kidney anomalies like enlarged and echogenic kidneys or renal pelvis dilatation. Finally, seven fetuses (26.92%) have heart defects like disproportionate heart, ventricular septal defect, ventricular outflow abnormalities, or tricuspid valve regurgitation, and six fetuses (23.08%) have omphalocele, which is an abdominal wall abnormality. Overall, the table suggests that fetuses with trisomy 13 have a higher likelihood of having various structural abnormalities than normal fetuses.

Table 4. Features of Ultrasound in the First Trimester

Features of ultrasound in the first trimester	Trisomy 13	Normal	P-value
Total number of fetuses examined by ultrasound in the first trimester	23	1,230	
Increased NT ≥ 3 mm	18 (78.26%)	40 (3.25%)	< 0.0001
NT < 3 mm	5 (21.74%)	1,190 (96.75%)	
Tricuspid valve regurgitation	1 (4.35%)	1 (0.08%)	< 0.0001

NT: nuchal translucency.

Table 5. Features of Ultrasound in the Second Trimester

Features of ultrasound in the second trimester	Fetuses with trisomy 13				Normal fetuses	P-value
	Total	Pure trisomy 13	Mosaicism	Translocation		
Total number of ultrasound fetuses in the second trimester	26	23	1	2	2,936	
Facial malformations	14 (53.85%)	12	0	2	10 (0.34%)	< 0.0001
Cleft lip, cleft palate	13 (50%)	11	0	2	9 (0.31%)	
Absent nasal bone	1 (3.85%)	1	0	0	2 (0.07%)	
Cyclopia	1 (3.85%)	1	0	0	0 (0%)	
Nasal proboscis	1 (3.85%)	1	0	0	0 (0%)	
Brain anomalies	7 (26.92%)	7	0	0	3 (0.10%	0.0005
Holoprosencephaly	3 (11.54%)	3	0	0	0 (0%)	
Ventriculomegaly	3 (11.54%)	3	0	0	3 (0.10%	
Enlarged cisterna magna	2 (7.69%)	2	0	0	0 (0%)	
Heart defects	7 (26.92%)	6	1	0	13 (0.44%)	< 0.0001
Disproportionate heart	4 (15.38%)	4	0	0	5 (0.17%)	
Ventricular septal defect	4 (15.38%)	3	1	0	7 (0.24%)	
Ventricular outflow abnormalities	3 (11.54%)	3	0	0	4 (0.14%)	
Tricuspid valve regurgitation	1 (3.85%)	1	0	0	2 (0.07%)	
Abdominal wall abnormalities	6 (23.08%)	6	0	0	3 (0.10%	0.0002
Omphalocele	6 (23.08%)	6	0	0	3 (0.10%	
Kidney anomalies	7 (26.92%)	6	0	1	13 (0.44%)	< 0.0001
Enlarged and echogenic kidneys	3 (11.54%)	3	0	0	2 (0.07%)	
Renal pelvis dilatation	4 (15.38%)	3	0	1	11 (0.37%)	

Table 6. Number of Anomalies of Fetuses Detected on the Second Trimester Ultrasound

Number of anomalies	Trisomy 13	Normal	P-value
No anomaly	4 (15.38%)	2,899 (98.74%)	< 0.0001
Only one anomaly	8 (30.77%)	33 (1.12%)	
2 - 3 anomalies	12 (46.15%)	4 (0.14%)	
More than three anomalies	2 (7.69%)	0 (0%)	
Total	26	2,936	

Some abnormalities were observed in the normal fetus group but in very small proportions compared to those of trisomy 13 group.

The P-values for each abnormality between the trisomy 13 and normal groups can be calculated using a statistical test such as Fisher's exact test or Chi-squared test. However, since the sample size for the normal group is quite large, even small differences between the two groups may lead to statistically significant results.

That being said, if we performed Fisher's exact test, these P-values suggested that there was a statistically significant difference in the prevalence of each abnormality between the trisomy 13 and normal groups.

We looked at other markers of fetal well-being: intrauterine growth restriction (IUGR), hydrops, polyhydramnios, umbilical Dopplers, limb anomalies, and gastrointestinal anomalies, but did not find any trisomy 13 fetus having these markers.

In terms of number of anomalies detected on the second trimester ultrasound, the proportions of fetuses having more than one anomaly on ultrasound of trisomy 13 group were significantly higher than those of normal group, with the P-value of < 0.0001 (Table 6).

Discussion

In Vietnam, fetal ultrasound is a common prenatal screening tool for chromosomal abnormalities, including trisomy 13, with most pregnant patients undergoing quarterly ultrasound examinations. However, to our knowledge, no studies have been conducted on the morphological features of fetuses with trisomy 13 on ultrasound in Vietnam. While several international articles have reported on this topic, they were based on small sample sizes. In contrast, our study observed 50 fetuses with trisomy 13, which is a relatively large sample size and provides valuable insights into the ultrasound features of this condition. Besides, we compared the trisomy 13 group with 4,166 normal fetuses to show the differences.

Characteristics of the pregnant patients

According to the American College of Obstetricians and Gynecologists, the rate of pregnancy with trisomy 13 increases with increasing maternal age, so maternal age of 35 years and older is considered a high risk of giving birth to a baby with chromosomal abnormalities, including trisomy 13 [2]. In our study, there were 20/50 pregnant patients aged 35 years and older, accounting for 40%. The percentage of pregnant patients under the age of 35 was 60%. The Chi-squared test gave χ^2 of 2.000 with P value of 0.157 (> 0.05) (Table 1). Thus, the percentage of pregnant patients aged 35 years or older and the percentage of pregnant patients under 35 years old in this study were not statistically significant with a 95% confidence interval.

Several reports in the world indicate that, from the 14th week of gestation, all major structural abnormalities of trisomy 13 can be detected by prenatal ultrasound [13]. With the advances in high-quality ultrasound equipment, from 11 weeks to 13 weeks and 6 days of gestation, some signs of fetal structural abnormalities such as holoprosencephaly, omphalocele, and/or bladder enlargement can be observed in about 50% of fetuses with trisomy 13 [11]. In our study, most of the structural abnormalities of trisomy 13 on ultrasound were detected in the first trimester (46%) and the second trimester (52%). There were several malformations in the group of major structural abnormalities that have been detected on ultrasound between 11 weeks and 13 weeks and 6 days of gestation. Omphalocele was observed in one fetus at 13 weeks and 1 day gestational age. There was one fetus with disproportionate heart defects, tricuspid valve regurgitation, and enlarged kidneys detected at 13 weeks and 2 days gestation. This was thanks to advances in ultrasound technology and the good skill of the sonographer. Only one fetus with trisomy 13 was detected with morphological abnormalities on ultrasound in the third trimester, at 24 weeks and 5 days of gestational age (Table 1). In this case, since 2017, the pregnant woman lived in Thanh Hoa province, the cause of late detection could be because the local ultrasound equipment had not been improved or the pregnant woman was not managed and monitored periodically.

Morphological features on ultrasound of fetuses with trisomy 13

In obstetric practice, the sign of increased NT and major structural abnormalities detected on fetal ultrasound is used to screen for trisomy 13 [4]. According to the American College of Obstetricians and Gynecologists, an increased NT (usually defined as 3.0 mm or above the 99th percentile for crown-rump length) between 11 weeks and 13 weeks and 6 days of gestation is associated with an increased risk for aneuploidy [2]. In our study, there were 23 fetuses that were examined by ultrasound in the first trimester, 18 of them had increased NT (78.26%),

and five of them had NT < 3.0 mm (21.74%). The Chi-squared test gives χ^2 of 7.348 with P value of 0.007 (< 0.01). Thus, the rate of fetuses with trisomy 13 in the two groups of NT ≥ 3 mm and NT < 3 mm was a statistically significant difference with a 99% confidence level. The rate of increased NT in fetuses without aneuploidy was very low (3.25%) (Table 4). It can be seen that increased NT is an important ultrasound sign in the first trimester suggesting an aneuploidy in the fetus. In consistent with our research, a study by Snijders et al showed that the rate of increased NT in fetuses with trisomy 13 was 72% [14]. A study by Spencer et al (2000) on 42 fetuses with trisomy 13 indicated that 62% of them had an increased NT [15].

Regarding ultrasound findings on second trimester, the results of our study show that among the major structural abnormalities, facial anomalies were the most common (53.85%), followed by brain anomalies, heart defects, and kidney anomalies with the same rate (26.92%), and finally abdominal wall abnormalities (23.08%). The sensitivity of each marker was not high, but some major structural abnormalities were relatively specific for trisomy 13. Abnormalities observed in fetuses with trisomy 13 fetus such as cyclopia, nasal proboscis, absent nasal bone, holoprosencephaly, and enlarged cisterna magna were almost not seen in normal fetuses. Abnormalities such as cleft lip, cleft palate, ventriculomegaly, heart defects, omphalocele, enlarged and echogenic kidney, and renal pelvis dilatation also had a higher incidence in fetuses with trisomy 13 than in normal fetuses (Table 5). The specificity of these abnormalities was very high, so it can help clinicians orient early diagnosis of trisomy 13.

This result is relatively consistent with other studies in the world when it showed that heart defects, facial anomalies and central nervous system (CNS) anomalies are the most common malformations detected in trisomy 13 on second trimester ultrasound. Papp et al [5] reported on 28 fetuses with trisomy 13, 89.3% of fetuses were found to have morphological abnormalities on ultrasound. Among the major structural abnormalities observed, facial malformations and brain anomalies were the most common (64.3%; n = 18). Among brain anomalies, holoprosencephaly and ventriculomegaly were most commonly observed. Heart defects were detected in 53.6% (n = 15) of fetuses with trisomy 13. Among the soft markers group, increased NT (21.4%) and echogenic small bowel (17.9%) were the most common. Watson et al [8] studied a total of 64 fetuses with trisomy 13 at six university medical centers, among whom, 54 fetuses received second trimester ultrasound, and the results showed that the most common ultrasound abnormalities were heart defects (34/54), brain anomalies (30/54), facial malformations (19/54) and kidney anomalies (9/54).

It is worthy that when compared with previous studies, the rate of fetuses with trisomy 13 having heart defects and CNS anomalies in our study was quite low (26.92%): in a study by Papp et al [5], heart defects were detected in 53.6% and CNS anomalies were detected in 64.3% of fetuses with trisomy 13; in a study by Watson et al [8], heart defects were detected in 63% and CNS anomalies were detected in 55.6% of fetuses with trisomy 13. Consistently, Lehman et al (1995) reported that holoprosencephaly was detected in 39%, other CNS anomalies were detected in 58% of fetuses with trisomy 13, and cardiac defects were detected in 48% of fetuses with trisomy 13 [16].

Advantages and limitations of the study

Our research had the strength that we studied cases of fetuses with trisomy 13 at the leading Obstetrics and Gynecology Hospital in Vietnam during the last decade, examined by a team of highly qualified and experienced doctors and relatively modern equipment. Therefore, we think that this study provided a true overview of the morphological abnormalities on ultrasound of fetuses with trisomy 13. The limitation of this study is the fact that most ultrasound abnormalities were not confirmed by autopsy findings to provide a pathological-clinical correlation.

Conclusions

In conclusion, our study provides valuable insights into the ultrasound features of fetuses with trisomy 13 in Vietnam, based on a relatively large sample size. Our findings indicate that the majority of fetuses with trisomy 13 display morphological abnormalities on ultrasound in the first and second trimesters, with increased NT and major structural abnormalities being important signs for early screening. However, it should be noted that a small number of fetuses with trisomy 13 can be missed on ultrasound, highlighting the importance of combining fetal ultrasound with other prenatal screening methods for the early detection of fetal abnormalities.

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Conflict of Interest

This study did not have any conflict of interest among the authors' group or with other authors.

Informed Consent

Not applicable.

Author Contributions

Danh Cuong Tran and Thi Trang Nguyen conceived the study.

Anh Linh Dang, Thi Bich Van Nguyen, Thi Ngoc Lan Hoang, and Thi Minh Phuong Le conducted the experiments. Thuy Linh Tran, Toan Anh Ngo, Phuong Thao Le, and Thi Tuyet Nhung Ngo analyzed the data. Thi Hue Nguyen, Van Anh Tran, and Thi Quyen Le wrote the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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