

The Application Value of Ultrasound Soft Markers in the Examination of Common Fetal Chromosomal Aneuploidy Abnormalities: A Retrospective Study

Dan Jiang

Sichuan Provincial Maternity and Child Health Care Hospital

Shizeng Fan

Department of Obstetrics, The Third Affiliated Hospital of Chengdu Medical College · Pidu District People's Hospital of Chengdu

Ping Zuo

Sichuan Provincial Maternity and Child Health Care Hospital

Jing Wang

Sichuan Provincial Maternity and Child Health Care Hospital

Xueyan Wang

wanxueyang@163.com

Sichuan Provincial Maternity and Child Health Care Hospital

Na Xi

Sichuan Provincial Maternity and Child Health Care Hospital

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Abstract

Objective

To carry out a retrospective cohort study focusing on prevalent soft markers observed in fetal ultrasounds, follow up the incidence of trisomy 21, 18 and 13, and investigate the positive predictive values of single and multiple soft markers for common chromosomal aneuploidy abnormalities.

Methods

A total of 19,997 pregnant women with ultrasound-detected soft markers underwent non-invasive prenatal testing (NIPT) or amniocentesis for karyotype analysis and evaluation of chromosomal copy number variations, with their pregnancy outcomes subsequently monitored. The risks of trisomy 21, 18, and 13 associated with various ultrasound soft markers were subjected to statistical analysis.

Results

A total of 5,530 pregnant women underwent amniocentesis directly, while 14,467 cases received non-invasive prenatal testing (NIPT), among which 23 high-risk cases proceeded to further amniocentesis. Out of 19,997 fetuses exhibiting ultrasound soft markers, 105 were identified with common chromosomal aneuploidy changes, including 93 cases of trisomy 21, 11 cases of trisomy 18, and 1 case of trisomy 13. The overall positive detection rate was 0.53%.

Based on the incidence of common chromosomal aneuploidy abnormalities relative to the risks associated with amniocentesis, the ultrasound soft markers were classified into two categories: high-risk ($\geq 0.5\%$) and low-risk ($<0.5\%$). Isolated ultrasound soft markers were linked to a 0.46% risk of target chromosomal aneuploidy. Among these, thickened nuchal translucency (NT), absence or hypoplasia of the nasal bone, and ventriculomegaly were associated with higher risks of aneuploidy at 4.25%, 2.28%, and 0.98%, respectively. Other markers such as choroid plexus cyst (CPC), single umbilical artery (SUA), aberrant right subclavian artery (ARSA), and echogenic intracardiac focus (EIF) indicated risks of 0.22%, 0.22%, 0.19%, and 0.06%, respectively. No instances of common fetal chromosomal aneuploidy abnormalities were observed in cases with urinary tract dilation, echogenic bowel, or shortened femur length.

The overall risk of fetal chromosomal aneuploidy in fetuses with two ultrasound soft markers was 0.92%, including a risk of 0.12% for those with two low-risk markers. When three or more ultrasound soft markers were present, the risk of target chromosomal aneuploidy increased to 4.82%, compared to a 1.6% risk observed in cases with three or more only low-risk soft markers.

Conclusions

Chromosomal detection strategies can be selected reasonably based on the varying risks of common chromosomal aneuploidy associated with different ultrasound soft markers according to this study. For

pregnant women with high-risk ultrasound soft markers, amniocentesis for prenatal diagnosis is recommended in genetic counseling regardless of the number of soft markers. Amniocentesis is also recommended for those with three or more ultrasound soft markers. For women with one or two low-risk ultrasound soft markers, NIPT targeting common aneuploidies can be an option under fully informed consent. In this way, medical resources can be reasonably allocated and utilized.

Background

Ultrasound soft markers can be detected during the first and second trimesters of pregnancy. Typically, these markers do not indicate structural abnormalities and often diminish by the third trimester. However, they are linked to a higher risk of aneuploidy, particularly trisomy 21. [1–2]. The incidence of ultrasound soft markers is approximately 10% [3]. Common ultrasound soft markers include echogenic intracardiac focus(EIF), thickened nuchal translucency (NT), choroid plexus cysts(CPC), ventriculomegaly, echogenic bowel(EB), urinary tract dilation(UTD), nasal bone absent or hypoplastic, shortened femur length, single umbilical artery(SUA), and aberrant right subclavian artery(ARSA) [4–5]. Amniocentesis is the gold standard for prenatal diagnosis of fetal chromosomal abnormalities, with a reported risk of miscarriage of approximately 0.5% [6]. Non-Invasive Prenatal Testing (NIPT) is one of the screening methods for common fetal chromosomal aneuploidies including trisomy 21, 18 and 13. Studies have shown that the probability of target aneuploidy is extremely low in NIPT-negative cases [7], although false negatives still exist. This retrospective study enrolled pregnant women with fetal ultrasound soft markers, followed their pregnancy outcomes, and analyzed the incidence of target chromosomal aneuploidy according to the type and number of ultrasound soft markers, aiming to provide evidence-based recommendations for chromosomal aneuploidy testing in clinical practice.

1 Materials and Methods

1.1 General Data

From January 2019 to December 2024, 19,997 pregnant women with fetal ultrasound soft markers detected by color Doppler ultrasound at our hospital were enrolled, including 14,467 cases undergoing NIPT and 5,530 cases receiving direct amniocentesis. Twenty-three NIPT-high-risk cases underwent subsequent amniocentesis. All pregnant women were followed up by telephone one-two years after their expected date of confinement(EDC). All participants received pre-test counseling explaining the significance and limitations of NIPT. Provide insurance claims for all those who choose NIPT, and conduct prenatal diagnosis for those at high risk of target chromosomal diseases. The maternal age ranged from 16 to 34 years (mean 27 ± 3 years), gestational age 23.6 ± 0.9 weeks, and BMI 23 ± 3.3 SD.

Inclusion criteria: singleton pregnancy, presence of study-defined ultrasound soft markers, and undergoing NIPT or amniocentesis.

Exclusion criteria: maternal age ≥ 35 , multiple pregnancy, structural abnormalities or fetal growth restriction detected by color Doppler ultrasound.

Diagnostic criteria for ultrasound soft markers: Detailed fetal ultrasound examinations were performed according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology [8]. A positive ultrasound soft marker was defined as meeting any one of the following:

Thickened NT: NT measurement $> 95^{\text{th}}$ percentile at 11–13⁺⁶ weeks of gestation.

Nasal bone absent or hypoplastic: nasal bone length < 2.5 mm, below the 2.5th percentile for gestational age, or non-visualization in the midsagittal view.

Echogenic bowel: bowel echogenicity similar to or greater than that of bone.

Single umbilical artery: only one umbilical artery identified in the umbilical cord.

Choroid plexus cyst: oval or round anechoic cystic structure in the choroid plexus in the second trimester.

Echogenic intracardiac focus: non-occupying hyperechoic spot in the cardiac ventricle with echogenicity equal to or greater than surrounding bone.

Ventriculomegaly: lateral ventricular width (unilateral or bilateral) ≥ 10 mm and < 15 mm.

Urinary tract dilation: anechoic area in the renal pelvis with maximum anteroposterior diameter ≥ 4 mm in the second trimester or ≥ 7 mm in the third trimester.

Shortened femur length: femur length > 2 standard deviations below the mean for gestational age.

Aberrant right subclavian artery: right subclavian artery arising directly from the aortic arch and passing posterior to the trachea and esophagus.

1.2 Methods

1.2.1 NIPT Testing

5mL of maternal venous blood was collected. After separating the plasma, extract the free fetal DNA in the plasma. Testing was performed using kits from BGI Genomics Co., Ltd. combined with high-throughput gene sequencing to measure the fetal nucleic acid fragments. The sequencing results are analyzed by bioinformatics and identified using the Z - value. When the Z - value is within (-3.0–3.0), it is considered a low - risk case; otherwise, it is determined as a high - risk case.

1.2.2 Amniocentesis Diagnosis

30mL of amniotic fluid was collected: 20 mL for cell culture, and 10 mL for molecular chromosomal copy number variation (CNV) analysis after excluding maternal contamination. Chromosomal aneuploidy was

determined by CNV analysis in cases of failed cell culture.

Cell culture procedure: Amniocytes were cultured and karyotyped following standard laboratory protocols. 20 mL of amniotic fluid was centrifuged, the supernatant discarded, and dual-line culture conducted for 7–9 days (37°C, 5% CO₂). Cells were harvested, slide-prepared, and G-banded. At least 20 metaphase spreads were counted and 5 karyotypes analyzed, with results described according to the International System for Human Cytogenetic Nomenclature (ISCN 2013).

Chromosomal microarray analysis(CMA): Genomic DNA was extracted using commercial DNA extraction kits. CytoScan 750K microarrays (Affymetrix, USA) were used for whole-genome analysis. Procedures included digestion, ligation, PCR amplification, purification and fragmentation of PCR products, labeling, hybridization, washing, staining and scanning.

High-throughput sequencing of chromosomes: Genomic DNA was extracted, randomly fragmented, end-repaired, and ligated with A-tails for library construction. Low-coverage whole-genome sequencing was performed using an Illumina sequencer. Pathogenicity of CNVs was evaluated against international genomic CNV polymorphism databases and relevant literature.

1.3 Outcome Measures

All types of ultrasound soft markers were recorded. Followed up the results of NIPT or amniocentesis for different soft markers. The risks of common chromosomal aneuploidy associated with different types and numbers of ultrasound soft markers were statistically analyzed.

2 Results

2.1 NIPT and Amniocentesis Results

Among 19,997 cases, 105 cases of common chromosomal aneuploidy were identified, with an overall positive rate of 0.53% (93 trisomy 21, 11 trisomy 18, 1 trisomy 13).

Of 14,467 chose to undergo NIPT cases, 23 cases were found to have a high risk of common chromosomal abnormalities and further underwent amniocentesis. Among them, 13 cases were true positives (including 10 trisomy 21, 2 trisomy 18, 1 trisomy 13). During the follow - up process, no cases of trisomy 21, trisomy 18, or trisomy 13 abnormalities were found among pregnant women with low - risk NIPT results.

Among 5,530 pregnant women who directly underwent amniocentesis, 92 cases of common chromosomal trisomy abnormalities were found, including 83 cases of trisomy 21 and 9 cases of trisomy 18. No cases of trisomy 13 were found. Details are shown in Table 1.

Table 1
Results of NIPT and Amniocentesis in Cases with Ultrasound Soft Markers

Testing Method	Number of Cases	Trisomy 21	Trisomy 18	Trisomy 13	Total	Rate of Common Chromosomal Aneuploidy(%)
NIPT	14467	10	2	1	13	0.09
Amniocentesis	5530	83	9	0	92	1.67
Total(n)	19997	93	11	1	105	0.53

2.2 Detection results of fetal chromosomal aneuploidy abnormalities with different types of isolated ultrasound soft markers

Among isolated ultrasound soft markers, echogenic intracardiac focus accounted for the highest proportion (69.27%) with an aneuploidy rate of only 0.06%. Thickened NT, nasal bone absent or hypoplastic and ventriculomegaly showed relatively higher rates (4.19%, 2.28% and 0.98%, respectively, all greater than 0.5%). No aneuploidies were detected in cases with urinary tract dilation, echogenic bowel and shortened femur length. Results are shown in Table 2.

Table 2
NIPT and Amniocentesis Results with different types of isolated ultrasound soft markers

Ultrasound category	Number of Cases	Proportion(%)	Trisomy 21	Trisomy 18	Trisomy 13	Rate of Common Chromosomal Aneuploidy(%)
Thickened NT	1264	7.04	47	6	0	4.19
nasal bone absent or hypoplastic	615	3.42	14	0	0	2.28
ventriculomegaly	407	2.27	4	0	0	0.98
SUA	456	2.54	0	0	1	0.22
CPC	1386	7.72	0	3	0	0.22
ARSA	523	2.91	1	0	0	0.19
EIF	12441	69.27	7	0	0	0.06
EB	152	0.85	0	0	0	0
SFL	156	0.87	0	0	0	0
UTD	559	3.11	0	0	0	0
Total	17959	100	73	9	1	0.46

2.3 Results of NIPT and amniocentesis in fetuses with different numbers of ultrasound soft markers

The overall risk of common chromosomal aneuploidy in fetuses with ultrasound soft markers was 0.53%. The risk was 0.46% for isolated soft markers, 0.92% for two soft markers, and 4.82% for three or more soft markers (Table 3).

Table 3

Results of NIPT and amniocentesis in fetuses with different numbers of ultrasound soft markers. Additionally, risks were analyzed for low-risk soft markers (single umbilical artery, choroid plexus cyst, aberrant right subclavian artery, echogenic intracardiac focus, shortened femur length, urinary tract dilation). Among 1,649 cases with two low-risk markers, 2 cases of trisomy 21 were detected (0.12%). Among 63 cases with three or more low-risk markers, 1 case of trisomy 18 was found (1.6%) (Table 4).

Number of Soft Markers	Number of Cases	Proportion(%)	Trisomy 21	Trisomy 18	Trisomy 13	Total	Rate of Common Chromosomal Aneuploidy(%)
1	17959	89.8	73	9	1	83	0.46
2	1955	9.78	17	1	0	18	0.92
≥ 3	83	0.42	3	1	0	4	4.82
Total	19997	/	93	11	1	105	0.53

Table 4

Detection of Chromosomal Aneuploidy by Number of Low-Risk Ultrasound Soft Markers

Number of Low-Risk Soft Markers	Number of Cases	Trisomy 21	Trisomy 18	Trisomy 13	Rate of Common Chromosomal Aneuploidy(%)
2	1649	2	0	0	0.12
≥ 3	63	0	1	0	1.6

3 Discussion

Ultrasound soft markers often indicate an increased risk of fetal chromosomal aneuploidy. NIPT shows favorable screening performance for common fetal aneuploidies. Studies reported that NIPT-negative results reduce the risk of trisomy 21, 18 and 13 by 333-, 47- and 100-fold, respectively [7], effectively reducing unnecessary amniocentesis and maternal-fetal risks.

In this study, the overall risk of common chromosomal aneuploidy in fetuses with ultrasound soft markers was 0.53% (105/19,997), lower than the 1.15%–6.4% reported in previous studies [9, 10]. This may be partly due to the high prevalence of some soft markers with low aneuploidy risk, such as echogenic intracardiac focus.

The positive rate for aneuploidy associated with isolated soft markers was 0.46%, which is lower than the rates of 2.47% to 5.2% reported in other studies [9, 11]. The risk varied depending on the category of the soft markers.

Among them, the incidence of echogenic intracardiac focus is the highest, accounting for 69.27% of all ultrasound soft markers. However, the probability of common chromosomal aneuploidy in its occurrence is relatively low, only 0.06%. Some studies have shown that there is a lack of correlation between isolated echogenic intracardiac focus and trisomy 21, with a likelihood ratio of 0.95. [12]. No aneuploidies were detected in cases with urinary tract dilation, echogenic bowel and shortened femur length. Some studies reported a likelihood ratio of trisomy 21 in cases of urinary tract dilation is approximately 1.5 [13], and a 3%–5% aneuploidy risk for echogenic bowel [2], which is slightly different from the result in our study. More data accumulation and analysis may be required. Fetuses with echogenic bowel should undergo follow-up ultrasound for bowel dilatation and growth restriction, which may indicate other chromosomal abnormalities, genetic disorders or intrauterine infection. Meta-analyses reported positive likelihood ratio of 0.61 for isolated short femur [14], possibly related to ethnic differences. Close longitudinal growth monitoring is recommended for fetuses with shorten femur length.

The risks of common chromosomal aneuploidies in fetuses with single umbilical artery, choroid plexus cyst, and aberrant right subclavian artery are extremely low (0.22%, 0.22%, 0.19%, respectively). Most fetuses with trisomy 18 have structural abnormalities, approximately one-third of them have choroid plexus cysts. When choroid plexus cysts are combined with other structural abnormalities, it often indicates an increased risk of trisomy 18. [15, 16]. Isolated choroid plexus cysts carry a trisomy 18 risk of 1/200–1/400 without increasing the risk of trisomy 21 [17-19]. Isolated single umbilical artery does not increase aneuploidy risk, [20-21] but may predict fetal growth restriction and preterm birth [22]. One meta-analysis found a 3.94-fold higher trisomy 21 risk with isolated aberrant right subclavian artery [14], which is higher than our incidence rate. This may also be related to the relatively small number of our study.

The rates of fetal chromosomal aneuploidy abnormalities in the groups with thickened NT, nasal bone absent or hypoplastic and ventriculomegaly were relatively high, all higher than 0.5%, which were 4.19%, 2.28%, and 0.98% respectively. This suggests that these types of ultrasound soft markers can serve as highly sensitive indicators for the diagnosis of chromosomal abnormalities. Some studies have shown that the positive likelihood ratio of nasal bone absent or hypoplastic for trisomy 21 is 6.6–23 [12], while the positive likelihood ratio of thickened NT combined with trisomy 21 is 11–23 [2]. Another meta-analysis literature reported that the risk of trisomy 21 in ventriculomegaly increased by 3.8 times [14]. In addition, for fetuses with ventriculomegaly, the degree of dilatation should also be evaluated.

In the group with two ultrasound soft markers, the chromosomal aneuploidy abnormality rate was 0.92%, and only 0.12% in those with two low-risk markers—lower than the 0.46% for isolated soft markers. This may be related to the relatively high proportion of some low - risk soft markers. Due to the high incidence

of echogenic intracardiac focus, subgroup of the low-risk was not carried out. In the group with ≥ 3 ultrasound soft markers, the chromosomal aneuploidy abnormality rate was 4.82%, while the incidence was about 1.6% in three or more low-risk markers. Other studies reported a 0.84%–4.95% risk for two or more markers [9, 10].

In summary, risks of chromosomal aneuploidy differ by ultrasound soft marker. Therefore, the clinical selection of fetal chromosomal testing protocols can be made in a step-by-step manner. NIPT is a reasonable option for women with one or two low-risk markers under fully informed consent. Amniocentesis is recommended for those with high-risk markers (regardless of the number) and those with three or more markers. In this way, medical resources can be reasonably allocated and utilized.

Advantages of this study: The sample size is large enough, and different ultrasound soft markers are classified as high risk or low risk, and the number of each type is statistically analyzed to evaluate the probabilities of common chromosomal aneuploidies. This can provide data support from our research center for clinical genetic counseling.

Limitations of this study: Although the overall sample size is large, the distribution of different types of soft markers varies greatly, making it impossible to conduct statistical difference analysis. Therefore, the data results are only described. Moreover, sex chromosome abnormalities or chromosomal copy number variations (CNVs) were not assessed due to incomplete follow-up data and will be explored in our future studies. Finally, the total amount of data from a single center is insufficient, and multi - center data support is expected to improve statistical stability.

Declarations

Ethics approval and consent to participate

Approval for this study was obtained from the Ethics Review Committee of Sichuan Provincial Maternal and Child Health Hospital. Prior to undergoing CMA, High-throughput sequencing of chromosomes, NIPT, or karyotyping in accordance with the Declaration of Helsinki, all participants provided written informed consent. The data underwent anonymization.

Consent for publication

Not applicable.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

There were no competing interests in the study.

Author Contribution

Ping Zuo and Jing Wang collected datas, Dan Jiang and Shizeng Fan collected datas and write the main body of the article, Xueyan Wang and Na Xi provided research directions, writing ideas and reviewed the article.

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