International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Chromosomal Abnormalities Detected by Chromosomal Microarray Analysis and Karyotype in Fetuses with Ultrasound Abnormalities

Liubing Lan[1,2], Dandan Luo[1,2], Jianwen Lian[1], Lingna She[1,3], Bosen Zhang[1,3], Hua Zhong[1], Huaxian Wang[1], Heming Wu[1]

[1]Department of Prenatal Diagnostic Center, Meizhou People's Hospital, Meizhou, People's Republic of China; [2]Department of Obstetrics, Meizhou People's Hospital, Meizhou, People's Republic of China; [3]Department of Ultrasound, Meizhou People's Hospital, Meizhou, People's Republic of China

Correspondence: Heming Wu, Department of Prenatal Diagnostic Center, Meizhou People's Hospital, Meizhou, People's Republic of China, Email wuheming1986@126.com

Objective: Chromosomal microarray analysis (CMA) is a first-line test to assess the genetic etiology of fetal ultrasound abnormalities. The aim of this study was to evaluate the effectiveness of CMA in detecting chromosomal abnormalities in fetuses with ultrasound abnormalities, including structural abnormalities and non-structural abnormalities.

Methods: A retrospective study was conducted on 368 fetuses with abnormal ultrasound who received interventional prenatal diagnosis at Meizhou People's Hospital from October 2022 to December 2023. Samples of villi, amniotic fluid, and umbilical cord blood were collected according to different gestational weeks, and karyotype and CMA analyses were performed. The detection rate of chromosomal abnormalities in different ultrasonic abnormalities was analyzed.

Results: There were 368 fetuses with abnormal ultrasound, including 114 (31.0%) with structural abnormalities, 225 (61.1%) with non-structural abnormalities, and 29 (7.9%) with structural combined with non-structural abnormalities. The detection rate of aneuploidy and pathogenic (P)/likely pathogenic (LP) copy number variations (CNVs) of CMA in fetuses with structural abnormalities was 5.26% (6/114), the detection rate of karyotype was 2.63% (3/114), and the additional diagnosis rate of CMA was 2.63%. In the fetuses with ultrasonic non-structural abnormalities, the detection rate of karyotype was 6.22% (14/225), the detection rate of aneuploidy and P/LP CNVs in fetuses with ultrasonic structural abnormalities was 9.33% (21/225), and the additional diagnosis rate of CMA was 3.11%. There was no significant difference in chromosome abnormality detection rate of CMA among structural abnormality, non-structural abnormality, and structural abnormality combined with non-structural abnormality groups (5.3%, 9.3%, and 13.8%, $p = 0.241$), also among multiple ultrasonic abnormality and single ultrasonic abnormality groups (14.8%, and 7.3%, $p = 0.105$).

Conclusion: CMA can significantly improve the detection rate of genetic abnormalities in prenatal diagnosis of ultrasonic abnormal fetuses compared with karyotype analysis. CMA is a more effective tool than karyotyping alone in detecting chromosomal abnormalities in fetuses with ultrasound abnormalities.

Keywords: chromosomal microarray analysis, copy number variation, abnormal ultrasound fetus, prenatal diagnosis

Introduction

China is one of the countries with the highest incidence of birth defects in the world. The incidence of birth defects in China is about 5.6%, and the number of new birth defects is about 900,000 each year, accounting for 20% of the world's birth defects.[1] Birth defects are the main causes of early abortion, stillbirth, perinatal death, infant death, and congenital disability, which not only seriously endangers children's survival and quality of life but also causes huge life loss and social and economic burden.[2,3] Prenatal diagnosis is an effective method to prevent birth defects, and prenatal ultrasound imaging and genetic testing are important means of prenatal diagnosis.[4,5]

Received: 30 July 2024
Accepted: 1 October 2024
Published: 14 October 2024

As a routine technique for screening fetal malformation, prenatal ultrasonography can effectively prevent birth defects.[6,7] Prenatal ultrasonography is the application of physical characteristics of ultrasound to the fetus and its appendages for imaging examination. It is the most common, non-invasive, and repeatable method to understand the embryo and the main anatomical structure and general shape of the fetus.[8,9] Prenatal ultrasonography can not only evaluate fetal anatomy but also observe fetal movement and behavior in utero in real time and evaluate fetal hemodynamic changes.[10,11] Transabdominal and transperineal ultrasound also play an important role in assessing the prediction of labor and its progression.[12,13] We regard the fetus as an individual, and prenatal ultrasound plays an irreplaceable role in how its phenotype is expressed. Ultrasound screening during pregnancy is mainly divided into 11–13^{+6} weeks and 20–24^{+6} weeks.[8,14] Among them, 11–13^{+6} weeks is an important time for ultrasound screening of early fetal structural abnormalities, and more than 80% of abnormalities have been formed at this stage.[8] Ultrasound screening during early pregnancy (FTS) can pass: The nasal bone (NB) was observed, the thickness of the nuchal translucency (NT) was measured, and the tricuspid regurgy (TR) and abnormal venous catheter (aDV) Doppler waveform were observed to evaluate the risk of fetal chromosome aneuploidy.[15] After 20 weeks, the ultrasound can be used for the fetal growth restriction (FGR) diagnosis and fetal Doppler study, which result is very important for the fetal management.[16,17] Fetal ultrasound abnormalities can be classified into fetal structural abnormalities and non-structural abnormalities.[18]

Chromosome abnormalities account for more than 80% of the genetic causes of birth defects, mainly including chromosome number abnormalities, large fragment deletion/duplication and genome copy number variation (CNV).[19,20] Studies have reported that fetal ultrasound abnormalities are caused by about 12.4–35% chromosomal aberrations, about 25% by chromosomal karyotype structure or number abnormalities, and about 10% by chromosomal microstructure abnormalities.[21] When the fetal ultrasound is abnormal, genetic examination should be performed. Chromosomal karyotype analysis of fetal specimens has always been the gold standard for prenatal analysis of chromosomal defects in pregnant women, which can detect balanced translocation, inversion, deletion, insertion, and rearrangement of large fragments.[20,22] However, karyotype analysis is not sufficient to detect chromosomal submicrostructure abnormalities smaller than 5 mega base (MB).[23] Chromosomal microarray analysis (CMA) is the detection of CNV in the whole genome using cloned DNA probe. CMA can detect unbalanced chromosomal CNVs at the whole genome level and can be used to identify chromosomal abnormalities, including those with fragments too small to be detected by karyotyping, as well as minute chromosomal abnormalities.[24,25] In 2009, American College of Obstetrics and Gynecology (ACOG) recommended CMA technology for the first time for fetuses with abnormal ultrasound structure and normal karyotype, opening the application of CMA in prenatal diagnosis.[26] CMA was detected 3% to 6% more often in fetuses with abnormal ultrasound but normal karyotype.[25,27–29]

CMA has become a first-line diagnostic technology for fetal chromosome copy number deletion or duplication abnormalities. Studies on the detection rate of structural abnormalities of different fetal systems with CMA technology have different reports. The incidence and characteristics of birth defects and genetic diseases vary from population to region.[30,31] There are also great differences in the results of related studies in different regions and different races. In this study, 368 cases of fetal ultrasound abnormalities in the Department of Prenatal Diagnostic Center of Meizhou People's Hospital were retrospectively analyzed. Interventional prenatal diagnosis and CMA analysis were performed after informed consent, so as to evaluate the clinical significance of CMA in fetal ultrasound structural abnormalities and ultrasound soft indicators.

Materials and Methods

Study Cohort

A retrospective study was conducted on 368 fetuses with abnormal ultrasound who received interventional prenatal diagnosis in the Prenatal Diagnosis Center of Meizhou People's Hospital from October 2022 to December 2023. The inclusion criteria as follows: (1) fetuses conceived by pregnant women with childbearing age; and (2) fetuses with at least one abnormal ultrasound marker. Exclusion criteria were as follows: (1) pregnant women with multiple pregnancies; (2) fetus with threatened abortion; and (3) pregnant women who did not consent to participate in this study.

Chorionic villus sampling (CVS) was conducted at 10 to 12 weeks of gestation; amniotic fluid (10mL) was collected at 15 to 22 weeks; and cord blood (1.0–2.0mL) was sampled at 18 to 28 weeks. This study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the Human Ethics Committee of Meizhou People's Hospital. The written informed consent of pregnant couples for invasive prenatal diagnosis was obtained. The possibility of maternal cell contamination (MCC) of all fetal samples has been ruled out using Short tandem repeat (STR) detection, and the quantity and quality of fetal DNA samples meet the requirements of CMA testing.

Fetal ultrasound abnormalities included:

(1) Fetal ultrasound abnormalities included:

Fetal ultrasound structural abnormalities: cardiovascular system abnormalities, urinary system abnormalities, thoracic abnormalities, cephalic facial abnormalities, nervous system abnormalities, digestive system abnormalities, skeletal system abnormalities, abdominal wall abnormalities, and other malformations.

(2) Fetal ultrasound non-structural abnormalities:

a) Abnormal ultrasound soft indicators: NT thickening, ventriculomegaly, nasal bone dysplasia, choroid plexus cyst, short long bones, pyelic separation, echogenic bowel, single umbilical artery, tricuspid regurgitation, and pyelectasis.
b) Fetal growth restriction (FGR);
c) Abnormalities of amniotic fluid volume.

Main diagnostic criteria of fetal ultrasonographic soft markers:[32,33]

(1) NT thickening: 11–13^{+6} weeks of pregnancy, NT ≥ 3.5 mm;
(2) Nasal bone dysplasia/loss: no ossified nasal bone can be detected, or the nasal bone is short in length;
(3) Thickening of cervical fold (NF), NF ≥6mm after 15 weeks of gestation;
(4) Mild lateral ventricular widening (VM), measuring the width of the front or back foot of the lateral ventricle at any gestatory week >10mm;
(5) Mild renal dilatation (MP), measured in the short section of the kidney anterior and posterior pelvis diameter, more than 4mm in 14–20 weeks of pregnancy, more than 5mm in 20–30 weeks, more than 7mm after 30 weeks;
(6) Ventricular intense light spot (EIF), one side of the heart ventricle of the ventricle appeared spot-like isolated focal echo, similar to fetal bone tissue echo intensity;
(7) Enhanced bowel echo (EB), usually defined as a bowel echo equal to or greater than the surrounding fetal skeletal echo;
(8) Long bone short, femur/humerus < tenth percentile;
(9) Choroid plexus cyst (CPC) refers to the strong echo in the lateral ventricle at 16–24 weeks, and the echoless cystic structure in the choroid plexus;
(10) Single umbilical artery (SUA) is most easily displayed in the transverse section of the free umbilical cord, and only one artery is seen on both sides of the bladder;
(11) Widening of the posterior cranial fossa means that the diameter of the posterior cranial fossa is greater than 10mm.

G-Banding Karyotype Analysis

After cell culture of the collected fetal samples, the G-banding chromosome division phase map was observed under optical microscope after cell collection, section, and Giemsa staining. Twenty divisions were counted, five karyotypes were analyzed, and the chimeric type count was increased to 50–100 divisions. Chromosomal karyotypes were determined according to the International System for human Cytogenetic Nomenclature (ISCN).

CMA Detection and Data Analysis

DNA extraction of fetal sample was performed in strict accordance with the operating instructions (Qiagen, Valencia, CA, USA). The extracted DNA samples were cleaved, ligated, amplified, pure, quantified, fragmented, labeled, hybridized, washed, stained, scanned, and analyzed according to standard operating procedures (SOP). The chip used for CMA detection is Affymetrix Cytoscan 750K Array chip (Affymetrix, USA). Finally, the obtained original data is analyzed by the corresponding software. Test data that meets the data quality standards set by the test platform were analyzed and interpreted.

The CMA test results were analyzed and interpreted in combination with public databases commonly used internationally, such as the University of California Santa Cruz Database (UCSC) (https://genome.ucsc.edu), Phenotype in Humans using Ensembl Resources (DECIPHER) (http://decipher.sanger.ac.uk), Clinical Genome Resource (ClinGen) (https://www.clinicalgenome.org/), Database of Genomic Variants (DGV) (http://dgv.tcag.ca/dgv/app/homr), and Online Mendelian Inheritance Database in Man (OMIM) (https://www.omim.org). According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the clinical significance of CNVs is divided into 5 grades: pathogenic (P) CNV, likely pathogenic (LP) CNV, variants of uncertain significance (VUS) CNV, likely benign (LB) CNV, and benign (B) CNV.[34,35] Deletion or duplication regions are defined as P/LP CNV if they contain key regions with known microdeletion/microduplication syndromes, carry OMIM pathogenic genes, or are clinically significant in relatives inherited from phenotypic abnormalities that have been reported in multiple literature or databases.

Results

Baseline Characteristics of Study Cohort

Of the 368 fetuses included in the study, there were 314 (85.3%) fetuses of pregnant women under the age of 35 years old, and 54 (14.7%) fetuses of pregnant women aged >35 years old. At the time of inclusion in this study, there were 93 cases (25.3%) with gestational weeks ≤13 weeks, 228 cases (61.9%) with gestational weeks 14–28 weeks, and 47 cases (13.0%) with gestational weeks >28 weeks. Among the fetuses undergoing interventional prenatal diagnosis due to abnormal ultrasound, there were 55 (14.9%), 312 (84.8%) and 1 (0.3%) samples were villus, amniotic fluid, and cord blood, respectively. Among the fetuses with abnormal ultrasound, 114 cases (31.0%) had structural abnormalities, 225 cases (61.1%) had non-structural abnormalities, and 29 cases (7.9%) had both structural and non-structural abnormalities (Table 1).

Table 1 Demographic Characteristics of Pregnant Women and General Characteristics of Fetuses

Characteristics	All Cases (n=368)
Age of mothers who had abortions (years)	
<35, n(%)	314(85.3%)
≥35, n(%)	54(14.7%)
Gestational week at the time of discovery of fetal abnormalities (weeks)	
≤13, n(%)	93(25.3%)
14–28, n(%)	228(62.0%)
>28, n(%)	47(12.8%)
Type of samples tested by invasive prenatal diagnosis	
Villus, n(%)	55(14.9%)
Amniotic fluid, n(%)	312(84.8%)
Cord blood, n(%)	1(0.3%)
Abnormal fetal ultrasound types	
Structural abnormalities, n(%)	114(31.0%)
Non-structural abnormalities, n(%)	225(61.1%)
Structural abnormalities + non-structural abnormalities, n(%)	29(7.9%)

The Relationship Between Fetal Ultrasonic Structural Abnormalities and Chromosomal Abnormalities

There were 110 (29.9%, 110/368) fetuses with single ultrasound structural abnormality and 4 (1.1%, 4/368) fetuses with multiple ultrasonic structural aberrations. In the fetuses with single structural abnormality of ultrasound, in order from the most to the least number of cases: 38 (33.33%) with cardiovascular system abnormality, 22 (19.30%) with urinary system abnormality, 11 (9.65%) with thoracic abnormality, 10 (8.77%) cephalic facial abnormality, 9 (7.89%) with nervous system abnormality, 6 (5.26%) with digestive system abnormality, 6 (5.26%) with skeletal system abnormality, and 2 (1.75%) with abdominal wall abnormality. The detection rate of aneuploidy and P/LP CNVs in fetuses with ultrasonic structural abnormalities was 5.26% (6/114), the detection rate of chromosome karyotype was 2.63% (3/114), and the additional diagnosis rate of CMA was 2.63%. In the fetuses with single structural abnormality of ultrasound, the detection rate of aneuploidy and P/LP CNVs in fetuses with ultrasonic structural abnormalities was 4.55% (5/110), the detection rate of chromosome karyotype was 1.82% (2/110), and the additional diagnosis rate of CMA was 2.73% (Table 2).

The Relationship Between Fetal Ultrasonic Non-Structural Abnormalities and Chromosomal Abnormalities

In this study, the fetuses with non-structural ultrasound abnormalities included 212 (57.6%, 212/368) fetuses with abnormal ultrasound soft markers, 30 (8.2%, 30/368) fetuses with growth restriction, 8 (2.2%, 8/368) fetuses with abnormal amniotic fluid volume, and 5 (1.4%, 5/368) fetuses with multiple non-structural abnormalities. In fetuses with abnormal ultrasound soft markers, there were 81 (36.00%) fetuses with NT thickening, 29 (12.89%) fetuses with ventriculomegaly, 24 (10.67%) fetuses with nasal bone dysplasia, 9 (4.00%) fetuses with choroid plexus cyst, 6 (2.67%) fetuses with short long bones, 6 (2.67%) fetuses with NT thickening + choroid plexus cyst, and 5 (2.22%) fetuses with pyelic separation. In the fetuses with abnormal ultrasound soft markers, the detection rate of chromosome karyotype was 7.69% (14/182), the detection rate of aneuploidy and P/LP CNVs in fetuses with ultrasonic structural abnormalities was 9.89% (18/182), and the additional diagnosis rate of CMA was 2.2%. In the fetuses with ultrasonic non-structural abnormalities, the detection rate of chromosome karyotype was 6.22% (14/225), the detection rate of aneuploidy and P/LP CNVs in fetuses with ultrasonic structural abnormalities was 9.33% (21/225), and the additional diagnosis rate of CMA was 3.11% (Table 3).

The Relationship Between Fetuses with Structural Abnormalities Combined with Non-Structural Abnormalities and Chromosomal Abnormalities

In this study, there were 29 fetuses with structural abnormalities combined with non-structural abnormalities. In fetuses with structural abnormalities combined with non-structural abnormalities, NT thickening combined with structural abnormalities (2.17%, 8/368) and ventriculomegaly combined with structural abnormalities (1.63%, 6/368) were common. In the fetuses with structural abnormalities combined with non-structural abnormalities, the detection rate of chromosome karyotype was 6.90% (2/29), the detection rate of aneuploidy and P/LP CNVs in fetuses with ultrasonic structural abnormalities was 13.79% (4/29), and the additional diagnosis rate of CMA was 6.89% (Table 4).

Comparison of Chromosome Abnormality Rate Among Different Abnormal Fetal Ultrasound Types and Groups of Different Number of Abnormal Ultrasonic Items

The rates of chromosomal abnormalities were compared between fetuses with different types of ultrasound abnormalities. There was no significant difference in chromosome abnormality detection rate of CMA among structural abnormality, non-structural abnormality, and structural abnormality combined with non-structural abnormality groups (all $p > 0.05$). According to the different ultrasonic abnormalities, these fetuses were divided into single ultrasonic abnormality group and multiple ultrasonic abnormalities group. The chromosome abnormality detection rate of CMA and karyotype in multiple abnormalities group was higher than those in single abnormality group, but the differences were not statistically significant ($p>0.05$) (Table 5).

Table 2 The Relationship Between Fetal Ultrasonic Structural Abnormalities and Chromosomal Abnormalities

Structural Abnormalities	n (%)*	CMA				Karyotype		
		Aneuploidy	P/LP CNVs	VUS	Detection Rate of Aneuploidy and P/LP CNVs	Aneuploidy	Abnormal Chromosomal Karyotype	Detection Rate of Aneuploidy and Abnormal Chromosomal Karyotype
Single structural abnormality								
Cardiovascular system abnormality	38(33.33%)	1	2	3	4.55%	1	0	1.82%
Urinary system abnormality	22(19.30%)	0	1	1		0	0	
Thoracic abnormality	11(9.65%)	0	0	1		0	1	
Cephalic facial abnormality	10(8.77%)	0	0	1		0	0	
Nervous system abnormality	9(7.89%)	0	0	2		0	0	
Digestive system abnormality	6(5.26%)	0	0	0		0	0	
Skeletal system abnormality	6(5.26%)	0	0	2		0	0	
Abdominal wall abnormality	2(1.75%)	0	1	0		0	0	
Other malformations	6(5.26%)	0	0	0		0	0	
Multiple structural aberrations								
Nervous system abnormality + Cardiovascular system abnormality	2(1.75%)	1	0	0	–	1	0	–
Cephalic facial abnormality + Skeletal system abnormality	1(0.88%)	0	0	0		0	0	
Skeletal system abnormality + Other malformations	1(0.88%)	0	0	0		0	0	
Total	114(100.0%)	2	4	10	5.26%	2	1	2.63%

Note: *Constituent ratio.

Abbreviations: CMA, chromosome microarray analysis; CNV, copy number variant; P/LP CNV, Pathogenic/Likely pathogenic CNV; VUS, variants of uncertain significance.

Table 3 The Relationship Between Fetal Ultrasonic Non-Structural Abnormalities and Chromosomal Abnormalities

Non-Structural Abnormalities	n (%)*	CMA				Karyotype		
		Aneuploidy	P/LP CNVs	VUS	Detection Rate of Aneuploidy and P/LP CNVs	Aneuploidy	Abnormal Chromosomal Karyotype	Detection Rate of Aneuploidy and Abnormal Chromosomal Karyotype
Abnormal ultrasound soft markers								
NT thickening	81(36.00%)	3	7	10	9.89%	4	4	7.69%
Ventriculomegaly	29(12.89%)	0	2	2		0	1	
Nasal bone dysplasia	24(10.67%)	1	0	2		1	0	
Choroid plexus cyst	9(4.00%)	0	1	0		0	2	
Short long bones	6(2.67%)	0	0	1		0	0	
NT thickening + Choroid plexus cyst	6(2.67%)	0	0	0		0	0	
Pyelic separation	5(2.22%)	0	0	2		0	0	
Echogenic bowel	4(1.78%)	0	0	0		0	0	
Single umbilical artery	3(1.33%)	0	0	0		0	0	
Tricuspid regurgitation	2(0.89%)	0	1	1		0	0	
Pyelectasis	2(0.89%)	0	1	1		0	0	
NT thickening + Nasal bone dysplasia	2(0.88%)	0	1	1		1	0	
Persistent left superior vena cava	1(0.44%)	0	0	0		0	0	
NT thickening + Single umbilical artery	1(0.44%)	0	1	0		0	0	
Nasal bone dysplasia + Echogenic bowel	1(0.44%)	0	0	0		0	0	
Nasal bone dysplasia + Single umbilical artery	1(0.44%)	0	0	0		0	0	
Nasal bone dysplasia + Choroid plexus cyst	1(0.44%)	0	0	0		0	1	
Ventriculomegaly + Renal cyst	1(0.44%)	0	0	0		0	0	
Single umbilical artery + Choroid plexus cyst	1(0.44%)	0	0	0		0	0	
Ventriculomegaly + Pyelic separation	1(0.44%)	0	0	0		0	0	
Ventriculomegaly + Pyelectasis	1(0.44%)	0	0	0		0	0	
Fetal growth restriction	30(13.33%)	0	2	3	6.67%	0	0	0
Abnormalities of amniotic fluid volume	8(3.56%)	0	0	1	0	0	0	0
Multiple non-structural aberrations								
NT thickening + Fetal growth restriction	2(0.89%)	0	1	0	20.0%	0	0	0
Single umbilical artery + Fetal growth restriction	1(0.44%)	0	0	1		0	0	
Nasal bone dysplasia + Fetal growth restriction + Abnormalities of amniotic fluid volume	1(0.44%)	0	0	0		0	0	
Pyelic separation + Abnormalities of amniotic fluid volume	1(0.44%)	0	0	0		0	0	
Total	225(100.0%)	4	17	25	9.33%	6	8	6.22%

Note: *Constituent ratio.

Abbreviations: CMA, chromosome microarray analysis; CNV, copy number variant; VUS, variants of uncertain significance.

Table 4 The Relationship Between Fetuses with Structural Abnormalities Combined with Non-Structural Abnormalities and Chromosomal Abnormalities

Fetal Ultrasound Structural Abnormalities Combined with Non-Structural Abnormalities	n	CMA				Karyotype		
		Aneuploidy	P/LP CNVs	VUS	Detection Rate of Aneuploidy and P/LP CNVs	Aneuploidy	Abnormal Chromosomal Karyotype	Detection Rate of Aneuploidy and Abnormal Chromosomal Karyotype
NT thickening + Other malformations	1	0	0	0		0	0	
NT thickening + Cephalic facial abnormalities + Skeletal system abnormalities	1	0	1	0		0	0	
NT thickening + Cephalic facial abnormalities + Abdominal wall abnormalities	1	0	0	0		0	0	
NT thickening + Cephalic facial abnormalities	1	0	0	0		0	0	
NT thickening + Abdominal wall abnormalities	1	0	0	0		0	0	
NT thickening + Cardiovascular system abnormalities	1	0	0	0		0	0	
NT thickening + Short long bones + Skeletal system abnormalities	1	0	0	0		0	0	
NT thickening + Nasal bone dysplasia + Thoracic abnormalities + Skeletal system abnormalities	1	1	0	0		1	0	
Nasal bone dysplasia + Skeletal system abnormalities	1	1	0	0		1	0	
Ventriculomegaly + Abnormalities of amniotic fluid volume + Cardiovascular system abnormalities	1	0	1	0		0	0	
Ventriculomegaly + Nervous system abnormalities	1	0	0	0		0	0	
Ventriculomegaly + Cardiovascular system abnormalities	1	0	0	1		0	0	
Ventriculomegaly + Cardiovascular system abnormalities	1	0	0	0		0	0	
Ventriculomegaly + Fetal growth restriction + Nervous system abnormalities	1	0	0	0		0	0	
Ventriculomegaly + nasal bone dysplasia + Nervous system abnormalities + Skeletal system abnormalities	1	0	0	0		0	0	
Echogenic bowel + Cardiovascular system abnormalities	1	0	0	0		0	0	
Echogenic bowel + Thoracic abnormalities	1	0	0	0		0	0	
Pyelectasis + Digestive system abnormalities	1	0	0	0		0	0	
Single umbilical artery + Abdominal wall abnormalities	1	0	0	0		0	0	
Single umbilical artery + Cardiovascular system abnormalities	1	0	0	0		0	0	
Short long bones + Pyelectasis + Abnormalities of amniotic fluid volume + Skeletal system abnormalities	1	0	0	0		0	0	
Posterior fossa malformations + Nervous system abnormalities	1	0	0	1		0	0	
Choroid plexus cyst + Cephalic facial abnormalities	1	0	0	0		0	0	
Choroid plexus cyst + Thoracic abnormalities	1	0	0	0		0	0	
Choroid plexus cyst + Cardiovascular system abnormalities	2	0	0	0		0	0	
Pyelectasis + Cardiovascular system abnormalities	1	0	0	0		0	0	
Abnormalities of amniotic fluid volume + Urinary system abnormalities	1	0	0	0		0	0	
Fetal growth restriction + Cardiovascular system abnormalities	1	0	0	0		0	0	
Total	29	2	2	3	13.79%	2	0	6.90%

Note: *Constituent ratio.

Abbreviations: CMA, chromosome microarray analysis; CNV, copy number variant; VUS, variants of uncertain significance.

Table 5 Comparison of Chromosome Abnormality Rate Among Different Abnormal Fetal Ultrasound Types and Groups of Different Number of Abnormal Ultrasonic Items

Groups	Number of Cases	CMA			Karyotype		
		Aneuploidy	P/LP CNVs	Aneuploidy and P/LP CNVs	Aneuploidy	Abnormal Chromosomal Karyotype	Aneuploidy and Abnormal Chromosomal Karyotype
Abnormal fetal ultrasound types							
Structural abnormalities	114	2(1.8%)	4(3.5%)	6(5.3%)	2(1.8%)	1(0.9%)	3(2.6%)
Non-structural abnormalities	225	4(1.8%)	17(7.6%)	21(9.3%)	6(2.7%)	8(3.6%)	14(6.2%)
Structural abnormalities + non-structural abnormalities, n(%)	29	2(6.9%)	2(6.9%)	4(13.8%)	2(6.9%)	0(0)	2(6.9%)
p values		0.189 (χ^2=3.302)	0.319 (χ^2=2.137)	0.241 (χ^2=2.801)	0.242 (χ^2=2.318)	0.333 (χ^2=3.064)	0.247 (χ^2=2.185)
Number of abnormal ultrasonic items							
Single abnormality	314	5(1.6%)	18(5.7%)	23(7.3%)	6(1.9%)	8(2.5%)	14(4.5%)
Multiple abnormalities	54	3(5.6%)	5(9.3%)	8(14.8%)	4(7.4%)	1(1.9%)	5(9.3%)
p values		0.098 (χ^2=3.403)	0.357 (χ^2=0.978)	0.105 (χ^2=3.351)	0.044 (χ^2=5.266)	1.000 (χ^2=0.094)	0.174 (χ^2=2.169)

Abbreviations: CMA, chromosome microarray analysis; CNV, copy number variant; P/LP CNV, Pathogenic/Likely pathogenic CNV.

https://doi.org/10.2147/IJGM.S483290

Discussion

Fetal structural development abnormalities are congenital birth defects characterized by morphological and structural abnormalities, often accompanied by changes in genetic material. Fetal structural abnormalities can be transmitted to offspring by genetic material of germ cells such as chromosomal abnormalities, gene mutations, environmental factors, and other unknown causes.[36,37] The fetus may also have some minor anatomical changes and abnormalities (known as non-structural abnormalities), and associated with an increased risk of fetal genetic abnormalities.[38] At present, prenatal ultrasonography can detect the vast majority of fetal morphological and structural abnormalities, as well as some minor anatomical changes.[39] Studies have shown that 2–4% of fetuses during pregnancy have structural abnormalities.[40] Ultrasound can detect most fetal structural abnormalities, and the detection rate varies according to different stages of pregnancy and different tissue systems.

In this study, in the group of single ultrasonic structural abnormalities, the number of cardiovascular system abnormalities was the largest (38 cases, 33.3%), which was consistent with the main types of fetal congenital structural abnormalities.[41] NT thickening is an independent marker of fetal chromosome aneuploidy and an indicator for further interventional prenatal diagnosis and genetic analysis.[42] Bromley et al reported that the detection rate of trisomy 21 was 41.7% in fetuses with NT thickening but no other structural malformations detected by ultrasound.[43] In this study, a total of 10 fetuses with chromosome aneuploidy were detected by karyotype analysis, and 6 of them showed NT thickening. Ventriculomegaly means that the width of the anterior or posterior foot of the lateral ventricle is measured between 10–15mm at any gestational week, and more than 50% of the non-isolated mild lateral ventricular widening is often associated with central nervous system abnormalities.[44,45] Nasal bone dysplasia/deletion refers to undetectable ossification of the nasal bone or short length of the nasal bone, which is closely related to trisomy 21 syndrome, trisomy 18 syndrome, and trisomy 13 syndrome and is an indication of interventional prenatal diagnosis.[46] CMA can not only detect chromosome aneuploidy but also detect chromosome microdeletion and microduplication.[47] Pan et al[48] conducted CMA analysis on fetuses with nasal bone abnormalities and found that 17.7% of fetuses had chromosomal abnormalities, and the detection rate was higher when nasal bone abnormalities combined with other soft markers or structural abnormalities. In this study, a total of 10 fetuses with chromosome aneuploidy were detected by karyotype analysis, and 3 of them showed nasal bone dysplasia. There are many kinds of fetal ultrasound soft indicators, the incidence of chromosomal abnormalities varies among different isolated ultrasound soft indicators.[33,49]

Compared with traditional karyotype analysis, CMA can improve the detection rate. The study of Ronald et al showed that 6.0% pCNVs were detected by CMA in fetuses with abnormal ultrasound but normal karyotype analysis.[27] Liao C has detected pCNVs in 11.4% of 446 fetuses with abnormal ultrasound but normal karyotype analysis.[50] In Malgorzata I Srebniak's study, aneuploid abnormalities were excluded in 1033 fetuses with abnormal ultrasound, and 7.3% pCNVs were detected by CMA.[51] Therefore, in the prenatal diagnosis of abnormal fetuses with ultrasound, in addition to chromosome karyotype analysis, it is recommended to further perform CMA detection, which can detect chromosome microdeletions and microduplications, and improve the detection rate of fetal chromosome abnormalities.

In addition, the detection rate of chromosome abnormalities in fetuses with non-isolated structural abnormalities is significantly higher than that in fetuses with isolated abnormalities.[52–54] In Shaffer's study, the detection rate of CMA in the group with multiple fetal structural abnormalities was higher than that in the group with single structural abnormalities, and the difference was statistically significant.[55] Mastromoro et al found that the detection rate of pathogenic CNVs was 19.47% for single structural abnormality and 27.47% for multiple structure abnormalities after CMA was performed on abnormal fetal ultrasound.[56] Lee et al found that the detection rate of pCNVs was 10.5% in fetuses with a single ultrasound structural abnormality and 15.4% in fetuses with multiple ultrasound structural abnormalities.[57] In this study, there was no significant difference in chromosome abnormality detection rate among structural abnormality group, non-structural abnormality group, and structural abnormality combined with non-structural abnormality group. However, the chromosome abnormality detection rate of the group with structural abnormality combined with non-structural abnormality was higher than that of the other two groups. According to the different ultrasonic abnormalities, they were divided into single ultrasonic abnormality group and multiple ultrasonic abnormality group. The detection rate of chromosome abnormalities in the multiple ultrasonic abnormality group was higher than that in the single ultrasonic

abnormality group, but the difference was not statistically significant. It may be related to the small sample size of this study.

Moreover, the detection rate of chromosome abnormality in FGR alone was 6.67%, but no chromosome abnormality was detected in amniotic fluid alone. The study by Dap et al found that the rate of chromosomal abnormalities in fetuses with FGR was 10.5%.[58] Zhu et al found that the rate of chromosomal abnormalities in fetuses with FGR was 10.5% detected by CMA.[59] Result from a multicenter study in Spain showed that chromosome abnormality detection rate of CMA in fetuses with FGR was 6.8%.[60] One study from Israel showed that the detection rate of P/LP variants was 6.3% in 174 FGR fetuses.[61] The differences between these findings may be due to the different genetic backgrounds of the population and the different sample sizes included in the studies.

Providing appropriate testing of genetic material for fetuses with abnormal ultrasound can help to discover the genetic causes of fetal abnormalities, at the same time, to evaluate the prognosis of the fetuses, formulate appropriate delivery methods and neonatal management plans, and provide re-fertility risk assessment.[62] It is believed that with the continuous improvement of CNV database, CMA will play a greater value in clinical application. The limitation of CMA is that it is difficult to detect low proportion of chromosome mosaicism and balance structural abnormalities. It is suggested that chromosome karyotype analysis combined with CMA detection should be performed on fetuses with ultrasound abnormalities. The two methods complement each other to improve the detection rate and accuracy of abnormal results.

There were some limitations in this study. First, because the sample size included in the study was not large, this study did not summarize the chromosomal abnormalities of various structural abnormalities. Because some types of structural abnormalities have their associated chromosomal abnormalities.[63,64] Second, due to the relatively small number of cases with multiple structural abnormalities in this study, it did not compare the chromosomal abnormalities of fetuses with single and multiple structural abnormalities. Some studies generally believe that the incidence of chromosomal aberrations in fetuses with multiple structural abnormalities is higher than that in fetuses with single structural abnormalities.[65] Third, due to the limitation of sample size, this study did not summarize the variation regions with significant directional characteristics for different fetal ultrasound structural abnormalities and fetal ultrasound non-structural abnormalities. Therefore, we need to conduct a larger sample size study to enrich the relevant data.

Conclusions

Compared with the traditional chromosome karyotype analysis, CMA can significantly improve the detection rate of genetic abnormalities in prenatal diagnosis of fetuses with ultrasound abnormalities. There was no significant difference in chromosome abnormality detection rate among structural abnormality, non-structural abnormality, and structural abnormality combined with non-structural abnormality groups, also among multiple ultrasonic abnormality and single ultrasonic abnormality groups, suggesting the necessity of CMA detection for all fetuses with abnormal ultrasound.

Data Sharing Statement

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

Ethics Approval

All participants were informed on the study procedures and goals and the study obtained written informed consent from all the participants. This study was approved by the Human Ethics Committees of Meizhou People's Hospital.

Acknowledgments

The author would like to thank other colleagues who were not listed in the authorship for their helpful comments on the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by and the Scientific Research Cultivation Project of Meizhou People's Hospital (Grant No.: PY-C2024018), and the Science and Technology Program for Social Development of Meizhou (Grant No.: 2023B37, and 2023B38).

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Zhang Y, Wang J, Zhao J, et al. Current status and challenges in prenatal and neonatal screening, diagnosis, and management of congenital heart disease in China. *Lancet Child Adolesc Health*. 2023;7(7):479–489. doi:10.1016/S2352-4642(23)00051-2
2. Mumpe-Mwanja D, Barlow-Mosha L, Williamson D, et al. A hospital-based birth defects surveillance system in Kampala, Uganda. *BMC Pregnancy Childbirth*. 2019;19(1):372. doi:10.1186/s12884-019-2542-x
3. Mitchell LE. Maternal effect genes: update and review of evidence for a link with birth defects. *HGG Adv*. 2022;3(1):100067. doi:10.1016/j.xhgg.2021.100067
4. Xie D, Liang C, Xiang Y, et al. Prenatal diagnosis of birth defects and termination of pregnancy in Hunan Province, China. *Prenat Diagn*. 2020;40(8):925–930. doi:10.1002/pd.5648
5. Huang W, Gu H. Identifying biomarkers for prenatal diagnosis of neural tube defects based on "omics". *Clin Genet*. 2022;101(4):381–389. doi:10.1111/cge.14087
6. Koukoura O, Kelesidou V, Delianidou M, Athanasiadis A, Dagklis T. Prenatal sonographic diagnosis of biliary tract malformations. *J Clin Ultrasound*. 2019;47(5):292–297. doi:10.1002/jcu.22705
7. Tonni G, Peixoto AB, Werner H, Grisolia G, Ruano R. Ultrasound and fetal magnetic resonance imaging: clinical performance in the prenatal diagnosis of orofacial clefts and mandibular abnormalities. *J Clin Ultrasound*. 2023;51(2):346–361. doi:10.1002/jcu.23403
8. Syngelaki A, Hammami A, Bower S, Zidere V. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2019;54(4):468–476. doi:10.1002/uog.20844
9. Hao X, Wu J, Fu W, et al. Prenatal diagnosis of fetuses with Emanuel syndrome: results of ultrasound examination and invasive genetic testing. *Prenat Diagn*. 2022;42(4):469–477. doi:10.1002/pd.6098
10. Lai J, Nowlan NC, Vaidyanathan R, Visser GHA, Lees CC. The use of actograph in the assessment of fetal well-being. *J Matern Fetal Neonatal Med*. 2020;33(12):2116–2121. doi:10.1080/14767058.2018.1540584
11. Nakamura M, Oba T, Salafia CM, et al. Ultrasonographic study of umbilical cord twist direction during second trimester. *J Matern Fetal Neonatal Med*. 2022;35(22):4233–4239. doi:10.1080/14767058.2020.1849098
12. Usman S, Wilkinson M, Barton H, Lees CC. The feasibility and accuracy of ultrasound assessment in the labor room. *J Matern Fetal Neonatal Med*. 2019;32(20):3442–3451. doi:10.1080/14767058.2018.1465553
13. La Verde M, De Franciscis P, Torre C, et al. Accuracy of fetal biacromial diameter and derived ultrasonographic parameters to predict shoulder dystocia: a prospective observational study. *Int J Environ Res Public Health*. 2022;19(9):5747. doi:10.3390/ijerph19095747
14. Sotiriadis A, Figueras F, Eleftheriades M, Papaioannou GK. First-trimester and combined first- and second-trimester prediction of small-for-gestational age and late fetal growth restriction. *Ultrasound Obstet Gynecol*. 2019;53(1):55–61. doi:10.1002/uog.19055
15. Traisrisilp K, Sirichotiyakul S, Tongprasert F, et al. First trimester genetic sonogram for screening fetal Down syndrome: a population-based study. *Taiwan J Obstet Gynecol*. 2021;60(4):706–710. doi:10.1016/j.tjog.2021.05.021
16. Baschat AA. Arterial and venous Doppler in the diagnosis and management of early onset fetal growth restriction. *Early Human Development. Early Hum Dev*. 2005;81(11):877–887. doi:10.1016/j.earlhumdev.2005.09.008
17. La Verde M, Savoia F, Riemma G, et al. Fetal aortic isthmus Doppler assessment to predict the adverse perinatal outcomes associated with fetal growth restriction: systematic review and meta-analysis. *Arch Gynecol Obstet*. 2024;309(1):79–92. doi:10.1007/s00404-023-06963-4
18. Benn P, Borrell A, Chiu RW, et al. Position statement from the chromosome abnormality screening committee on behalf of the board of the international society for prenatal diagnosis. *Prenat Diagn*. 2015;35(8):725–734. doi:10.1002/pd.4608
19. Zeng W, Qi H, Du Y, et al. Analysis of potential copy-number variations and genes associated with first-trimester missed abortion. *Heliyon*. 2023;9(8):e18868. doi:10.1016/j.heliyon.2023.e18868
20. Liu X, Liu S, Wang H, Hu T. Potentials and challenges of chromosomal microarray analysis in prenatal diagnosis. *Front Genet*. 2022;13:938183. doi:10.3389/fgene.2022.938183
21. Badeau M, Lindsay C, Blais J, et al. Genomics-based non-invasive prenatal testing for detection of fetal chromosomal aneuploidy in pregnant women. *Cochrane Database Syst Rev*. 2017;11(11):Cd011767. doi:10.1002/14651858.CD011767.pub2
22. Ozkan E, Lacerda MP. Genetics, Cytogenetic Testing And Conventional Karyotype. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing LLC.; 2024. PMID: 33085440.
23. Sato T, Migita O, Hata H, Okamoto A, Hata K. Analysis of chromosome microstructures in products of conception associated with recurrent miscarriage. *Reprod Biomed Online*. 2019;38(5):787–795. doi:10.1016/j.rbmo.2018.12.010
24. Xie Y, Sun X. Chromosomal microarray analysis in prenatal diagnosis. *Clin Exp Obstet Gynecol*. 2017;44(2):177–179. PMID: 29746015.
25. Xia M, Yang X, Fu J, Teng Z, Lv Y, Yu L. Application of chromosome microarray analysis in prenatal diagnosis. *BMC Pregnancy Childbirth*. 2020;20(1):696. doi:10.1186/s12884-020-03368-y

26. ACOG Committee Opinion No. 446: array comparative genomic hybridization in prenatal diagnosis. *Obstet Gynecol*. 2009;114(5):1161–1163. doi:10.1097/AOG.0b013e3181c33cad
27. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med*. 2012;367(23):2175–2184. doi:10.1056/NEJMoa1203382
28. Hillman SC, McMullan DJ, Hall G, et al. Use of prenatal chromosomal microarray: prospective cohort study and systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2013;41(6):610–620. doi:10.1002/uog.12464
29. Rodriguez-Revenga L, Madrigal I. Chromosome microarray analysis should be offered to all invasive prenatal diagnostic testing following a normal rapid aneuploidy test result. *Clin Genet*. 2020;98(4):379–383. doi:10.1111/cge.13810
30. Le MT, Shumate CJ. The prevalence of birth defects among non-Hispanic Asian/Pacific Islanders and American Indians/Alaska Natives in Texas, 1999–2015. *Birth Defects Res*. 2019;111(18):1380–1388. doi:10.1002/bdr2.1543
31. Duong SQ, Elfituri MO, Zaniletti I, et al. Neighborhood childhood opportunity, race/ethnicity, and surgical outcomes in children with congenital heart disease. *J Am Coll Cardiol*. 2023;82(9):801–813. doi:10.1016/j.jacc.2023.05.069
32. Hu T, Tian T, Zhang Z, et al. Prenatal chromosomal microarray analysis in 2466 fetuses with ultrasonographic soft markers: a prospective cohort study. *Am J Obstet Gynecol*. 2021;224(5):516.e511–516.e516. doi:10.1016/j.ajog.2020.10.039
33. Pan L, Wu J, Liang D, et al. Association analysis between chromosomal abnormalities and fetal ultrasonographic soft markers based on 15,263 fetuses. *Am J Obstet Gynecol MFM*. 2023;5(10):101072. doi:10.1016/j.ajogmf.2023.101072
34. Riggs ER, Andersen EF, Cherry AM, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). *Genet Med*. 2020;22(2):245–257. doi:10.1038/s41436-019-0686-8
35. Brandt T, Sack LM. Adapting ACMG/AMP sequence variant classification guidelines for single-gene copy number variants. *Genet Med*. 2020;22(2):336–344. doi:10.1038/s41436-019-0655-2
36. Jin SC, Homsy J, Zaidi S, Lu Q. Contribution of rare inherited and de novo variants in 2871 congenital heart disease probands. *Nat Genet*. 2017;49(11):1593–1601. doi:10.1038/ng.3970
37. Simpson JL, Rechitsky S, Kuliev A. Before the beginning: the genetic risk of a couple aiming to conceive. *Fertil Steril*. 2019;112(4):622–630. doi:10.1016/j.fertnstert.2019.08.002
38. Costa BC, Grangeia A, Galvão J, et al. Prenatal diagnosis study using array comparative genomic hybridization for genotype-phenotype correlation in 772 fetuses. *Ann Diagn Pathol*. 2022;61:152059. doi:10.1016/j.anndiagpath.2022.152059
39. Ramirez Zegarra R, Ghi T. Use of artificial intelligence and deep learning in fetal ultrasound imaging. *Ultrasound Obstet Gynecol*. 2023;62(2):185–194. doi:10.1002/uog.26130
40. Hui AS, Chau MHK. The role of chromosomal microarray analysis among fetuses with normal karyotype and single system anomaly or nonspecific sonographic findings. *Acta Obstet Gynecol Scand*. 2021;100(2):235–243. doi:10.1111/aogs.14003
41. Findley TO, Northrup H. The current state of prenatal detection of genetic conditions in congenital heart defects. *Transl Pediatr*. 2021;10(8):2157–2170. doi:10.21037/tp-20-315
42. Ji X, Li Q, Qi Y, et al. When NIPT meets WES, prenatal diagnosticians face the dilemma: genetic etiological analysis of 2328 cases of NT thickening and follow-up of pregnancy outcomes. *Front Genet*. 2023;14:1227724. doi:10.3389/fgene.2023.1227724
43. Bromley B, Shipp TD, Lyons J, Groszmann Y, Navathe RS, Benacerraf BR. What is the importance of second-trimester ”soft markers” for trisomy 21 after an 11- to 14-week aneuploidy screening scan? *J Ultrasound Med*. 2014;33(10):1747–1752. doi:10.7863/ultra.33.10.1747
44. Giorgione V, Haratz KK. Fetal cerebral ventriculomegaly: what do we tell the prospective parents? *Prenat Diagn*. 2022;42(13):1674–1681. doi:10.1002/pd.6266
45. Vasung L, Rollins CK, Zhang J, et al. Abnormal development of transient fetal zones in mild isolated fetal ventriculomegaly. *Cereb Cortex*. 2023;33(4):1130–1139. doi:10.1093/cercor/bhac125
46. Zhou Y, Wu S, Han J, et al. Prenatal diagnosis of ultrasound soft markers in a single medical center of mainland China. *Mol Cytogenet*. 2023;16(1):3. doi:10.1186/s13039-022-00633-x
47. Kang H, Chen Y, Wang L, Gao C, Li X, Hu Y. Pathogenic recurrent copy number variants in 7078 pregnancies via chromosomal microarray analysis. *J Perinat Med*. 2024;52(2):171–180. doi:10.1515/jpm-2022-0580
48. Pan L, Liang H, Meng Z, Wang J, Zhang R, Wu Y. Assessing the value of second-trimester nasal bone hypoplasia in predicting chromosomal abnormalities: a retrospective chromosomal microarray analysis of 351 fetuses. *Arch Gynecol Obstet*. 2023;308(4):1263–1270. doi:10.1007/s00404-022-06808-6
49. D’Addario V. Diagnostic approach to fetal ventriculomegaly. *J Perinat Med*. 2024;51(1):111–116. doi:10.1515/jpm-2022-0312
50. Liao C, Fu F, Li R, et al. Implementation of high-resolution SNP arrays in the investigation of fetuses with ultrasound malformations: 5 years of clinical experience. *Clin Genet*. 2014;86(3):264–269. doi:10.1111/cge.12271
51. Srebniak MI, Boter M, Oudesluijs GO, et al. Genomic SNP array as a gold standard for prenatal diagnosis of foetal ultrasound abnormalities. *Mol Cytogenet*. 2012;5(1):14. doi:10.1186/1755-8166-5-14
52. Hu T, Zhang Z. Prenatal diagnosis of chromosomal aberrations by chromosomal microarray analysis in fetuses with ultrasound anomalies in the urinary system. *Prenat Diagn*. 2019;39(12):1096–1106. doi:10.1002/pd.5550
53. Jenkins M, Seasely AR, Subramaniam A. Prenatal genetic testing 2: diagnostic tests. *Curr Opin Pediatr*. 2022;34(6):553–558. doi:10.1097/MOP.0000000000001174
54. Mone F, Mellis R, Gabriel H, et al. Should we offer prenatal exome sequencing for intrauterine growth restriction or short long bones? A systematic review and meta-analysis. *Am J Obstet Gynecol*. 2023;228(4):409–417.e404. doi:10.1016/j.ajog.2022.09.045
55. Shaffer LG, Rosenfeld JA, Dabell MP, et al. Detection rates of clinically significant genomic alterations by microarray analysis for specific anomalies detected by ultrasound. *Prenat Diagn*. 2012;32(10):986–995. doi:10.1002/pd.3943
56. Mastromoro G, Guadagnolo D, Khaleghi Hashemian N, Marchionni E. Molecular approaches in fetal malformations, dynamic anomalies and soft markers: diagnostic rates and challenges-systematic review of the literature and meta-analysis. *Diagnostics*. 2022;12(3):575. doi:10.3390/diagnostics12030575
57. Lee CN, Lin SY, Lin CH, Shih JC, Lin TH, Su YN. Clinical utility of array comparative genomic hybridisation for prenatal diagnosis: a cohort study of 3171 pregnancies. *BJOG*. 2012;119(5):614–625. doi:10.1111/j.1471-0528.2012.03279.x

58. Dap M, Gicquel F, Lambert L, Perdriolle-Galet E, Bonnet C, Morel O. Utility of chromosomal microarray analysis for the exploration of isolated and severe fetal growth restriction diagnosed before 24 weeks' gestation. *Prenat Diagn*. 2022;42(10):1281–1287. doi:10.1002/pd.6149
59. Zhu H, Lin S, Huang L, et al. Application of chromosomal microarray analysis in prenatal diagnosis of fetal growth restriction. *Prenat Diagn*. 2016;36(7):686–692. doi:10.1002/pd.4844
60. Borrell A, Grande M, Meler E, et al. Genomic microarray in fetuses with early growth restriction: a multicenter study. *Fetal Diagn Ther*. 2017;42(3):174–180. doi:10.1159/000452217
61. Tzadikevitch Geffen K, Singer A, Maya I, et al. The yield of chromosomal microarray in pregnancies complicated with fetal growth restriction can be predicted according to clinical parameters. *Fetal Diagn Ther*. 2021;48(2):140–148. doi:10.1159/000511475
62. Zemet R, Krispin E. Implication of chromosomal microarray analysis prior to in-utero repair of fetal open neural tube defect. *Ultrasound Obstet Gynecol*. 2023;61(6):719–727. doi:10.1002/uog.26152
63. Xie X, Huang B, Su L. Prenatal diagnosis and genetic etiology analysis of talipes equinovarus by chromosomal microarray analysis. *BMC Med Genomics*. 2023;16(1):298. doi:10.1186/s12920-023-01733-2
64. Sun Y, Zhang W, Wang Z, Guo L, Shi S. Chromosomal microarray analysis vs. karyotyping for fetal ventriculomegaly: a meta-analysis. *Chin Med J*. 2021;135(3):268–275. doi:10.1097/CM9.0000000000001683
65. Wu X, He S, Shen Q, et al. Etiologic evaluation and pregnancy outcomes of fetal growth restriction (FGR) associated with structural malformations. *Sci Rep*. 2024;14(1):9220. doi:10.1038/s41598-024-59422-8