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Comparison of conventional karyotype analysis and CMA results with ultrasound findings in pregnancies with normal QF-PCR results

QF-PCR sonuçları normal olan gebeliklerde konvansiyonel karyotip analizi ve KMA sonuçlarının ultrason bulguları ile karşılaştırılması

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Abstract

Objective: In cases requiring fetal diagnostic testing, conventional karyotype analysis is initially preferred. However, quantitative fluorescent-polymerase chain reaction (QF-PCR) or fluorescent *in situ* hybridization methods are used alongside conventional karyotype analysis to obtain rapid results. If results cannot be obtained from conventional karyotype analysis, chromosomal microarray analysis (CMA) is a reasonable option in necessary cases. In this study, we analyzed the conventional karyotype and CMA results from pregnancies reported as having normal karyotypes by QF-PCR and assessed their correlation with ultrasound imaging results.

Materials and Methods: Between 2020 and 2023, pregnant women with fetal structural anomalies detected by ultrasound and magnetic resonance imaging at the Eskişehir City Hospital, Clinic of Perinatology were referred to our prenatal diagnosis center. In samples obtained using appropriate diagnostic methods, QR-PCR and conventional karyotype analysis were performed initially. Pregnancies with chromosomal anomalies detected by QF-PCR were excluded from the study. For pregnancies with normal karyotypes, CMA was applied.

Results: In 203 pregnancies with a normal karyotype result from QF-PCR, 202 (99.5%) were reported as normal in conventional karyotype analysis, while 1 (0.5%) case showed deletion of chromosome 7. Among the remaining pregnancies, CMA examination revealed abnormal karyotype results in 25 (12.3%) cases. A relationship was found only between ventriculomegaly detected by ultrasound and CMA results. The prevalence of ventriculomegaly was higher in those with CMA abnormalities (16%) compared to those with normal CMA (4.5%), and this difference was statistically significant (p=0.045).

Conclusion: The benefit of CMA analysis in detecting chromosomal anomalies such as copy number variations, especially in cases reported as having a normal karyotype by QF-PCR and karyotype analysis, is evident. To evaluate the relationship between ultrasound anomalies and CMA results, each community should assess its own results.

Keywords: Chromosomal microarray analysis, conventional karyotyping, fetal anomalies, quantitative fluorescent polymerase chain reaction

PRECIS: Comparison of conventional karyotype analysis and CMA results with ultrasound findings in pregnancies with normal QF-PCR results.

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Öz

Amaç: Fetal tanı testi gerektiren durumlarda, başlangıçta konvansiyonel karyotip analizi tercih edilir. Ancak hızlı sonuç elde etmek için konvansiyonel karyotip analizinin yanı sıra kantitatif floresan-polimeraz zincir reaksiyonu (QF-PCR) veya floresan *in situ* hibridizasyon yöntemleri de kullanılmaktadır. Konvansiyonel karyotip analizinden sonuç alınamaması durumunda kromozomal mikroarray analizi (KMA) gerekli olgularda uygun bir seçenektir. Bu çalışmada, QF-PCR ile normal karyotiplere sahip olduğu bildirilen gebeliklerin konvansiyonel karyotip ve KMA sonuçlarını analiz ettik ve ultrason görüntüleme sonuçları ile korelasyonlarını değerlendirdik.

Gereç ve Yöntemler: 2020-2023 yılları arasında Eskişehir Şehir Hastanesi Perinatoloji Kliniği'nde ultrason ve manyetik rezonans görüntüleme ile fetal yapısal anomali saptanan gebeler prenatal tanı merkezimize yönlendirildi. Uygun tanı yöntemleri kullanılarak elde edilen örneklerde ilk olarak QR-PCR ve konvansiyonel karyotip analizi yapıldı. QF-PCR ile kromozomal anomali saptanan gebelikler çalışma dışı bırakıldı. Karyotipleri normal olan gebelere KMA analizi uygulandı.

Bulgular: QF-PCR ile normal karyotip sonucu elde edilen 203 gebeliğin 202'si (%99,5) konvansiyonel karyotip analizinde normal olarak rapor edilirken, 1 (%0,5) olguda delesyon 7 saptandı. Geri kalan gebelikler arasında, CMA incelemesi 25 (%12,3) olguda anormal karyotip sonuçları ortaya koymuştur. Sadece ultrason ile tespit edilen ventrikülomegali ile KMA sonuçları arasında bir ilişki bulunmuştur. Ventrikülomegali prevalansı KMA anormalliği olanlarda (%16) normal KMA olanlara (%4,5) kıyasla daha yüksekti ve bu fark istatistiksel olarak anlamlıydı (p=0,045).

Sonuç: Özellikle QF-PCR ve karyotip analizi ile normal karyotipe sahip olduğu bildirilen olgularda kopya sayısı varyasyonları gibi kromozomal anomalilerin tespit edilmesinde KMA analizi faydası belirgindir. Ultrason anomalileri ile KMA sonuçları arasındaki ilişkiyi değerlendirmek için her grup kendi sonuçlarını değerlendirmelidir.

Anahtar Kelimeler: Kromozomal mikroarray analizi, geleneksel karyotipleme, fetal anomaliler, kantitatif floresan polimeraz zincir reaksiyonu

Introduction

Fetal structural anomalies detectable by ultrasound imaging (USI) occur at an average frequency of 3%[1]. When fetal structural anomalies are suspected or detected by USI, genetic examination is usually preferred. Chromosome abnormalities are found in 50-60% of miscarriages and stillbirths and in 1 in 150 live births[2]. These chromosome abnormalities primarily include trisomies, aneuploidies, chromosomal rearrangements, and monogenic disorders[3]. Although amniocentesis is the most commonly preferred method for genetic examination, techniques such as chorionic villus sampling (CVS) and cordocentesis are also used[4]. In recent years, non-invasive prenatal testing has become a part of our lives because it is free from both maternal and fetal complications[5]. However, although the accuracy rate is quite high, invasive diagnostic testing is still recommended for cases where chromosomal anomalies are detected[6]. The most common indications for these tests are advanced maternal age, increased risk in prenatal screening, and as previously mentioned, the detection of fetal structural anomalies by ultrasound[7].

Genetic examination technology first entered our lives in the 1960s with conventional cytogenetic analysis. Initially, G-banding technology was prominent. In the 1990s, fluorescent *in situ* hybridization and later quantitative fluorescent-polymerase chain reaction (QF-PCR) methods were introduced to overcome the limitations of fetal cell cultures, and to provide faster results by targeting selected chromosomes[8]. The QF-PCR method relies on the amplification of chromosome-specific DNA sequences (short tandem repeats) that vary in length. This technique, which is applied to chromosomes 13, 18, 21, and the sex chromosomes, provides results within 24-48 hours[9].

Subsequently, it has evolved into chromosomal microarray analysis (CMA). CMA, which detects imbalances in the kilobase range, easily demonstrates its superiority over standard karyotyping, which is limited to imbalances over 7-10 million bases[10]. Techniques for detecting submicroscopic pathogenic copy number variations (CNVs) are more successful in identifying imbalances of low mega base size (<50 kb)[11,12]. CNVs are often clinically insignificant, meaning that individuals with these CNVs are typically considered normal; however, this is not always the case. However, if they occur in a critical gene region or an important regulatory region, they may have functional effects. CMA is used not only during the prenatal period but also in the postnatal period[13]. In cases of structural anomalies that could not be diagnosed prenatally, as well as in cases with developmental delays and intellectual disability, the frequency of sub-chromosomal anomalies is found to be between 12% and 15%.

In this study, we compared the conventional karyotype analysis and CMA results, in fetuses with fetal structural anomalies detected by ultrasound in our tertiary care center, of pregnancies with normal karyotype reports from QF-PCR analysis.

Materials and Methods

This study was conducted after obtaining ethical approval from the Ethics Committee of Eskişehir City Hospital (no: ESH/GOEK 2024/80, date: 14.03.2024) and after informing all parents verbally and obtaining their written consent. Between 2020 and 2023, pregnant women with fetal structural anomalies detected by our most frequently used prenatal imaging methods, ultrasound and magnetic resonance imaging, were referred to our prenatal diagnostic center. Ultrasound findings were recorded by the same perinatologist (ZB) using a Voluson E8 (General Electric Company, Istanbul, Türkiye). Fetal samples were collected through chorionic villus sampling, amniocentesis, and cordocentesis. The choice of method was determined, in consultation with the parents, based on the gestational age. Verbal and written consent was obtained from all families. The invasive procedures were performed by the same perinatologist (ZB), and no complications were observed. Multiple pregnancies, cases with inadequate material in invasive

diagnostic tests, cases with placental mosaicism, and cases with positive anomalies in QF-PCR were excluded from the study.

Karyotype Analysis

Two hundred and eighty-two pregnant women who met the study criteria, were included in the study. QF-PCR analysis was performed for X, Y, sex chromosome anomalies and for chromosomes numbered 13, 18, and 21. Cases with normal karyotypes were removed from consideration, resulting in a final sample of 203 study cases. Following this, conventional karyotype analysis was performed using standard G-banding technology.

CMA Analysis

Array analysis was performed using the Affymetrix Cytoscan Optima Suite method with a 315k resolution, utilizing the GRCh37 reference genome. Duplications greater than 200.000 and deletions greater than 400.000 were considered significant for prenatal diagnosis. According to ACMG Guidelines, smaller deletions and duplications were considered significant in the presence of clinical results.

Statistical Analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) was used for variable analysis. The normality of the data was assessed using the Shapiro-Wilk test. For comparing quantitative variables between two groups, Mann-Whitney U tests with Monte Carlo simulation results were used. Categorical variables were compared using the Fisher's exact test with Monte Carlo simulation techniques. The odds ratio, along with 95% confidence intervals, was employed to quantify the likelihood of individuals with a risk factor relative to those without it. Quantitative variables are expressed as mean (standard deviation) and median (minimum/maximum) in the tables, while categorical variables are shown as n (%). Variables were examined at a 95% confidence level, and a p-value of less than 0.05 was considered significant.

Results

Two hundred and three pregnancies that met the inclusion criteria and had normal karyotype results from QF-PCR, were included in the study for conventional karyotype analysis and CMA results. The parity, gestational age, risk level values from the screening test, the number of findings in the ultrasound, and the procedures performed for the included pregnancies are listed in Table 1. The average participant has one previous pregnancy, as indicated by a mean of 1 and a standard deviation of 1.03. The average gestation period among participants is approximately 20 weeks, with a median gestation week of 21. This median indicates that half of the participants are at or beyond the 21-week mark, highlighting a distribution that encompasses both early and later stages of pregnancy, with gestation weeks ranging from 12 to 31.

The data further elucidate the prevalence of specific prenatal diagnostic procedures. A significant majority of the women (78.3%) underwent amniocentesis, a widely accepted prenatal diagnostic intervention. In contrast, cordocentesis was performed on 9.9% of participants, while CVS was conducted on 11.8%. These figures underscore the predominant reliance on amniocentesis compared to the other diagnostic options, reflecting its established role in prenatal care.

Moreover, the analysis of USI findings reveals that 21.2% of participants reported no abnormalities, while the majority reported a single finding, which was noted in 39.4% of cases. As the number of findings increased, the frequency of occurrences decreased, indicating that cases involving multiple ultrasound findings are less common. Specifically, only 2% of women exhibited five findings, and 1% displayed six findings.

The QF-PCR result indicated a normal karyotype. The conventional karyotype and CMA analyses for the 203 pregnant women included in the study are presented in Table

Table 1. Demographic characteristics of pregnant women

	Mean (standard deviation)	Median (minimum/maximum)
Parity (n)	1 (1.03)	1 (0/8)
Gestation week (week)	19.93 (3.75)	21 (12/31)
Risk in screening test (10000)	32.76 (59.64)	5.47 (1/476.19)
Process		
Amniocenteses	159 (78.3)	
Cordocentesis	20 (9.9)	
CVS	24 (11.8)	
Number of USI findings (n)		
0	43 (21.2)	
1	80 (39.4)	
2	44 (21.7)	
3	23 (11.3)	
4	7 (3.4)	
5	4 (2.0)	
6	2 (1.0)	

USI: Ultrasound imaging, CVS: Chorionic villus sampling

Table 2. Distribution of chromosomal microarray analysis and conventional karyotype results of pregnant women

	n (%)
Microarray (anormal)	25 (12.3)
Karyotype	
Normal	202 (99.5)
Deletion 7	1 (0.5)

2. The distribution of USI findings of pregnant women who underwent genetic analysis and had a normal karyotype as a result of QF-PCR is shown in Table 3. The most commonly observed abnormalities, including an increase in nuchal fold measurements and hyperechogenic bowel, were reported in 25 cases (12.3%). Similarly, an intracardiac hyperechogenic focus was noted in 24 cases (11.8%).

Among the other notable anomalies, pyelectasis and muscular ventricular septal defect were each identified in 20 cases (9.9%). The findings also included ventriculomegaly, observed in 12 cases (5.9%). Additional notable conditions consisted of aberrant right subclavian artery, identified in 10 cases (4.9%), and nasal bone hypoplasia, found in 9 cases (4.4).

As the analysis of ultrasound findings continues, microcephaly and cervical cystic hygromas were reported in 7 instances each (3.4%). Moreover, a range of abnormalities, such as clenched hand, forearm dysplasia, and early-onset intrauterine growth restriction, accounted for 6 cases (3%). These findings highlight the varied nature of potential anomalies detectable during prenatal imaging.

Among the less frequently identified abnormalities, more complex conditions emerged, including mega cisterna magna and posterior urethral valve, each found in 5 cases (2.5%). Additionally, a remarkable array of anomalies was documented in single instances (0.5%), such as syndactyly and interrupted aortic arch, emphasizing the diversity of developmental issues that may be encountered during prenatal assessments.

The findings presented in this table highlight the complexity and range of abnormalities that can be detected through USI in a population that ultimately demonstrates normal chromosomal results.

No statistically significant difference was found in the comparison of the demographic characteristics of those who were pregnant, based on the CMA results (p>0.05) (Table 4).

Among the ultrasound findings and CMA results in pregnant women, only ventriculomegaly was found to be associated with the outcomes. The incidence of ventriculomegaly was significantly higher in those with abnormal CMA (16%) compared to those with normal CMA (4.5%) (p=0.045). Pregnant women with abnormal CMA had a fourfold (1.1-14.6 times higher) rate of ventriculomegaly compared to those with normal CMA (Table 5).

Table 3. Distribution of USI findings of pregnant women, who underwent genetic analysis and had a normal karyotype as a result of QF-PCR

	n (%)
Nuchal fold increase, hyperechogenic bowel	25 (12.3)
Intracardiac hyperechogenic focus	24 (11.8)
Pyelectasis	20 (9.9)
Muscular VSD	20 (9.9)
Ventriculomegaly	12 (5.9)
Aberrant right subclavian artery	10 (4.9)
Nasal bone hypoplasia	9 (4.4)
Microcephaly	7 (3.4)
CPC	7 (3.4)
Clenched Hand, forearm dysplasia, early onset IUGR	6 (3)
Mega Cisterna Magna, CSP width, posterior urethral valve, NT increase	5 (2.5)
hypoplasia of the cerebellum, cleft palate and lip, pericardial effusion, toxoplasma, rhizomelia	4 (2)
Pes Equinovarus, partial corpus callosum agenesis, aortic coarctation	3 (1.5)
Placental calcification, double outlet right ventricle, hypoplasia of the thorax, micromelia, ambiguous genitalia, FL shortness, stomach width, right aortic arch, single artery single vein, AVSD, encephalocele, liver calcification, megacystis, corpus callosum agenesis	2 (1)
Syndactyly, double collecting system, ınterrupted aortic arch, hypoplastic stomach, cell-free DNA Anomaly, myopathy carrier, hyperechogenic kidney, gallbladder agenesis, rocker bottom feet, costa hypoplasia, acrocephaly, double renal artery, CMV, corrected TGA, ductus venosus agenesis, hypoplastic kidney, left superior vena cava, thymus hypoplasia, SMA carrier, CPAM, gastroschisis, isomerism, holoprosencephaly, microphthalmia, flat face, Cantrell, PKU carrier, abdominal ascites, blake pouch cyst, polycystic kidney, micrognathia, leg dysplasis, hypotonia, low ear, persistent right umbilical vein, renal agenesis, arachnoid cyst, clinodactyly, vermis hypoplasia, diaphragmatic hernia	1 (0.5)

USI: Ultrasound imaging, QF-PCR: Quantitative fluorescent-polymerase chain reaction, VSD: Ventricular septal defect, IUGR: Intrauterine growth restriction, NT: Nuchal translucency, CMV: Cytomegalovirus, AVSD: Atrioventricular septal defect, TGA: Transposition of the great arteries, SMA: Spinal musculer atrophy, CPAM: Cystic pulmonary airway malformation, PKU: Phenylketonuria

Table 4. Comparison of demographic characteristics of pregnant women according to CMA results

	Microarray (normal) (n=178) Median (minimum/maximum)	Microarray (anormal) (n=25) Median (minimum/maximum)	p
Parity (n)	1 (0/8)	1 (0/2)	0.450[u]
Gestation week (week)	21 (12/31)	21 (12/26)	0.340[u]
Risk in screening test (10000)	3.56 (1/263.16)	10.33 (1/476.19)	0.073[u]
Invasive test indication (n)	1 (0/2)	1 (0/2)	0.090[u]
	n (%)	**n (%)**	
Process			0.367[f]
Amniocentesis	141 (79.2)	18 (72.0)	
Cordocentesis	18 (10.1)	2 (8.0)	
CVS	19 (10.7)	5 (20.0)	
Number of USI findings (n)			0.820[f]
0	38 (21.3)	5 (20.0)	
1	71 (39.9)	9 (36.0)	
2	39 (21.9)	5 (20.0)	
3	18 (10.1)	5 (20.0)	
4	6 (3.4)	1 (4.0)	
5	4 (2.2)	0 (0.0)	
6	2 (1.1)	0 (0.0)	

[f]: Fisher exact test (Monte Carlo), [u]: Mann-Whitney U test (Monte Carlo), CMA: Chromosomal microarray analysis, USI: Ultrasound imaging, CVS: Chorionic villus sampling

Table 5. Comparison of USI findings with CMA results

	Microarray (normal) (n=178) n (%)	Microarray (anormal) (n=25) n (%)	Odds ratio (95% confidence interval)	p
Microcephaly	5 (2.8)	2 (8)		0.208
Rhizomelic	2 (1.1)	2 (8)		0.075
CPC	7 (3.9)	0 (0)		0.600
Nuchal fold increase	21 (11.8)	4 (16)		0.521
Pyelectasis	18 (10.1)	2 (8)		0.999
Ventriculomegaly	8 (4.5)	4 (16)	4 (1.1-14.6)	0.045
Nasal bone hypoplasia	9 (5.1)	0 (0)		0.605
Early onset IUGR	5 (2.8)	1 (4)		0.55
Hyperechogenic bowel	24 (13.5)	1 (4)		0.325
Cerebellum hypoplasia	4 (2.2)	0 (0)		0.999
Intracardiac hyperechogenic focus	21 (11.8)	3 (12)		0.999
Muscular VSD	17 (9.6)	3 (12)		0.719
Toxoplasma	4 (2.2)	0 (0)		0.999
Mega cisterna magna	4 (2.2)	1 (4)		0.486

Table 5. Continued

	Microarray (normal) (n=178) n (%)	Microarray (anormal) (n=25) n (%)	Odds ratio (95% confidence interval)	p
Cleft palate and lip	4 (2.2)	0 (0)		0.999
CSP width	4 (2.2)	1 (4)		0.485
Posterior urethral valve	4 (2.2)	1 (4)		0.485
Pericardial effusion	3 (1.7)	1 (4)		0.411
Clenched hand	6 (3.4)	0 (0)		0.999
Forearm dysplasia	6 (3.4)	0 (0)		0.999
NT increase	5 (2.8)	0 (0)		0.999

Fisher's exact test (Monte Carlo), USI: Ultrasound imaging, CMA: Chromosomal microarray analysis, IUGR: Intrauterine growth restriction, NT: Nuchal translucency, VSD: Ventricular septal defect, CSP: Cavum septum pellusidi, CPC: Choroid plexus cyst

Discussion

Although the QF-PCR method is advantageous in terms of cost and time, further evaluation is recommended for cases with normal karyotype results. Bartels et al.[14] assessed the outcomes of QF-PCR and amniocentesis in 528 cases over a 5-year period. QF-PCR identified genetic anomalies in 32% of the cases, including trisomy 21, 18, 13, and other conditions. Standard karyotype analysis revealed anomalies in 36.2% of cases. In 21 instances, different results were observed, with DiGeorge syndrome being the most common anomaly, occurring in 7 cases. Liao et al.[15] analyzed amniocentesis materials and found a genetic anomaly rate of 2.5%. Out of 211 cases with genetic abnormalities, QF-PCR failed to diagnose 43. The overall residual risk was calculated to be 0.1%. Comas et al.[16] identified 110 abnormal karyotypes, representing a rate of 2.8%, and found that 27% of these could not be diagnosed by QF-PCR. In their study, the overall residual risk was 0.75%. According to these findings, QF-PCR is a cost-effective and acceptable method for selected cases. Papoulidis et al.[17] reviewed their study results, which included a larger number of cases compared to other studies. Chromosomal abnormalities were detected in 2.37% of cases. Out of 320 cases, 70 could not be diagnosed by QF-PCR. Approximately half of these were already at high risk. When evaluating USI findings and genetic history, 13 cases were identified as missed by QF-PCR, which corresponds to 0.1%. Given this information, although "selective dual testing" is recommended, the 0.1% error rate indicates that alternative options should be considered. In our study, abnormal karyotype results were found in only 1 (0.5%) of the cases where QF-PCR results were reported as normal. This rate is lower than that reported in previous studies.

CMA is particularly successful in analyses involving CNVs that conventional karyotype analysis fails to detect. In a study by Wapner et al.[18], which examined more than 4,000 samples from 29 centers, cases reported as normal karyotypes by conventional methods were evaluated by CMA. Accordingly, 6% of small deletions and duplications (CNVs) were detected. The study found that CMA was useful for identifying aneuploidies and unbalanced rearrangements. However, it may be insufficient for detecting balanced translocations and triploidies. In the review prepared by Callaway et al.[19], CMA was performed on pregnant women, who had normal results from conventional karyotype testing. The CNV rate ranged from 0.8% to 5.5%, with a mean rate of 2.4%. The rate of abnormal fetal USI results in these pregnant women varied from 6.0% to 11.1%, with an average of 6.5%. The review also included an analysis of pregnant women with abnormal fetal USI results, finding CNVs in 7% of fetuses with abnormal USI. Based on these results, CMA was recommended as a primary test. In our study, the CNV detection rate was 12.3%, which is consistent with that reported in the literature.

Approximately half of pregnancy losses have been associated with genetic anomalies[20]. In a meta-analysis of 9 studies by Dhillon et al.[21], it was found that CMA and conventional karyotype analyses produced the same results in 86% of cases, while CMA provided additional information in 13% of cases. The rate of variants of unknown significance (VUS) was 2%. Interestingly, karyotype analysis detected additional anomalies that CMA missed in 3% of cases. Another meta-analysis by Pauta et al.[22] focused on cases of early pregnancy loss. In addition to karyotype analysis, CMA revealed pathological CNVs in 2% of cases and VUS in 4%. The most common CNVs identified were deletions at 22q11.21 and 1p36.33. Reddy et al.[23] evaluated pregnant women who experienced stillbirth. Compared to conventional karyotyping, CMA demonstrated a 41.9% relative increase in the detection of genetic abnormalities. For stillbirths with fetal anomalies, this increase was approximately 53%. In the meta-analysis by Martinez-Portilla et al.[24], the success rate of conventional karyotyping was 75%, while CMA achieved a success rate of 90%. In CMA, CNV was detected in 4% and VUS

in 8%. In our study, genetic materials of fetuses that resulted in miscarriage and stillbirth were excluded.

First and second trimester screenings with fetal USI identify pregnant women who require detailed USI and targeted USI fetal chromosome analysis. Grande et al.[25] analyzed the CMA results of pregnant women with NT ≥3.5 mm, and a normal karyotype. CNVs were detected at a rate of 5%. The most common anomalies included deletions and duplications at 22q11.2 and deletions at 10q26.1, q26.3. In our study, there was no statistically significant difference in NT measurements between cases with normal and abnormal CMA results. In a systematic review by de Wit et al.[26] evaluating 18 studies, the presence of CNV ranging from 3.1-7.9%, was found in the presence of one anatomical system anomaly detected by USI. In the presence of multiple anomalies, this rate was found to be 9.1%. In our study, there was no statistically significant difference between the frequencies of USI anomalies and the frequencies of CMA results. This is not aligned with findings reported in the general literature. We believe this situation occurred because our study included fewer patients compared to the large case series we discussed.

Hui et al.[27] compared single system anomalies and non-specific results. Thus, cardiac anomalies were identified as present in the group with the greatest risk. Among the non-specific results, fetal growth retardation was present in the group with the highest rate of CNV. In our study, it was very difficult to evaluate growth retardation because the USI weeks were usually between weeks 18 and 22. Shaffer et al.[28] conducted a more detailed study on USI anomalies. CNV was detected in 5.6% for a single USI anomaly and 9.5% for multiple USI anomalies. What is important is the subanalysis of USI anomalies. In the analysis performed without considering the association with another anomaly, isolated left heart hypoplasia was found in 16.2%, posterior fossa anomaly in 14.6%, and skeletal system anomaly in 10.7%. In our study, only ventriculomegaly was statistically different between the normal and abnormal groups in CMA analysis. We think that the reason for the different results in our study may be due to the small number of patients and/or racial factors.

The correlation observed between ultrasound findings and CMA results is particularly insightful. The significant association of ventriculomegaly with abnormal CMA results raises important clinical considerations. The predominance of certain anomalies, such as increases in nuchal fold measurement, aligns with existing literature emphasizing the importance of these markers in prenatal screenings. However, the identification of more rare conditions like interrupted aortic arch and syndactyly highlights the necessity for thorough ultrasound evaluations to ensure no significant anomaly is overlooked, even in populations where normal chromosomal results are expected. This demonstrates the critical role of advanced imaging in conjunction with genetic testing to improve prenatal counselling and management strategies.

Study Limitation

One limitation of our study is that it was conducted at a single center, involving the same ethnicity, and involving a small number of patients.

Conclusion

CMA is especially useful for detecting chromosomal abnormalities when QF-PCR and karyotype analysis report normal results. To understand the relationship between USI abnormalities and CMA results, each society should analyze its results based on its own socio-demographic characteristics.

Ethics

Ethics Committee Approval: This study was conducted after obtaining ethical approval from the Ethics Committee of Eskişehir City Hospital (no: ESH/GOEK 2024/80, date: 14.03.2024).

Informed Consent: Verbal and written consent was obtained from all families.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.B., M.K., G.Ş., E.A., E.E.G., S.A., Concept: Z.B., Design: M.K., E.A., Data Collection or Processing: M.K., E.A., Analysis or Interpretation: G.Ş., E.E.G., S.A., Literature Search: G.Ş., Writing: Z.B., M.K.

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