Prenatal Diagnosis of Chromosome Abnormalities: 21 Years of Experience

Kromozomal Anomalilerin Prenatal Tanısı: 21 YıllıkTecrübe

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ABSTRACT

Objective: In this study, we aimed to evaluate the demographic data and cytogenetic results of prenatal diagnoses performed in a single genetics laboratory setting over a period of 21 years.
Methods: This study is a retrospective analysis of patients who underwent prenatal diagnosis in our center between 2000 and 2021. A total of 2,385 cases between the ages of 18-48 were included in the study. Age, indication, pregnancy week, type of prenatal diagnosis, and the result of cytogenetic analysis of the cases were evaluated.
Results: The mean age of the patients was 33.97 ± 4.96 years and 1,205 (50.5%) patients were under 35 years. Amniocentesis was performed in 1,965 (82.4%) patients, chorionic villus sampling in 279 (11.7%) patients, and cordocentesis in 141 (5.9%) patients. A total of 2,114 (88.6%) were normal and 253 (10.6%) were found to have abnormal karyotypes. The most frequently observed abnormal karyotypes were trisomy 21, translocation, and inversion of chromosome 9 (3.6%, 1.4% and 1.0% respectively. The most common indications were: abnormal ultrasonography results in 695 (29.1%), abnormal first trimester test results in 513 (21.5%), and advanced maternal age in 399 (16.7%) patients. The highest positive predictive value for prenatal diagnosis (or abnormal result) was 73.9% for Non-invasive Prenatal Test (NIPT), followed by in paternal chromosome anomaly (17.4%), and an abnormal USG evaluation (14.5%).
Conclusion: It is necessary to carry out more studies on NIPT, which has a high positive predictive value, and develop the results for genetic counselling together with conventional and molecular cytogenetic methods.

Keywords: Amniocentesis, trisomy 21, down syndrome, prenatal diagnosis, chromosome abnormalities, pregnancy

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ÖZET

Amaç: Bu çalışmada, 21 yıllık bir süre boyunca Memorial genetik Tanı Merkezi Laboratuvarında yapılan prenatal tanıların demografik verilerini ve sitogenetik sonuçlarını değerlendirmeyi amaçladık.
Yöntemler: Bu çalışma 2000-2021 yılları arasında merkezimizde prenatal tanı için başvuran hastaların retrospektif analizidir. Çalışmaya 18-48 yaş arası toplam 2.385 olgu dahil edildi. Olguların yaş, endikasyon, gebelik haftası, prenatal tanı türü ve sitogenetik analiz sonuçları değerlendirildi.
Bulgular: Hastaların ortalama yaşı 33.97 ± 4.96 yıl ve 1.205 (%50.5) hasta 35 yaşın altındaydı. 1.965 (%82.4) hastaya amniyosentez, 279 (%11.7) hastaya koryon villus örneklemesi ve 141 (%5.9) hastaya kordosentez yapıldı. Toplam 2.114'ü (%88.6) normal, 253'ünde (%10.6) anormal karyotip bulundu. En sık gözlenen anormal karyotipler trizomi 21 ve 9.kromozomun translokasyonu ve inversiyonu (sırasıyla %3.6, %1.4 ve %1.0) idi. En sık prenatal tanı endikasyonları; 695 hastada(%29.1) anormal ultrason bulgusu, 513 hastada anormal 1.trimester testi %21,5 (%) ve399 hastada ileri anne yaşı (%16.7) olarak hesaplandı. Non-invaziv Prenatal Test (NIPT) için Prenatal tanı (veya anormal sonuç) için pozitif prediktif değer %73,9 idi.
Sonuç: Pozitif prediktif değeri yüksek olan NIPT ile ilgili daha fazla çalışma yapılması ve sonuçlarının konvansiyonel ve moleküler sitogenetik yöntemlerle birlikte genetik danışmanlık için geliştirilmesi gerekmektedir.

Anahtar Sözcükler: Amniyosentez, trizomi 21, down sendromu, prenatal tanı, kromozom anomalileri, gebelik

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INTRODUCTION

Invasive prenatal diagnosis, which gained more importance in 1966 by the separation of fetal chromosomes from amniotic fluid for chromosome analysis by Steele and Breg (1), has been an important medical technology for two centuries. Prenatal diagnosis has become even more effective with the Italian biologist Simoni et al. (2) performing the first trimester chorionic villus sampling (CVS). Thanks to these methods, accurate diagnosis can be done prenatally for chromosomal abnormalities such as Down syndrome, Edwards syndrome, and hereditary diseases like sickle cell anemia and cystic fibrosis can cause mental and physical disability and even death of the newborn (3).

Parents can be offered various prenatal diagnosis methods to get conclusive information about fetal health. As one of the most reliable and commonly used methods, amniocentesis can be performed between 17 and 23 weeks, and is often reliably applied for diagnosing many congenital diseases due to its high accuracy and relatively simpler technique with regard to CVS and cordocentesis (4). However, they all carry some risk of pregnancy loss, the rate depending on the expertise of different centers, albeit small. The earliest possible procedure is CVS, which can be undertaken after 11 completed weeks of pregnancy usually at 11-14 weeks. The only disadvantage is when a report of mosaicism is the result of the analysis (which may be confined to the placenta); thus, an amniocentesis after 15 completed weeks is needed to verify or exclude that situation.

Cordocentesis performed 18-23$^{rd.}$ gestational week is usually appropriate in second trimester pregnancies. Blood samples are taken directly from the fetal umbilical vein with this method. Cordocentesis can be used to diagnose fetal chromosomal abnormalities and gene defects that cannot be detected by CVS or amniocentesis (4). Amniocentesis, CVS and cordocentesis are invasive procedures and are usually found somewhat aversive for the expectant mother; however, the presented risk may be small. Many scientists are developing Non-invasive Prenatal Test (NIPT) techniques to reduce the risk of miscarriage caused by these interventions. These techniques include first and second trimester screening tests, cell-free fetal DNA/mRNA in maternal blood, and fetal cell screening in maternal blood (3) in addition to detailed ultrasonography (USG).

A parents' decision to learn whether their child will be born with any congenital abnormalities is very personal and complex. Family history of any genetic disease, previous pregnancy history, education levels, religious beliefs, and economic concerns are all factors influencing this decision (5). Clarifying all of these factors and helping couples to make an informed decision must be the aim of genetic counseling services. For this reason, the researchers evaluated the results of their long-term study in this context and opened them to discussion. In this study, we aimed to evaluate the demographic data and cytogenetic results of 2,385 prenatal diagnosis cases, which we performed in our center for 21 years.

MATERIALS and METHODS

This is a retrospective study of patients who underwent prenatal diagnosis in Istanbul Memorial Hospital Genetic Diagnosis Center between 2000 and 2021. A total of 2,385 cases between the ages of 18-48 were included in the study. Age, type of prenatal diagnosis, time of prenatal diagnosis, indication of prenatal diagnosis, and results of cytogenetic analysis of the cases were evaluated.

Ethical Consent

Ethical approval was obtained from Memorial Şişli Hospital (date: 26/02/2021, number: 10)

Statistical analysis

SPSS 20 statistical package program (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used to analyze the data. Data was expressed as mean ± standard deviation, median, minimum, maximum, percentage and frequency values. Variables were evaluated after checking the preconditions for normality and homogeneity of variances (Shapiro Wilk and Levene Test). Continuous variables were evaluated using the Mann-Whitney U if the distribution was not normal and Kruskal Wallis tests. Categorical variables were analyzed with Fisher's Exact Test and Chi-Square test. In cases where the expected frequencies were less than 20%, an evaluation was made with the "Monte Carlo Simulation Method" to include these frequencies in the analysis. A value of p less than 0.05 was accepted as significant.

RESULTS

A total of 1,282 of the patients (53.8%) were before 2010 and and 1,085 (45.5%) of them were after 2010. The mean age of the patients was 33.97 ± 4.96 years old and 1,205 (50.5%) patients were under 35 years old, while 1,157 (49.5%) patients were 35 years old and above. Amniocentesis was performed in 1,965 (82.4%) patients, CVS in 279 (11.7%) patients, and cordocentesis in 141 (5.9%) patients for karyotype analysis. Amniocentesis was performed at an average of 17.86 ± 2.23 weeks of gestation, CVS at an average of 12.81 ± 1.18 weeks of gestation, and cordocentesis at an average of 23.08 ± 2.47 weeks of gestation. Of the karyotype analyses, 2,114 (88.6%) were normal, 253 (10.6%) were found to be abnormal, and chromosome analysis result could not be given in 18 samples because there was no cell growth in cell The most common indications for karyotype analysis were pathological USG findings in 695 (29.1%) patients, abnormal first trimester test results in 513 (21.5%), and advanced maternal age (AMA) in 399 (16.7%) patients. There were 24 patients who underwent mosaic embryo transfer (MET) and 23 patients had pathological NIPT result. Of the 253 (10.6%) patients who had abnormal karyotype, 85 (3.6%) had trisomy 21, 34 (1.4%) had translocation, and 25 (1.0%) had pericentric inversion of chromosome 9.

In the comparison of under 35 and over 35 with other parameters the most common abnormality in karyotype analysis in both age groups was trisomy 21. Although translocation and Klinefelter syndrome were observed to be more common under 35 years of age, this difference was not significant. There was no relationship between having an abnormal sex karyotype and maternal age.

The comparison of the type of prenatal diagnosis technique applied and other parameters are given in Table 1. Before 2010, cordocentesis was performed significantly more than amniocentesis and CVS, while it was performed significantly less after 2010 ($p<0.0001$). In karyotype analysis, detection of anomalies in CVS was more than that in the amniocentesis and cordocentesis procedures ($p<0.0001$). While AMA, multiple pregnancy, mosaic embryo transfer, and abnormal triple test indications for were significantly higher for amniocentesis, abnormal first trimester test, PGD and parental chromosome anomaly for CVS and pathological USG results were significantly more observed indications for cordocentesis ($p<0.0001$). As a result of CVS, inv(9) was less; trisomy18 and trisomy13 were more common.

Table 1. Prenatal diagnosis type and comparison with other parameters. Continuous variables are given as mean ± S.D, median (minimum-maximum), and categorical variables as n (%).

Variables	AS, n (%)	CVS, n (%)	CS, n (%)	X^2	p
Date					
≤2010	1040_a (81.1%)	129_b (10.1%)	113_c (8.8%)	**40.746**	**<0.0001**
>2010	908_a (83.7%)	149_b (13.7%)	28_c (2.6%)		
Total	1948 (82.3%)	278 (11.7%)	141 (6.0%)		
Karyotype analysis					
Normal	1791_a (84.7%)	193_b (9.1%)	130_a (6.1%)	**111.887**	**<0.0001**
Abnormal	161_a (63.6%)	81_b (32.0%)	11_a (4.3%)		
No result	13_a (72.2%)	5_a (27.8%)	0_a (0.0%)		
Total	1965 (82.4%)	279 (11.7%)	141 (5.9%)		
Indication					
AMA	358_a (89.7%)	21_b (5.3%)	20_a (5.0%)	**280.932**	**<0.001**
Sperm Factor	20_a (95.2%)	1_a (4.8%)	0_a (0.0%)		
Abnormal USG Results	501_a (72.1%)	88_b (12.7%)	106_c (15.3%)		
Abnormal 1st Trimester Test	432_a (84.2%)	81_b (15.8%)	0_c (0.0%)		
Abnormal Triple Test	148_a(94.9%)	4_b (2.6%)	4_b (2.6%)		
PGD	74_a (81.3%)	17_a (18.7%)	0_b (0.0%)		
Paternal Chromosome Abnormality	100_a (72.5%)	38_b (27.5%)	0_c (0.0%)		
History Of Baby With Anomaly	56_a (90.3%)	6_{ab} (9.7%)	0_b (0.0%)		
Maternal Anxiety	35_a (94.6%)	2_a (5.4%)	0_a (0.0%)		
ICSI Pregnancy	9_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Consanguineous Marriage	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Rh Incompatibility	0_a (0.0%)	0_a (0.0%)	1_a (100.0%)		
Toxoplasma Infection	1_a (50.0%)	1_a (50.0%)	0_a (0.0%)		
Poor Obstetric History	1_a (50.0%)	1_a (50.0%)	0_a (0.0%)		
Abnormal Quad Test	23_a (95.8%)	0_a (0.0%)	1_a (4.2%)		
Recurrent Pregnancy Losses	2_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
NIPD	20_a (87.0%)	3_a (13.0%)	0_a (0.0%)		
Multiple Pregnancy	23_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Mosaic Embryo Transfer	23_a (95.8%)	1_a (4.2%)	0_a (0.0%)		
Multiple Indications	137_a (89.5%)	14_{ab} (9.2%)	2_b (1.3%)		
Total	1965 (82.7%)	278 (11.7%)	134 (5.6%)		
Abnormal USG Results					
Heart Anomaly	38_a (67.9%)	6_b (10.7%)	12_b (21.4%)	**127.915**	**<0.001**
Increased NT	82_a (81.2%)	17_b (16.8%)	2_c (2.0%)		
Hyperechogenic Focus	59_a (98.3%)	0_b (0.0%)	1_b (1.7%)		
IUGR	29_a (87.9%)	1_a (3.0%)	3_a (9.1%)		
Urinary System Anomaly	23_a (88.5%)	1 (3.8%)	2_a (7.7%)		
Choroid Plexus Cyst	33_a (97.1%)	0_a (0.0%)	1_a (2.9%)		
Skeletal System Anomaly	21_a (87.5%)	0_a (0.0%)	3_a (12.5%)		
Multiple Congenital Anomalies	91_a (86.7%)	1_b (1.0%)	13_a (12.4%)		
Single Umbilical Artery	3_a (100.0%)	0_a (0.0%)	0 (0.0%)		
Polyhydramnios	7_a (100.0%)	0_a (0.0%)	0 (0.0%)		
Nasal Bone Hypoplasia	21_a (87.5%)	0_a (0.0%)	3_a (12.5%)		
Cord Cyst	2_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Cranial Calcification	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Anhydramnios	1_a (50.0%)	0_a (0.0%)	1_a (50.0%)		
Toxoplasma	1_a (50.0%)	1_a (50.0%)	0_a (0.0%)		
Fetal Hydrops	4_a (66.7%)	0 (0.0%)	2_a (33.3%)		
Double Bubble	2_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Ventriculomegaly	4_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Unilateral Pleural Effusion	0_a (0.0%)	0_a (0.0%)	1_a (100.0%)		
ARSA	11_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
PPROM	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Hydrothorax	4_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Microcephaly	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Hydrocephalus	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Cleft Palate-Lip	2_a (66.7%)	1_a (33.3%)	0_a (0.0%)		
Trisomy 13	1_a (50.0%)	1_a (50.0%)	0_a (0.0%)		
Trisomy 21	11_a (84.6%)	2_a (15.4%)	0_a (0.0%)		
Trisomy 18	2_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Pulmonary Atresia	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Encephalocele	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Ambiguous Genitalia	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Di George Syndrome	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Megacystis	1_a (50.0%)	1_a (50.0%)	0_a (0.0%)		
Omphalocele	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Turner Syndrome	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Placental Transfusion Syndrome	4_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Acrania	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Placental Mesenchymal Dysplasia	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Fetal Parvovirus İnfection	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
CCAM	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
Total	471 (86.1%)	32 (5.9%)	44 (8.0%)		
Chromosome abnormality					
Trisomy 21	50_a (58.8%)	32_a (37.6%)	3_a (3.5%)	**127.071**	**<0.001**
Translocation	25_a (73.5%)	8 (23.5%)	1_a (2.9%)		
Turner	4_a (44.4%)	5_{aa} (55.6%)	0_a (0.0%)		
inv (9)	24_a (96.0%)	1_b (4.0%)	0_{ab} (0.0%)		
Klinefelter	6_a (85.7%)	1_a (14.3%)	0_a (0.0%)		
Trisomy 18	9_a (42.9%)	11_b (52.4%)	1_{ab} (4.8%)		
Mosaic 3	4_a (57.1%)	0_a (0.0%)	3_a (42.9%)		
15ps$^+$	2_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
9qh$^+$	0_a (0.0%)	1_a (100.0%)	0_a (0.0%)		
1qh$^+$	4_a (80.0%)	0_a (0.0%)	1_a (20.0%)		
Inv Y	2_a (100.0%)	0_a (0.0%)	0_a (0.0%)		
47,XXX	1_a (100.0%)	0_a (0.0%)	0_a (0.0%)		

47,XXY	1 $_a$ (33.3%)	2 $_a$ (66.7%)	0 $_a$ (0.0%)		
69,XXX	2$_a$ (22.2%)	7$_b$ (77.8%)	0$_{ab}$ (0.0%)		
Trisomy13	0 $_a$ (0.0%)	0 $_a$ (0.0%)	1 $_a$ (100.0%)		
Del22	0 $_a$ (0.0%)	1 $_a$ (100.0%)	0 $_a$ (0.0%)		
Del1p	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Ring9	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
inv1	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Multiple chrm. abnormality	1 $_a$ (20.0%)	4 $_a$ (80.0%)	0 $_a$ (0.0%)		
Mosaic chrm. abnormality	2 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
22ps$^+$	0 $_a$ (0.0%)	1 $_a$ (100.0%)	0 $_a$ (0.0%)		
Der 16	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Ring Y	2 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
15cenh +	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Mosaic 45	2 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
69,XXY	1 $_a$ (50.0%)	1 $_a$ (50.0%)	0 $_a$ (0.0%)		
14ps$^+$	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Mosaic1	2 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
16qh$^+$	3 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
inv10	0 $_a$ (0.0%)	1 $_a$ (100.0%)	0 $_a$ (0.0%)		
Mosaic 20	2 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
inv12	1 $_a$ (33.3%)	2 $_a$ (66.7%)	0 $_a$ (0.0%)		
Marker chromosome	0 $_a$ (0.0%)	1 $_a$ (100.0%)	0 $_a$ (0.0%)		
inv11	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Partial trisomy 2	0 $_a$ (0.0%)	2 $_a$ (100.0%)	0 $_a$ (0.0%)		
Mosaic X	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Mosaic 18	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
21PS	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
XIX	0 $_a$ (0.0%)	0 $_a$ (0.0%)	1 $_a$ (100.0%)		
47 XYY	1 $_a$ (100.0%)	0 $_a$ (0.0%)	0 $_a$ (0.0%)		
Total	161 (63.6%)	81 (32.0%)	11 (4.3%)		
				z	**p**
Week	17.86±2.23 17.00 (11.00-33.00)	12.81±1.18 13.00 (11.00-23.00)	23.08±2.47* 23.00 (19.00-34.00)	**-953.311**	**<0.001**
Age, year	34.03±4.98 35.00 (18.00-48.00)	33.75±4.64 34.00 (20.00-45.00)	33.25±4.34 34.00 (21.00-42.00)	-2.396	0.302

Subscripts *a* and *b* show the difference between measurements in the same group. Measurements with the same letter are similar. **χ2:** Chi-square test, Fisher Exact Test, ***z*:** Kruskal Wallis test

AMA; Advanced Maternal Age, **ARSA**; Aberrant Right Subclavian Artery**, AS;** Amniocentesis, **CCAM;** Congenital Cystic Adenomatoid Malformation, **CS;** Cordocentesis, **CVS;** Chorionic Villus Biopsy, **ICSI;** Intracytoplasmic Sperm Injection, **IUGR;** Intrauterine growth retardation, NIPT**;** Non-invasive Prenatal Test, **NT;** Nuchal Translucency, **PGD;** Prenatal Genetic Diagnosis, **PPROM:** Preterm *premature rupture of membranes*, **USG;** Ultrasonography,

The comparison of karyotype analysis results with other parameters is given in Table 2. The indication with the highest Positive Predictive Value (PPV) in determination of abnormal karyotype was NIPT with 73.9%. Then, paternal chromosome anomaly with 17.4%, multiple indications with 15.7%, pathological USG results with 14.5%, and sperm factors with 14.3% was present. In patients with MET, only amniocentesis was performed and 87.5% of normal karyotype was observed. Among abnormal USG results, trisomy 21 suspicion had the highest PPV value with 84.6% (n=11).

Table 2. Comparison of karyotype analysis with other parameters. Continuous variables are given as mean ± S.D, median (minimum-maximum), and categorical variables as n (%).

Variables	**Normal karyotype, n (%)**	**Abnormal karyotype, n (%)**	**X^2**	**p**
Date				
≤2010	1181 $_a$ (92.1%)	101$_b$ (7.9%)	**21.921**	**<0.001**
>2010	935 $_a$ (86.2%)	150$_b$ (13.8%)		
Total	2116 (89.4%)	251 (10.6%)		
Indication				
AMA	374$_a$ (93.7%)	25$_b$ (6.3%)		
Sperm Factor	18$_a$ (85.7%)	3 $_a$ (14.3%)		
Abnormal USG Results	594$_a$ (85.5%)	101$_b$ (14.5%)		
Abnormal 1st Trimester Test	479$_a$ (93.4%)	34$_b$ (6.6%)		
Abnormal Triple Test	144$_a$ (92.3%)	12 $_a$ (7.7%)		
PGD	86$_a$ (94.5%)	5 $_a$ (5.5%)		
Paternal Chromosome Anomaly	114$_a$ (82.6%)	24$_b$ (17.4%)		
History Of Baby With Anomaly	57$_a$ (91.9%)	5$_a$ (8.1%)		
Maternal Anxiety	37$_a$ (100.0%)	0$_b$ (0.0%)		
ICSI Pregnancy	9$_a$ (100.0%)	0a (0.0%)		
Consanguineous Marriage	1$_a$ (100.0%)	0$_a$ (0.0%)	**109.260**	**<0.001**
Rh Mismatch	1$_a$ (100.0%)	0$_a$ (0.0%)		
Toxoplasma İnfection	2$_a$ (100.0%)	0$_a$ (0.0%)		
Poor Obstetric History	2$_a$ (100.0%)	0$_a$ (0.0%)		
Abnormal Quad Test	24$_a$ (100.0%)	0$_a$ (0.0%)		
Recurrent Pregnancy Losses	2$_a$ (100.0%)	0$_a$ (0.0%)		
NIPD	6$_a$ (26.1%)	17$_b$ (73.9%)		
Multiple Pregnancy	23$_a$ (100.0%)	0$_a$ (0.0%)		
Mosaic Embryo Transfer	21$_a$ (87.5%)	3$_a$ (12.5%)		
Multiple İndications	129$_a$ (84.3%)	24$_b$ (15.7%)		
Total	2124 (89.4%)	253 (10.6%)		
Abnormal USG Results				
Heart Anomaly	47$_a$ (83.9%)	49$_a$ (16.1%)		
Increased NT	82$_a$ (81.2%)	19$_a$ (18.8%)		
Hyperechogenic Focus	52$_a$ (86.7%)	8$_a$ (13.3%)		
IUGR	29$_a$ (87.9%)	4$_a$ (12.1%)		
Urinary System Anomaly	25$_a$ (96.2%)	1$_a$ (3.8%)	**80.322**	**<0.001**
Choroid Plexus Cyst	34$_a$ (100.0%)	0$_b$ (0.0%)		
Skeletal System Anomaly	24$_a$ (100.0%	0$_b$ (0.0%)		
Multiple Congenital Anomalies	90$_a$ (85.7%)	15$_a$ (14.3%)		
Single Umbilical Artery	3$_a$ (100.0%)	0$_a$ (0.0%)		
Polyhydramnios	7$_a$ (100.0%)	0$_a$ (0.0%)		

Nasal Bone Hypoplasia	22_a (91.7%)	2_a (8.3%)		
Cord Cyst	1_a (50.0%)	1_a (50.0%)		
Cranial Calcification	1_a (100.0%)	0_a (0.0%)		
Anhydramnios	2_a (100.0%)	0_a (0.0%)		
Toxoplasma	2_a (100.0%)	0_a (0.0%)		
Fetal Hydrops	5_a (83.3%)	1_a (16.7%)		
Double Bubble	1_a (50.0%)	1_a (50.0%)		
Ventriculomegaly	4_a (100.0%)	0_a (0.0%)		
Unilateral Pleural Effusion	1_a (100.0%)	0_a (0.0%)		
ARSA	11_a (100.0%)	0_a (0.0%)		
PPROM	1_a (100.0%)	0_a (0.0%)		
Hydrothorax	4_a (100.0%)	0_a (0.0%)		
Microcephaly	1_a (100.0%)	0_a (0.0%)		
Hydrocephalus	1_a (100.0%)	0_a (0.0%)		
Cleft Palate-Lip	2_a (66.7%)	1_a (33.3%)		
Trisomy 13	1_a (50.0%)	1_a (50.0%)		
Trisomy 21	2_a (15.4%)	11_b (84.6%)		
Trisomy 18	0_a (0.0%)	2_b (100.0%)		
Pulmonary Atresia	1_a (100.0%)	0_a (0.0%)		
Encephalocele	1_a (100.0%)	0_a (0.0%)		
Ambiguous Genitalia	1_a (100.0%)	0_a (0.0%)		
Di George Syndrome	1_a (100.0%)	0_a (0.0%)		
Megacystis	2_a (100.0%)	0_a (0.0%)		
Omphalocele	1_a (100.0%)	0_a (0.0%)		
Turner	0_a (0.0%)	1_b (100.0%)		
Placental Transfusion Syndrome	4_a (100.0%)	0_a (0.0%)		
Acrania	1_a (100.0%)	0_a (0.0%)		
Placental Mesenchymal Dysplasia	1_a (100.0%)	0_a (0.0%)		
Fetal Parvovirus İnfection	1_a (100.0%)	0_a (0.0%)		
CCAM	1_a (100.0%)	0_a (0.0%)		
Total	470 (85.9%)	77 (14.1%)		
			z	**p**
Week	17.72±3.03 17.00 (11.00-34.00)	16.11±3.38 16.00 (11.00-30.00)	**-7.965**	**<0.001**
Age, year	33.94±4.93 35.00 (18.00-48.00)	34.20±5.14 35.00 (18.00-45.00)	-0.657	0.511

Subscripts *a* and *b* show the difference between measurements in the same group. Measurements with the same letter are similar. χ2: Chi-square test, Fisher Exact Test, *z*: Mann-Whitney *U* test

AMA; Advanced Maternal Age, **ARSA**; Aberrant Right Subclavian Artery**, AS;** Amniocentesis, **CCAM;** Congenital Cystic Adenomatoid Malformation, **CS;** Cordocentesis, **CVS;** Chorionic Villus Biopsy, **ICSI;** Intracytoplasmic Sperm Injection, **IUGR;** Intrauterine growth retardation, NIPT**;** Non-invasive Prenatal Test, **NT;** Nuchal Translucency, **PGD;** Prenatal Genetic Diagnosis, **PPROM:** Preterm *premature rupture of membranes*, **USG;** Ultrasonography,

DISCUSSION

One of the most important causes of congenital anomalies is chromosomal abnormalities. The rate of chromosomal abnormalities diagnosed prenatally in Europe is approximately 76% (1). Prenatal diagnosis of children with chromosomal abnormalities is important for both parents to make informed decisions about the continuation of the pregnancy and can provide more efficient planning of medical and surgical care to be performed after birth (6).

In our retrospective study, 2,385 prenatal diagnoses were evaluated. As the analysis shows, amniocentesis is the most frequently utilized method of prenatal diagnosis amongst others with 1,965 (82.4%) patients. While the two most common indications of prenatal diagnosis were pathological USG results with 695 (29.1%) patients and abnormal first trimester test results with 513 (21.5%) patients, AMA was the main indication with 390 patients aged 35 and over (33.7%). The likelihood of detecting anomalies after chorionic villus biopsy was higher than amniocentesis and cordocentesis (29.0% vs 8.2% and 7.8% respectively). Similar to our study results in Norton et al. (7) study, amniocentesis constitutes 71.1% of prenatal diagnostic tests and CVS 12%. In the study of Durmaz et al. (8), it was reported that 8,363 (89.95%) patients had amniocentesis, 626 (6.73%) patients had CVS, and 308 (3.31%) patients underwent cordocentesis. The same study also reported that the main indications for prenatal diagnosis are AMA and abnormal maternal serum screening CVS tests. Similarly, while the most common indications for prenatal testing in previous studies were AMA (9, 10), over the years MSSs have become a more common indication for prenatal diagnosis (11). In a retrospective study from 2009 to 2014, a shift in prenatal diagnosis indications from AMA to MSS was identified (12). In the study conducted by Lostchuck et al. (13), it was stated that the abnormal USG result became the most common indication for prenatal diagnostic tests with 29.4% between 2013 and 2016. With regard to the results of our study, both the most frequent indications and the most frequent prenatal diagnosis figures are consistent with the results of the former study.

In our study, 253 (10.6%) patients were found to have abnormal karyotype, 85 of them (3.6%) had trisomy 21, 34 (1.4%) had translocation, 25 (1.0%) had inv(9), and 21 had (0.9%) trisomy 18. were observed. Among those with abnormal karyotypes, the trisomy 21 rate was 33.59%, the translocation rate was 13.43%, the inv(9) rate was 9.88%, and the trisomy 18 rate was 9.48%. Norton et al. (7) reported in their study that they got 2,993 (11.5%) abnormal results. They determined that 53.2% of chromosome abnormalities had trisomy 21, 17% had trisomy 18, 4.6% had trisomy 13, and 8.2% had sex chromosome aneuploidies. They concluded that 83.1% of the abnormal karyotypes could be detected by non-invasive prenatal diagnostic methods, but 16.9% could not be detected by noninvasive prenatal diagnosis tests. Durmaz et al. (8) found chromosome abnormalities in 538 cases (5.8%) out of 9,297 cases. They observed that 60.1% of chromosome abnormalities were numerical and 39% were structural abnormalities. Of the numerical chromosome abnormalities, they stated that 31% had trisomy 21, 10.6% had sex chromosome abnormalities, and 7.8% had trisomy 18. Santoro et al. (6) reported that 59.1% had trisomy 21, 15.2% had trisomy 18, 5.9% had Turner Syndrome, 4.5% had trisomy 13 and 4.1% had Klinefelter Syndrome. While the rate of chromosomal abnormalities diagnosed by prenatal diagnostic tests in our study was similar to Norton et al study's results, our trisomy case rates were lower. The trisomy rates were similar to the rates of Durmaz et al., which is another study conducted in our country. These differences in trisomy rates with Norton et al. and Santoro et al. studies may be related to the ages and ethnic origins of the cases included in the study.

Positive prediction of chromosome abnormalities by non-invasive methods is as important as invasive diagnostic tests. In most studies an abnormal USG yielded the highest PPV between 5.3-20.3% (14, 15). In the study of Durmaz et al. (8), the PPV value of 81.8% was observed when AMA was together with the history of a previous pregnancy with chromosome abnormality. In Sun et al study (16) the PPV value of a diagnostic test was 46.97% when NIPT was the indication. While the sensitivity of NIPT is approximately 99%, PPV rate was reported to be between 40% and 90%, and the false positive rates are below 1% [18,19].

In the Dai et al. (17) study, trisomy 21 PPV rate was 84.38%, trisomy 18 PPV rate was 61.54%, autosomal abnormalities PPV rate was 52.94%, sex chromosomal abnormalities PPV rate was 38.46% and trisomy 13 PPV rate was 33.33%. In the study by Petersen et al. (18), the PPV rate for trisomy 21 was 84%, the PPV rate for trisomy 18 was 76%, the PPV rate for trisomy 13 was 45%, and the PPV rate for monosomy X was 26%. In another study evaluating sex chromosome aneuploidies, it was observed that the overall PPV rate with NIPT was 40.56%. (19). In our study, the PPV rate was 73.9% in NIPT, 17.4% in paternal chromosome anomaly, and 14.5% with an abnormal USG result. In our study, there were 23 (1.0%) patients who underwent NIPT. Amniocentesis was performed in 20 patients and CVS was performed in 3 patients for prenatal diagnosis in patients with NIPT. Of the 17 (73.9%) individuals with NIPT who had chromosomal abnormality as a result of karyotype analysis, 13 had trisomy 21, 2 had trisomy 18, one had trisomy 13, and another Turner syndrome. Sixteen (94.11%) of 17 individuals who were predicted to have trisomy with NIPT were confirmed as trisomy after karyotype analysis. In our study, PPV value for trisomy 21 was 100%, PPV value for trisomy 18 was 100% and for trisomy 13 was 50%. Our results are similar to the results of previous studies.

The use of preimplantation genetic testing (PGT-A) to detect aneuploidy in the treatment of in vitro fertilization (IVF) has improved the live birth rate (20-22). However, in some patients, the no euploid embryo can be found**,** and a few mosaic embryos can be observed. Recent studies by Viotti (23) and Capalbo (24) showed that the live birth rate after with low or moderate degree mosaic embryo transfer is not statistically significantly different than the transfer of uniformly euploid embryos. Kahraman et al. (27) reported the first true fetal mosaicism case resulting in a live birth following the transfer of a known mosaic embryo. Following this publication Lee et al. (25) evaluated the euploidy and mosaic embryo groups. The euploid group had a higher rate of implantation (65.7% versus 51.8%) and higher ongoing pregnancy (64.8% versus 47.0%) compared to the mosaic group. They did not find any congenital anomalies in all samples taken from amniocentesis (28). They suggested that mosaic trophectoderms at the blastocyst stage can be self-corrected or confined to placenta. They reported that embryos with MET resulted in euploid babies. In our study, there were 24 patients who underwent MET followed by prenatal diagnosis. As a result of prenatal diagnosis, 21 (87.5%) cases were euploid. This ratio is close to the rate of the Lee et al study and confirms that mosaic embryos can self-correct during pregnancy.

With technological advances in DNA amplification and genome analysis, the PGD method now enables faster, more accurate analysis and has the potential to increase IVF success rates (26). However, PGD is still controversial in terms of its practicality and diagnostic accuracy due to the avoidance of invasive biopsy as much as possible and the potential mosaicism of embryos (27).

In conclusion, the rate of abnormal chromosome detection in our center was 10.6% and the most common indication was abnormal USG result according to the 21-years analysis results. In addition, the most common chromosome abnormality was trisomy 21 and the highest PPV rate was NIPT. The high PPV rates in NIPTs suggest that more studies are needed in this field and more emphasis, effort, and budget by the governments and health insurances should be placed in the field of NIPT for availability and scientific progression.

Conflict of interest

No conflict of interest was declared by the authors.

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