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Original Article

Retrospective analysis of prenatal invasive diagnostic procedures in a tertiary center

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ABSTRACT

Objective: This study aimed to analyze the indications and outcomes of prenatal invasive diagnostic procedures performed in a single tertiary center.

Material and methods: The invasive procedure indications and karyotype results of 1666 pregnant women who underwent prenatal invasive procedures between March 2016 and November 2018 were retrospectively analyzed. The indications and results of prenatal invasive diagnostic procedures were recorded.

Results: Amniocentesis (AS) was performed to 1060 (63.6%) patients, chorion villus sampling (CVS) to 299 (17.9%), and cordocentesis (CS) to 307 (18.4%) patients. Among the prenatal invasive procedure indications, the most frequent indication was abnormal ultrasound (US) findings, with a rate of 48.3% (n= 805). A normal karyotype was detected in 85% (n= 1416) of the cases, and chromosomal abnormality was detected in 12.2% (n= 204) of the cases. Abnormal karyotype results were found in 111 (10.5%) of 1060 patients who underwent AS, 87 (29.1%) of 299 patients who underwent CVS, and 52 (16.9%) of 307 patients who underwent CS. Among the numerical chromosomal abnormalities, trisomy 21 was the most common abnormality with a rate of 46% (94/204), while inversions were the most common abnormality of structural chromosomal abnormalities at 8.8% (18/204).

Conclusion: This study shows that AS is still the most commonly used prenatal diagnostic invasive procedure. We obtained the highest fetal chromosomal anomaly rate in patients who experienced CVS. Choosing the most appropriate invasive procedure for a patient with a high risk of chromosomal anomaly is related to the obstetricians' experience, medical history of the patient, the gestational week at admission, maternal prenatal serum screening test results, and abnormal US findings.

Keywords: amniocentesis; cordocentesis; chorion villus sampling

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Introduction

Every pregnant woman has a risk of having a fetus with chromosomal abnormalities. Chromosomal anomalies are detected in approximately 50-60% of spontaneous abortions and 2-4% of all newborns. Fetuses with chromosomal abnormalities are at risk for adverse fetal outcomes, and these abnormalities cause 20% of deaths in the first year of life [1-4]. Chromosomal abnormalities represent approximately 15% of the major congenital anomalies diagnosed before the age of 1 year in Europe [5]. The traditional cytogenetic analysis enables to identify numerical and structural disorders of chromosomes [6,7]. At the same time, molecular DNA techniques enable the detection of single-gene diseases [8]. Approximately 90% of chromosomal anomalies are numerical disorders of 13th, 18th, 21st chromosomes, and sex chromosomes (X, Y). Trisomies 13, 18, 21 are the most common autosomal trisomies.

Turner syndrome and Klinefelter syndrome are the most common numerical sex chromosome anomalies [9]. Non-invasive prenatal screening tests are used to evaluate the risk of chromosomal anomalies in pregnant women. Maternal serum screening tests (double-test in the first trimester, triple and quadruple screening tests in the second trimester), and ultrasonography (US) to detect fetal structural disorders are the most commonly used non-invasive prenatal screening tests. Also, extracellular free fetal DNA test, an essential prenatal screening test, has been widely used in recent years. Prenatal invasive diagnostic procedures are used to determine whether there is a chromosomal anomaly in the fetus in pregnant women at high risk for chromosomal abnormalities; chorionic villus sampling (CVS) can be done in the first trimester, amniocentesis (AS) in the second trimester, and cordocentesis (CS) for further weeks of gestation [10]. These procedures can also be performed in intrauterine fetal transfusion (red cell alloimmunization), detecting

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enzyme-associated metabolic diseases, and congenital infections [11].

Although frequently used in obstetric follow-up, maternal serum screening tests and the US are auxiliary tests for prenatal screening, and they may cause false-positive results and following unnecessary invasive procedures. On the other hand, prenatal invasive diagnostic procedures do have a small added fetal loss risk over the natural or spontaneous pregnancy loss rate. These risks should be considered with parents, and prenatal invasive diagnostic tests should only be applied to pregnant women with indications, including advanced maternal age, history of baby with numerical or structural chromosomal anomalies in a previous pregnancy, increased risk for aneuploidy in maternal serum screening tests or extracellular fetal DNA test, presence of ultrasonographic fetal anomaly, presence of translocation, inversion or chromosomal anomaly in one of the parents, and maternal anxiety. Parent counseling for these procedures requires proper patient information with the fetal-specific genetic depth of analysis and testing level suggested assisting in the informed consent duration [12]. Detecting fetal chromosomal disorders during the prenatal period is important in informing the family about the prognosis of the current abnormality. Because as a result of this situation, the family may request the continuation of the pregnancy or terminate the pregnancy. Also, detecting chromosomal anomalies is important for the follow-up of subsequent pregnancies.

Our maternal-fetal medicine unit conducts prenatal invasive diagnostic procedures for fetal karyotype analysis for both patients detected at our hospital or those referred from other medical institutions. However, data concerning the outcomes of these diagnostic procedures in our hospital have rarely been published. To counsel the parents accurately, it is crucial to present the best options utilizing center-specific outcome data. Therefore, this study aimed to analyze the indications and outcomes of prenatal invasive diagnostic procedures performed in our tertiary center.

Material and methods

This study included a retrospective analysis of 1666 pregnant women who underwent prenatal invasive diagnostic procedures in the perinatology department of Kanuni Sultan Süleyman Training and Research Hospital between March 2016 and November 2018. Data were evaluated in terms of indications and results of these procedures. Ethical approval for this study was obtained from the ethics committee of our hospital (2019/03/43). Before the procedure, a detailed US examination was performed to detect structural abnormalities in each patient with invasive procedure indications. Indications for the prenatal invasive procedure were as follows: cystic hygroma, advanced maternal age, presence of fetal anomalies in ultrasonography, increased risk for aneuploidy in maternal serum screening tests, history of a child with chromosomal or structural abnormalities, increased nuchal translucency (NT), fetal anemia, suspicion of fetal infection, and maternal anxiety.

Advanced maternal age was defined as 35 years and above, and maternal serum screening tests were not performed on these patients. The presence of a fetal anomaly in the US was defined as a major anomaly or the presence of ≥2 minor markers in US examination. US minor markers, known as soft markers, included single umbilical artery (SUA), mild pyelectasis (renal pelvis ≥4 mm), unilateral or bilateral choroid plexus cysts (CPC) (≥2 mm), echogenic bowel, and echogenic intracardiac focus [13]. We included patients with abnormal US findings in a single group, even if they had other indications. Maternal serum prenatal screening (double, triple, and quadruple test) results were collected in a single group. The first trimester combined risk or second-trimester biochemical risk was defined as 1/270 for down syndrome and 1/100 for trisomy 13, and 18. Nuchal translucency increase was accepted as ≥3.5 mm. All pregnant women with invasive procedure indication and their spouses were informed in detail about the risk of a possible chromosomal abnormality, the method of performing the invasive procedure, the possible benefits and risks, and they were provided with genetic counseling. Informed consent forms were signed by couples who accepted the invasive procedure. Before the procedure, all pregnant women were evaluated in terms of blood group and Rh incompatibility, and 300 mcg anti D Ig was administered to pregnant women with Rh incompatibility. Procedures were performed using the Voluson 730 Expert (General Electric Healthcare, Milwaukee, WI, USA) device and 3.5 MHz transabdominal convex probes with the US.

Before the procedure was performed, US has performed on all patients again, and according to the procedure to be applied, the most appropriate place for the procedure was determined by evaluating the amniotic fluid, the location of the placenta, the entry place of the cord into the placenta and the position of the fetus. CVS was performed between 11-14 weeks of gestation, under sterile conditions, using an 18 Gauge (G) spinal needle only transabdominal. AS was preferred in patients not suitable for CVS sampling with active vaginal bleeding and patients with posterior placenta at appropriate weeks of gestation. AS was performed between 16-22 weeks of gestation, under sterile conditions, transabdominal, with a 20 Gauge (G) spinal needle, if possible transamniotic without passing through the placenta and umbilical cord, and transplacentally in unsuitable cases. A total of 27.5 amniotic fluid were aspirated into 2.5 ml (x1) and 5 ml (x5) sterile syringes. CS was performed transabdominal, under sterile conditions, in pregnancies above the 22nd gestational week, by entering the umbilical vein from the umbilical cord's placenta insertion area or the free-floating part of the cord with a 22 Gauge (G) spinal needle. 2.5 ml of fetal blood was collected into the syringe washed with sterile heparin. A maximum of two-needle entries was made to obtain the material.

The procedure was repeated 1 week later in cases that could not be successful. The material samples taken were delivered to the genetic laboratory. Patients were discharged on the same day after being observed in the hospital for 2 hours after the procedure. Maternal characteristics such as age, gravity, and parity of the patients indicate a prenatal invasive procedure, type of procedure, and results were recorded.

Statistical analysis

Nominal and ordinal parameters were described with frequency analysis, whereas maternal age was described with mean and standard deviation. The Chi-square likelihood ratio was used for comparison of nominal and ordinal differences. Statistical analysis of the data was performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) package program at a 95% confidence interval. Differences were considered statistically significant at p-value <0.05.

Results

During the study period, 1666 patients underwent prenatal invasive procedures. Maternal age, indications, and results of prenatal invasive diagnostic procedures are given in Table 1.

AS was performed to 1060 (63.6%) patients, CVS to 299 (17.9%), and CS to 307 (18.4%) patients. The mean age of the study cohort was 31.59±6.73 years. Among the prenatal invasive procedure indications, the most frequent indication was US abnormalities, with a rate of 48.3% (n= 805). The other common prenatal invasive procedure indications were advanced maternal age (23.9%, n= 399), and maternal serum screening test with high risk for aneuploidy (21.1%, n= 351). A normal karyotype was detected in 85% (n= 1416) of 1666 pregnant women who underwent invasive procedures and chromosomal abnormalities were found in 12.2% (n= 204). Abnormal karyotype results were found in

111 (10.5%) of 1060 patients who underwent AS, 87 (29.1%) of 299 patients who underwent CVS, and 52 (16.9%) of 307 patients who underwent CS.

Table 1. Maternal age, indications and results of prenatal invasive diagnostic procedures

Parameter	Value
Maternal age, years	31.59±6.73
Prenatal invasive diagnostic method, n (%)	
Amniocentesis	1060 (63.6)
Cordosentesis	307 (18.4)
Chorionic villus sampling	299 (17.9)
Indication, n (%)	
Abnormal US findings	805 (48.3)
Advanced maternal age	399 (23.9)
Screening test positivity	351 (21.1)
Previous history of fetus with chromosomal or structural anomaly history	36 (2.2)
Suspected congenital infection	20 (1.2)
Fetal anemia	20 (1.2)
Maternal anxiety	17 (1.0)
Increased NT	10 (0.6)
Cystic hygroma	8 (0.5)
Results, n (%)	
Normal	1416 (85.0)
Down syndrome	94 (5.6)
Edwards syndrome	35 (2.1)
Non-growth samples in culture	31 (1.9)
Inversion	18 (1.1)
Turner syndrome	17 (1.0)
Maternal contamination	15 (0.9)
Translocation	10 (0.6)
Triploidy	10 (0.6)
Patau syndrome	9 (0.54)
Insertion	4 (0.24)
Trisomy	3 (0.18)
Deletion	2 (0.12)
Pallister Killian syndrome	1 (0.06)
Klinefelter syndrome	1 (0.06)

Of 50 patients with insufficient material, culture failure, procedural failure, and maternal contamination, four patients agreed to undergo a second invasive procedure, and the results were detected as a normal karyotype. Fetal karyotype determination failed in 46 (2.76%) patients due to exhibiton no growth in the sample culture; 10 (0.6%) patients in AS group, 17 (1%) patients in CVS group, and 19 (1.1%) patients in CS group. Of those, 31 patients (1.9%) due to culture failure, insufficient material, procedure failure, and 15 (0.9%) due to maternal contamination. While 82.9% (169/204) of 204 fetuses with chromosomal anomalies have numerical chromosome anomalies, 17.1% (35/204) of fetuses with chromosomal anomalies had structural chromosome anomalies. The most common numerical chromosomal abnormality trisomy 21 (46%, 94/204), and the most common structural chromosomal abnormality was inversions (8.8%, 18/204).

When we analyzed the indication differences between the prenatal invasive diagnostic procedure groups, in AS group, advanced maternal age (30.9%, n= 328), maternal serum screening test with high risk for aneuploidy (25.8%, n= 273), and maternal anxiety (1.4%, n= 15) was significantly higher than CS and CVS groups ($p<0.05$) (Table 2). In the CVS group, the previous history of children with chromosomal or structural anomalies (5.4%, n= 16), increased NT (2%, n= 6), and cystic hygroma (1%, n= 3) was significantly higher than AS and CVS groups ($p<0.05$). In the CS group, abnormal US findings (77.2%, n= 237) and fetal anemia (5.5%, n= 17) was significantly higher than the other groups ($p<0.05$).

Table 2. The indications and results of prenatal invasive diagnostic procedures of the participants

	Invasive method		
	Amniocentesis (n=1060)	Chorionic villus sampling (n=299)	Chordocentesis (n=307)
Indications n (%)*			
Abnormal US finding	397 (37.5)	171 (57.2)	237 (77.2)
Advanced maternal age	328 (30.9)	56 (18.7)	15 (4.9)
Screening test positivity	273 (25.8)	45 (15.1)	33 (10.7)
Previous history of pregnancy with chromosomal or structural anomaly	17 (1.6)	16 (5.4)	3 (1.0)
Suspected congenital infection	20 (1.9)	-	-
Maternal anxiety	15 (1.4)	2 (0.7)	-
Cystic hygroma	4 (0.4)	3 (1.0)	1 (0.3)
Increased NT	3 (0.3)	6 (2.0)	1 (0.3)
Fetal anemia	3 (0.3)	-	17 (5.5)
Results, n (%)*			
Normal	949 (89.5)	212 (70.9)	255 (83.1)
Down syndrome	49 (4.6)	29 (9.7)	16 (5.2)
Edwards syndrome	12 (1.1)	14 (4.7)	9 (2.9)
Non-growth samples in culture	10 (0.9)	6 (2.0)	15 (4.9)
Inversion	10 (0.9)	7 (2.3)	1 (0.3)
Patau syndrome	7 (0.7)	1 (0.3)	1 (0.3)
Turner syndrome	7 (0.7)	10 (3.3)	-
Maternal contamination	-	11 (3.7)	4 (1.3)
Translocation	7 (0.7)	1 (0.3)	2 (0.7)
Triploidy	4 (0.4)	5 (1.7)	1 (0.3)
Insertion	2 (0.2)	-	2 (0.7)
Deletion	1 (0.1)	1 (0.3)	-
Pallister Killian syndrome	1 (0.1)	-	-
Klinefelter syndrome	1 (0.1)	-	-
Trisomy	-	2 (0.7)	1 (0.3)

**p values are <0.05*

We also summarized the prenatal invasive diagnostic procedure results of the participants in Table 2. Normal karyotype results were significantly higher in the AS group than CS and CVS groups ($p <0.05$). In the CVS group, trisomy 21, trisomy 18, turner syndrome, inversion, and triploidy rates were found to be significantly higher than AS and CS groups ($p <0.05$).

We presented the prenatal invasive diagnostic procedure results as normal or abnormal in terms of indications in Table 3. The most common indications for abnormal prenatal invasive diagnostic procedure results were abnormal US findings (64%, 160 patients), maternal serum screening test with high risk for aneuploidy (14.8%, 37 patients), and advanced maternal age (17.2%, 43 patients).

Discussion

The most common indications for the prenatal invasive diagnostic procedure in our study are abnormal US findings (48.3%), advanced maternal age (23.9%), and maternal serum screening test with a high risk for aneuploidy (21.1%). Previous studies reported that the most common indications for these interventions were advanced maternal age and maternal serum screening tests with a high risk for aneuploidy [6,14-16]. As a prenatal invasive diagnostic procedure indication, the rate of maternal serum screening tests with high risk for aneuploidy has been reported to vary between 3.48% and 28.2% in other studies [6,17-21]. The

reason for this difference may be that previous studies more often focused on AS procedure results. Abnormal US findings are mostly detected late in the second trimester or third trimester of pregnancy. Therefore, CS, which is an invasive procedure appropriate in gestational weeks, was not included in the studies. Another reason why the most frequent indication was found to be different in our study is the widespread use of extracellular fetal DNA tests in recent years. This widespread use may cause decreased invasive intervention rates may due to advanced maternal age or maternal serum screening tests with high risk for aneuploidy [22]. We consider that our high rate of abnormal US findings was because our clinic is a tertiary referral clinic and the pregnant women with abnormal US findings were commonly referred to us.

Table 3. The distribution of the prenatal invasive diagnostic procedure results according to the indications*

	Results		Total
	Normal	Abnormal	
Abnormal US finding	645 (45.6%)	160 (64.0%)	805 (48.3%)
Advanced maternal age	356 (25.1%)	43 (17.2%)	399 (23.9%)
Screening test positivity	314 (22.2%)	37 (14.8%)	351 (21.1%)
Previous history of pregnancy with chromosomal or structural anomaly	31 (2.2%)	5 (2.0%)	36 (2.2%)
Suspected congenital infection	20 (1.4%)	0 (0%)	20 (1.2%)
Fetal anemia	19 (1.3%)	1 (0.4%)	20 (1.2%)
Maternal anxiety	16 (1.1%)	1 (0.4%)	17 (1.0%)
Increased NT	9 (0.6%)	1 (0.4%)	10 (0.6%)
Cystic hygroma	6 (0.4%)	2 (0.8%)	8 (0.5%)

**p value is <0.001*

In our study, we detected 12.2% of fetuses with chromosomal anomalies in prenatal diagnostic invasive procedures. The chromosomal anomaly was detected in 10.5% of patients who underwent AS, 29.1% of patients who underwent CVS, and 16.9% of patients who underwent CS. In the literature, the rate of chromosomal anomaly detection in invasive procedures ranges from 0.9% to 20.27% [17,23,24]. The rate of detecting chromosomal anomalies in our study was found to be higher than reported in the literature. We consider that the higher rate is due to our proper invasive procedure indications, the widespread use of prenatal serum screening tests in our clinic, and our experienced team in detecting abnormal US findings. Among the indications, the rate of abnormal karyotype results was higher in patients with a history of cystic hygroma, abnormal US findings, and a fetus with structural or chromosomal abnormalities.

The chromosomal anomaly was found in 19.9% of pregnant women with abnormal US findings. This rate has been reported in the literature varying between 4.43% and 22.7% [6,10]. The reason for these different rates may be that some studies did not include CS procedures for anomalies detected in advanced gestational weeks and did not perform karyotype determination due to minor US markers. Previous studies reported that the use of AS was more frequent than CVS and CS [16]. Researches stated that AS is an easily applicable method, and the morbidity risk is lower than the other procedures. Likewise, AS was the most common diagnostic procedure in our study.

Conclusion

The results of the current study show that AS is the most common prenatal diagnostic invasive procedure. We obtained the highest fetal chromosomal anomaly rate in patients who experienced CVS. Abnormal US findings were the most common prenatal invasive diagnostic procedure indication in our study. Choosing the most appropriate invasive procedure for a patient with a high risk for chromosomal anomaly is related to the obstetricians' experience, medical history of the patient, the gestational week at admission, maternal prenatal serum screening test results, and abnormal US findings.

Disclosure

Authors have no potential conflicts of interest to disclose.

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