Chromosome analysis results of first-second trimester anomaly screening tests: Single center experience

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Abstract

Aim: The Objective of our study was to evaluate the chromosomal analysis results that were obtained from amniocentesis, cordocentesis and chorionic villus sampling (CVS) inpatients whom had applied to the perinatology unit of Cukurova University Faculty of Medicine gynecology and obstetrics clinic with high risk in terms of chromosome anomaly according to Ultrasonography (USG).

Material and Methods: Our study was conducted as a retrospective pattern. CVS, amniocentesis and cordosentesis were performed in 1298 pregnant women whom had applied to the Çukurova University Faculty of Medicine, Gynecology and Obstetrics Clinic, Perinatology Unit in the date interval between 1st December 2014-31st December 2016 with the indication of abnormal maternal serum screening tests, maternal request because of advanced maternal age, history of fetal anomaly with previous pregnancies, history of relatives with Trisomy 21, fetal abnormalities or signs of trisomy which were detected by ultrasonography and only depending on maternal request without any risk factors. Data obtained in the study were assessed using the SPSS (Statistical Package for Social Sciences) 22.0 package program. The relationships between categorical variables were determined by Chi-Square test. Relationship between normal distribution-matched, numerical data were assessed by ANOVA, Independent Sample t-test, and relationship between non-normal distributions of numerical data were assessed using Mann-Whitney U and Wilcoxon Test. Statistical significance level was determined as p <0.05.

Results: Fetal anomalies were observed in 28.9% (n: 366) of the patients while 369 (28.4%) of the 1298 patients who had prenatal diagnosis had abnormalities in the maternal screening results. No chromosomal abnormalities were detected in 1120 (86.2%) of the 1298 patients who were taken into the study. 49 patients had Trisomy 21, 27 patients had Trisomy18 and 14 patients had Trisomy13. Turner syndrome was seen in 10 of the patients. In our study, chromosomal abnormality rate of patients with more than one minor marker was found to be statistically significant (p: 0.01). Chromosomal anomaly was detected in 319 (8.4%) of 349 patients with combined test. Chromosomal anomaly was detected in 70 (19.1%) of the 366 patients who detected fetal anomaly. Chromosomal anomaly was detected in 27 (24.1%) of the 112 increased NT patients.

Conclusion: In our study, 1298 invasive procedures are listed as follows; amniocentesis was performed in 841 (64.8%), cordocentesis in 57 patients (4.4%) and CVS in 400 patients (30.8%). As a result of karyotype analysis of the patients, nochromosomal anomaly was detected in 1120 patients (86.28%). In 178 patients, chromosomal anomaly (13.71%) was detected. This study aimed to determine the prevalence of fetal chromosomal anomaly in the Mediterranean region by determining the prevalence of invasive prenatal test indications and evaluating the results of invasive prenatal tests performed in our clinic in the 2-year period.

Keywords: Chromosomal abnormalities; pregnancy; trisomy

INTRODUCTION

Major congenital anomalies are identified during pregnancy or immediately after delivery in 2-3% of pregnancies (1). Prenatal detection of chromosomal anomalies paves the way for various indications, including early diagnosis, genetic counseling and even termination of pregnancy. Prenatal diagnosis involves the recognition of genetic and structural malformations (2). Prenatal diagnosis is crucial for providing parents with an option to end pregnancy, planning postpartum treatment methods and counseling for the next pregnancy.

Screening and diagnosis of fetal aneuploidy in pregnancies can be made using non-invasive or invasive procedures. Non-invasive screening tests include first trimester combined tests (maternal age, serum free beta-human chorionic gonadotropin (B-hcg), pregnancy-associated
plasma protein-A (PAPP-A) and fetal nuchal translucency (NT), second trimester screening tests (alpha-fetoprotein (AFP), B-hcg and estriol (E3) and / or inhibin A) and analysis of fetal DNA (cf-DNA) in maternal blood, which is a widespread method nowadays (3,4). Invasive procedures for prenatal diagnosis include amniocentesis, chorionic villus sampling (CVS), and cordocentesis. Among the invasive procedures mentioned, CVS is a valuable diagnostic method since it allows diagnosis at 11-14 weeks of pregnancy and it is possible to perform chromosomal analysis by direct evaluation of cells (5). Indications for invasive procedures include a history of pregnancy with chromosomal anomaly, abnormal prenatal screening test results, abnormal findings on ultrasonography (USG) and previously diagnosed maternal-paternal chromosomal anomalies (6). After detecting a risk factor for fetal chromosomal anomaly, detailed counseling is required.

Advances in USG technology have enabled better diagnosis of fetal structural anomalies and soft markers associated with chromosomal anomalies in the first weeks of pregnancy (7,8). It has been reported that the combination of first and second trimester detailed USG evaluations can identify major structural anomalies with a detection rate of 95% (7,8). The developments in prenatal diagnostic technologies followed the necessity of explaining the advantages and disadvantages of new techniques in detail (9). For example, the chromosomal microarray technique can detect deletions or duplications in 1.7% of cases with a positive genetic scan, which normally exhibits a classic karyotype. Therefore, it is important to recommend and use the most appropriate diagnostic test to detect a fetal genetic pathology (10).

Cukurova University Faculty of Medicine, where the study was conducted, is one of the main centers that offer the option of performing invasive prenatal tests in the Mediterranean and Southeastern Anatolia Region. In this study, it was aimed to determine the prevalence of fetal chromosomal anomaly in the Mediterranean region by evaluating the results of invasive prenatal tests performed in our clinic, and to determine the relationship between indications and anomalies. Data from this study can help clinicians choose for or between invasive procedures and provide detailed counseling to patients.

MATERIAL and METHODS

Our study was planned retrospectively and ethical approval was approved by Cukurova University Faculty of Medicine Ethics Committee on May 4, 2018 with number of 77. The results of patients who underwent invasive diagnostic procedures between 1 December 2014 and 31 December 2016 with at least one of the 3 main indications in Cukurova University Faculty of Medicine Obstetrics and Gynecology Perinatology Unit were examined. 1298 pregnant women who applied for CVS, amniocentesis and cordocentesis were included because of: 1) High risk presence in double / triple test for trisomy; 2) Advanced maternal age, history of an infant with anomaly in previous pregnancy, anamnesis of any relative with trisomy 21, or maternal request, and 3) Marker suggestive of anomaly and / or aneuploidy detected by ultrasonography. Voluson E6 and Voluson Pro730 (GE Healthcare, Milwaukee, WI, USA) ultrasonography devices were used for fetal ultrasonography in our perinatology department. The patient data were compiled from the ultrasound records of our center, external laboratory data with chromosome analysis and the Medical Genetics and Biology Department of our hospital. Written informed consents of the participants were obtained before the procedure. Pregnant women with multiple pregnancies, and cell culture failure after invasive intervention were excluded from the study.

Genetic information was given to the patients whose invasive diagnostic procedures were recommended with the above indications. CVS, AS or CS was recommended for diagnosis, verification and karyotyping. CVS was done between 11 and 14 weeks, AS was done between 16 and 22 weeks and CS was done between 22 and 24 weeks of gestation.

Statistical Analysis

The data obtained from the study were evaluated using SPSS (Statistical Package for Social Sciences) 22.0 package program (SPSS Inc., Chicago, IL). The suitability of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. The data that fit the normal distribution were expressed as mean ± standard Deviation (SD), and the data that do not fit the normal distribution were expressed as median. The relationship between categorical variables was determined by Chi-Square test. Relations between normal distribution and numerical data were evaluated using ANOVA, Independent Sample t-Test, and relationships between numerical data that do not fit normally distributed using Mann-Whitney U and Wilcoxon Test. Statistical significance level was determined as p <0.05.

RESULTS

The average age of the study group was 32.03 ± 6.59 (15-50) years. 1298 invasive prenatal test results were evaluated and pregnant women with numerical or structural fetal chromosome anomalies were identified as a result of the invasive procedure. The 1298 invasive

<table>
<thead>
<tr>
<th>Table 1. Indications for Inclusion of Patients</th>
</tr>
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<tbody>
<tr>
<td>Indications for Inclusion in the Study (n: 1298)</td>
</tr>
<tr>
<td>High Risk in Double Test</td>
</tr>
<tr>
<td>Fetal Anomaly and / or minor marker</td>
</tr>
<tr>
<td>High Risk in Triple Test</td>
</tr>
<tr>
<td>Advanced Maternal Age</td>
</tr>
<tr>
<td>Increased Nuchal Translucency</td>
</tr>
<tr>
<td>Mother's Request</td>
</tr>
<tr>
<td>High Risk in Quadruple Test</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
In the karyotype analysis of the patients, no chromosomal anomaly was detected in 1120 (86.28%) patients. Chromosomal anomaly was found in 178 (13.71%) patients. When the relationship between karyotype analysis results and invasive prenatal diagnosis indications was examined; Chromosomal anomaly was found in 31 (8.4%) of 369 patients who underwent karyotype analysis due to fetal anomaly. Chromosomal anomaly was found in 70 (19.1%) of 366 patients with fetal anomaly. Chromosomal anomaly was found in 27 (24.1%) of 112 patients with increased NT. Chromosomal anomaly was found in 11 (6.8%) of 162 patients who underwent invasive prenatal testing due to advanced maternal age. Chromosomal anomaly was found in 29 (14.7%) of 197 patients who underwent invasive prenatal test due to high risk in triple test. Chromosomal anomaly was detected in 2 (8.33%) of 24 patients who underwent karyotype analysis due to mother's request, while it was detected in 1 (5.88%) of 17 patients who underwent karyotype analysis due to the quadruple test result. Chromosomal anomaly was found in 7 (13.72%) of 51 patients who underwent karyotype analysis due to the presence of other indications. Trisomy 21 was found in 9 (2.4%) of 369 patients who underwent karyotyping due to high risk in double test, while trisomy 18, trisomy X, Triploidy and Turner Syndrome were detected each in 1 patient (0.3%). Among 366 patients who underwent karyotyping due to fetal anomaly; Trisomy 21 was detected in 19 (5.1%), trisomy 18 in 17 (4.6%), trisomy 13 in 12 (3.2%), Turner syndrome in 7 (1.9%) Triploidy in 3 (0.8%) and structural anomaly was detected in 10 (2.7%) patients.

Among 197 patients who underwent karyotyping due to high risk in triple test, Trisomy 21 was found in 2 (1%), Trisomy X in 1 (0.5%), Klinefelter Syndrome in 1 (0.5%), and structural anomaly was found in 6 (3%) patients. Among 112 patients underwent karyotyping due to increased NT; Trisomy 21 was detected in 15 (13.3%), Trisomy 18 in 6 (5.3%) Trisomy 13 in 2 (1.7%), Turner Syndrome and Klinefelter Syndrome each in 1 patient (0.8%), and finally structural anomaly was detected in 1 (0.8%) patient. 162 patients underwent karyotyping due to advanced maternal age; trisomy 21 was found in 2 (1.3%), trisomy 18 in 1 (0.6%), and structural anomaly was detected in 7 (4.3%) patients.

When the amniocentesis indications for 841 patients who underwent amniocentesis were examined; the procedure was applied to 27.7% of patients due to fetal anomaly, 25.1% due to high risk in double test, 23.2% due to high risk in triple test, and applied to 13.4% of patients due to advanced maternal age. CVS was performed in 39.5% of 400 patients due to high risk in double test and applied to 22.0% of patients due to increased NT. An invasive test was performed to 52 of 57 patients who underwent cordocentesis (91.2%) due to fetal anomaly.

Only one minor marker was detected in 64% (n: 124) of 194 patients with minor markers. Among these patients; 44 of them had increased nuchal translucency, 17 patients had fetal hyperechogenic bowel and 3 patients had short femurs. A total of 255 minor markers were observed in 194 patients. Minor markers detected in patients are shown in Table 2.

<table>
<thead>
<tr>
<th>Minor Marker (n:255)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Nuchal Translucency</td>
<td>44</td>
<td>17.2</td>
</tr>
<tr>
<td>Nasal Hypoplasia</td>
<td>31</td>
<td>12.1</td>
</tr>
<tr>
<td>Single Umbilical Artery</td>
<td>21</td>
<td>8.2</td>
</tr>
<tr>
<td>Fetal Echogenic Bowel</td>
<td>17</td>
<td>6.6</td>
</tr>
<tr>
<td>Choroid Plexus Cysts</td>
<td>19</td>
<td>7.4</td>
</tr>
<tr>
<td>Intracardiac Echogenic Focus</td>
<td>18</td>
<td>7.0</td>
</tr>
<tr>
<td>Pyelectasis</td>
<td>10</td>
<td>3.9</td>
</tr>
<tr>
<td>Short Femur</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Aberrant Right Subclavian Artery</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Nasal Hypoplasia + Increased Nuchal Translucency</td>
<td>11</td>
<td>4.3</td>
</tr>
<tr>
<td>Short Humerus + Short Femur</td>
<td>8</td>
<td>3.1</td>
</tr>
<tr>
<td>Increased Nuchal Translucency + Pyelectasis</td>
<td>6</td>
<td>2.3</td>
</tr>
<tr>
<td>Nasal Hypoplasia + Intracardiac Echogenic Focus</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>Other</td>
<td>61</td>
<td>23.9</td>
</tr>
</tbody>
</table>

Cardiac anomaly was observed in 3 of 49 patients diagnosed with trisomy 21 (6.1%). The diagnosis in all 3 patients is VSD-AVSD. While 12 of 27 patients with trisomy 18 were diagnosed with cardiac anomaly (44.4%), 5 of 14 patients with trisomy 13 were diagnosed with cardiac anomaly (35.7%).

Minor markers were observed in 30 (61.2%) of 49 patients diagnosed with trisomy 21. 4 of these patients had nasal hypoplasia (21.1%), 5 of them had nasal hypoplasia and increased nuchal translucency. Minor markers were detected in 11 (40.7%) of 27 patients diagnosed with trisomy 18. Choroidal plexus cyst was detected in 3 (11.1%) of these patients and short femur was found in 2 patients. Minor markers were detected in 5 of 14 (35.7%) patients diagnosed with trisomy 13. These 5 markers are listed as follows; Nasal hypoplasia (n: 1), pyelectasis (n: 1), nasal hypoplasia and increased NT (n: 1), fetal echogenic bowel and choroid plexus cyst (n: 1) and persistent right umbilical vein with single umbilical artery (n: 1).
Table 3. Relationship Between Karyotype Analysis Results and Indications for Inclusion in the Study

<table>
<thead>
<tr>
<th>Indication</th>
<th>Normal</th>
<th>Trisomy X</th>
<th>No Result</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
<th>Triploidy</th>
<th>Turner Syndrome</th>
<th>Kleinfelter Syndrome</th>
<th>Structural Anomaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>High risk in Double Test</td>
<td>338</td>
<td>91</td>
<td>1</td>
<td>0.3</td>
<td>8</td>
<td>2.2</td>
<td>9</td>
<td>2.4</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>High risk in triple test</td>
<td>168</td>
<td>85</td>
<td>1</td>
<td>0.5</td>
<td>19</td>
<td>9.6</td>
<td>2</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Advanced Maternal Age</td>
<td>151</td>
<td>93</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.6</td>
<td>2</td>
<td>1.2</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Mother's Request</td>
<td>22</td>
<td>91</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fetal Anomaly</td>
<td>296</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.5</td>
<td>19</td>
<td>5.2</td>
<td>17</td>
<td>4.6</td>
</tr>
<tr>
<td>Increased NT</td>
<td>85</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.9</td>
<td>15</td>
<td>13.4</td>
<td>6</td>
<td>5.4</td>
</tr>
<tr>
<td>High risk in Quadruple Test</td>
<td>16</td>
<td>94</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>44</td>
<td>86.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2.0</td>
<td>2</td>
<td>3.9</td>
<td>0</td>
</tr>
</tbody>
</table>

When the patients were divided into two groups as ≥35 years old (n: 522) and <35 years old (n: 776) groups and the invasive prenatal test indications were examined, the most common indications for women under 35 years of age were fetal anomaly (37%) and high risk in double test (26.9%). The most common indications for pregnant women over 35 years of age were listed as high risk in the double test (30.7%) and advanced maternal age (29.5%). Other indications (51 patients-3.9%) include non-classifiable ultrasonographic fetal abnormalities, abnormal chemical markers, chromosomal abnormality in the family, and high-risk non-invasive prenatal test result.

Patients with high risk in double test 338 of the 369 resulted (91%) in normal karyotype and the most common pathological result was Trisomy 21 in 9 patients. 168 (85%) of the 197 patients with high risk in triple test resulted as normal karyotype and 4 patients had pathological karyotype. Indications of chromosome analysis of patients and patients with pathology detected in karyotype analysis results are shown in Table 3.

**DISCUSSION**

This study evaluated the rate of fetal chromosomal anomaly in the Eastern Mediterranean region and the relationship between fetal chromosomal anomalies and invasive prenatal test indications. The rate of fetal chromosomal anomaly was found as 13.7% and the most common fetal chromosomal anomaly was trisomy 21. The widespread use of screening tests and detailed USG examinations led to an increase in the number of invasive procedures (11). Jacops et al. analyzed the results of 26,261 invasive procedures and reported the rate of fetal chromosomal abnormalities as 5.6% (12). The rate of fetal chromosomal abnormalities in pregnant women who underwent invasive procedures was reported between 3.2-4.98% in several studies conducted in Turkey (13-15).

The first trimester combined test, including nuchal transparency and biochemical parameters, detects 90% of all trisomy 21 cases and the false positivity rate is 5%. If this test is strengthened by combining it with other USG parameters (nasal bone, ductus venous and tricuspid regurgitation), the detection rate reaches 91-96% (16).

The rate of detection of chromosomal anomaly with invasive tests ranges from 0.9% to 20.27% in the literature (17-19). The rate of detection of chromosomal anomaly was found as 13.71% in this study. Chromosomal anomaly was found in 102 (12.1%) of 841 patients who underwent amniocentesis. Chromosomal anomaly was detected in 17% (n: 68) of 400 patients who underwent CVS. The rate of chromosomal anomaly in patients undergoing cordocentesis was 14%. According to these data, the rate of detection of chromosomal anomaly in our study is similar to the literature.

In our study 1298 patients were included. An abnormality in the double test result was the indication for the invasive diagnostic method in 28.4% of the 1298 patients. Zhang et al. evaluated about 40,000 pregnant women retrospectively and reported that the most common indication (43.61%) for invasive diagnostic method was abnormal maternal serum screening test (20). The double, triple and quadruple test results were collected in a single group. In our study, the rate of patients with high risk in double, triple and quadruple test was found as 44.9%. Inan et al. conducted a study with 2136 patients from Turkey’s Thrace region, and reported the rate of serum screening tests as 46% similar to our study (21). In another study...
by Danilidis et al, an increase in maternal serum markers was observed in 68% of patients who underwent invasive treatment (22).

Another major reason for being included in the study was fetal anomalies. Fetal anomaly was detected in 28.2% of our study group. Erdemoglu et al. (23) reported 26.7% of fetal anomaly in their study conducted in Turkey, similar to our study. Zhang et al. reported that fetal anomaly was observed in 13.25% of patients (20). There are some studies in the literature that at even lower rates. 4% of the patients in the study of Danilidis et al. (22) and 3.48% of patients in the study of An et al. had fetal anomalies (24).

Chromosomal anomaly was found in 29 (14.7%) of 197 patients who underwent invasive prenatal test due to high risk in triple test. Different rates have been reported in the literature. In the study of Wenström et al, fetal karyotype anomaly was found in 15 (3%) of the 516 patients who had risk in triple screening test (25). In the study conducted by Chaabouni et al, chromosome anomaly was found in 3.33% of the patients who have high risk in triple test (26). Similarly, Demirhan et al reported the rate of chromosomal anomaly in the invasive procedure performed in the high-risk triple screening test as 3.2% (13). Xiao et al reported a rate of 3.46% in their study conducted with 12365 patients (27). Tao et al found chromosomal anomaly in 42 patients (1.18%) in the amniocentesis examination of 2227 patients who have high risk of second trimester maternal serum screening (28).

There are different data in the literature about advanced maternal age. In our study, 12.5% of patients were given indications for advanced maternal age. Amniocentesis was performed due to advanced maternal age in 29.18% of patients in study of Zhang et al. (20). In Sjögren et al. study, the most common reason for application was the advanced maternal age with a rate of 57% (29-30), while this rate reported as 87% in Milewczyk et al. study (31). Although advanced maternal age was not seen as the most common cause of intervention in our study, advanced maternal age has been reported as the most common cause of intervention in some studies published in our country (32-34).

Chromosomal anomaly was found in 70 (19.1%) of 366 pregnant women with fetal anomaly detected by ultrasonography. In the literature, rates ranging from 4% to 27.1% were observed (34-37). Stoll et al. determined chromosome anomaly as 8.9% after amniocentesis in 119 patients with anomaly in fetal ultrasonography (37). Rizzo et al. detected chromosome anomaly at the rate of 16.8% in 173 fetuses with fetal anomaly in ultrasonography (35). Hsieh et al. found 20.27% chromosomal anomaly in 148 patients with anomaly in fetal ultrasonography (38). This rate was reported as 8.10% in the thesis study of Rafioğlu (39) and 11.3% in Ekin et al. study (40).

In a study conducted by Toker (41), pregnant women with various sonographic anomalies as a result of genetic sonography in the second trimester were examined and their effectiveness in predicting aneuploidy was investigated. In the study, the incidence of nasal bone hypoplasia / absence, short femur, short humerus, tricuspid regurgitation, and left echogenic intracardiac focus were significantly higher in patients with aneuploidy (p<0.05). In our study, chromosomal anomaly detection rates of short femur and nasal bone hypoplasia and intracardiac echogenic focus were significantly higher than other parameters.

The relative shortness of the study period, the absence of patient data that reject prenatal invasive procedure, and the lack of data on the complications resulting from invasive procedures also constitute the limiting factor of our study. Compared to the literature, the frequency of fetus with chromosomal anomaly was higher in our study, and it can be explained by the fact that our hospital is a tertiary hospital and risky pregnancies are referred to us for evaluation from outside centers.

CONCLUSION

Our study guides clinicians due to reporting invasive prenatal test results and fetal chromosomal abnormality prevalence in Turkey's Eastern Mediterranean and Western Southeastern Anatolia Regions and also evaluating the effectiveness of invasive test indications in predicting fetal chromosomal anomalies.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Cukurova University ethical committee's decision number 32 at the meeting no. 76 dated 13 April 2018.

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