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# RETROSPECTIVE EVALUATION OF RESULTS OF 3617 INVASIVE PRENATAL DIAGNOSIS CASES APPLIED BETWEEN 1997-2015 YEARS

# 1997-2015 YILLARINDA İNVAZİF PRENATAL TANI YÖNTEMLERİ UYGULANAN 3617 OLGUNUN RETROSPEKTİF DEĞERLENDİRİLMESİ

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**ABSTRACT**

**Objective**: Statistical analysis of results of 3617 invasive prenatal diagnosis cases (chorion villus sampling-CVS, amniocentesis-AS, and cordocentesis-CS) has been described in this work.

**Methods**: Cultivation of the fetal materials (CVS, AS, CS) for prenatal diagnosis and cytogenetic analysis. Unsuccessful karyotyping cases were excluded from statistical evaluation of results.

**Results**: The majority of indication was high risk in screening tests (*n*= 1205, 33.31%), advanced maternal age (*n*=1106, 30.58%) and abnormal ultrasonographic examination (*n*=766, 21.18%). 83 of 3167 AS, 14 of 394 CS, and 37 of 190 CVS materials failed to grow because of infections or cell culture failure. In summary, cultures were successful in 3617 of 3751 cases (96.4%). Chromosome aberration was detected in 180 of 3617 cases (4.98%). 156 (4.37%) of these chromosomal aberration were number abnormalities, 24 (0.65%) were structural abnormalities. Karyotype aberration rate was higher in abnormal ultrasonographic examination (10.84%), high risk in screening test (4.11%), and advanced maternal age (3.35%).

**Conclusion**: The majority of indication was high risk in screening test 33.11(%), advanced materexamination (21.18%). Tissues cultures were successful in nal age (30.58%) and abnormal ultrasonographic 96.4% of cases. Chromosome aberrations were detected in 4.98% of cases.

**Keywords**: Chorion villus sampling, amniocentesis, cordocentesis, and chromosome aberration.

**ÖZ**

**Amaç:** 3617 invazif prenatal tanı (koryon villus örneklemesi-CVS, amniyosentez-AS), kordosentez-KS) olgusunun istatistiksel analizi.

**Yöntem:** 1997–2015 yıllar arasında fetal örnekleme (CVS, AS, KS) materiyallerinden yapılan prenatal tanı amaçlı doku kültürü ve sitogenetik analiz. Başarısız karyotipleme olguları istatistiksel değerlendirmeden hariç tutulmuştur.

**Bulgular:** Çalışmamızda fetal tarama testlerinde yüksek risk (*n*=1205, %33.31), ileri anne yaşı (*n*=1106, % 30.58) ve anormal ultrasonografik bulgu (*n*=766, % 21.18) en sık görülen endikasyonlardır. Amniyosentez yapılan 3167 olgunun 83'ünde, kordosentez yapılan 394 olgunun 14'ünde, CVS yapılan 190 olgunun 37'inde doku kültürü başarısız olmuştur. Toplam 3751 olgudan 3617'ne (%96.4) doku kültürü başarılı olmuştur. Prenatal tanı için sitogenetik analiz yapılan 3617 olgunun 180 (%4.98)'ünde kromozom anomalisi saptanmıştır. Bu kromozom anomalilerinin 156 (%4.37)'sı sayısal anomali iken, 24 (%0.65)'si yapısal anomalidir. Endikasyonlara göre en sık kromozom anomalisi saptanan ilk üç grup sırasıyla anormal ultrasonografik bulgu (%10.84), fetal tarama testleri (%4.11) ve ileri anne yaşı (%3.35)'dir.

**Sonuç:** Çalışmamızda tarama testlerinde yüksek risk (% 33.11), ileri anne yaşı (%30.58) ve anormal ultrasonografik bulgu (%21.18) prenatal tanı yapılan tüm gebeler için en sık görülen endikasyonlardır. Tüm olgularda elde ettiğimiz kültür başarısı %96.4'dır. Prenatal tanı için sitogenetik çalışma yapılan ve sonuç verilen gebelerin %4.98'inde anomali saptanmıştır.

**Anahtar kelimeler:** Koryon villus örneklemesi, amniyosentez, kordosentez, kromozom anomalisi.

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## INTRODUCTION

The main parameter of prenatal diagnosis is to diagnose abnormalities as early as possible in order to make the necessary decision. Obtaining the accurate information about the fetus will assist the family in making their own decision in regards to personal, social and ethical principles is the priority of the prenatal diagnosis (1).

Thera are two methods in prenatal diagnosis: invasive and noninvasive. The main non-invasive methods are ultrasound studies and biochemical tests performed on the blood of mother. In multi-centered studies from many European countries, the statistical evaluation of USG results obtained during prenatal diagnosing showed that the detection capacity of this method without using other methods is 50% (2, 3). Other non-invasive method such as screening tests can be divided into three parts according to the gestational week and markers of interest: The Double Test measures two markers- β-hCG (beta subunit of human chorionic gonadotrophin) and PAPP-A (pregnancy associated placental protein-A), the Triple Test measures three markers- hCG, AFP (serum alpha fetoprotein) and uE3 (unconjugated estriol) and the Quadruple Test measures four markers- hCG, AFP, uE3 and inhibin A preformed between 14-22 weeks (4). In the first trimester (10-14 weeks), nuchal test in which PAPP-A (pregnancy associated placental protein-A), hCG and nuchal thickness are evaluated together are done.

It has become possible to obtain knowledge about fetal karyotype through the invasive

methods used in prenatal diagnosis. In the first and second trimesters, in order to prenatal diagnosis, Chorion Villus Sampling (CVS), Amniocentesis (AS) and Cordocentesis (CS) have been applied as the invasive classical methods performed these days. Each method is different in terms of time, convenience, lenght of receiving laboratory results and complications. Amniocentesis is an invasive method that is mostly performed between 14-20$^{th}$ weeks and is often used in prenatal diagnosis. Ager and Oliver have stated in their intermediate evaluations that the risk of fetal loss has increased by 0.2-2.1% in the amniocentesis group in comparison with the control group (5,6) Chorion Villus Sampling (CVS) has been preferred because it can be performed early (at about the 11$^{th}$ week of pregnancy) as there is no direct intervention with the fetus, and material can be obtained which is regarded as an advantage for the DNA studies. In the CVS material, cells at the metaphase can be directly evaluated and cytogenetic studies can be done (7,8). The fetal loss risk was found to be 2.5% at transcervical approach, 2.3% at transabdominal approach and the difference between them was insignificant (9). CS or cord blood sampling (from 18$^{th}$ week on) is a pensable method for prenatal diagnosis studies. In the cases of being late for applying for the prenatal diagnosis and being unsuccessful with AS, CS comes into effect. Although it is known that in problematic pregnancies, the fetal mortality depending on invasive procedure may be higher, it is accepted that common average is 1-2% (10,11). In this study, the results of the cytogenetic analysis for prenatal diagnosis is being evaluated from the samples refferred to the Department of Medical Genetics, Erciyes University Medical School between 1997-2015 (first six months of the year) have been evaluated retrospectively.

## METHODS

Between the years of 1997 – 2015 (first six months of year), in the Department of Gynecology and Obstetrics of Gevher Nesibe Research Hospital and other hospitals, the samples from 3751 pregnant women were taken after doing chorion villus sampling, amniocentesis and cordocentesis with the aim of prenatal diagnosis and these samples were given a chromosome analysis that were retrospectively studied in terms of the success of cell culture, invasive indications and their genetic results. All pregnant women and their husbands were informed of the procedure and possible complications before the application and a written consent was taken from the couples that had accepted the procedure. All the pregnant women were examined in terms of being a hepatitis porter and having an Rh disagreement.

A detailed fetal genetic sonogram was performed. The chorion villus sampling was performed with the transabdominal chorion villus sampling method technique and about 10 mg of fetal tissue was taken into the transport medium (12). The amniocentesis was done in accord with the classical amniocentesis rules during the 16$^{th}$–20$^{th}$ weeks. In order to reduce the maternal contamination, the first 2 ml was aspired into a separate injector; then a total of 18–20 ml of amniotic liquid was taken into two different injectors. Cordocentesis was performed by taking 2 cc of fetal blood into the injector which has 0.5 cc heparin, depending on the localization of placenta, either from the free cord or from the spot 1–2 cm away from the place where the cord enters the placenta between the 19$^{th}$ – 28$^{th}$ weeks of pregnancy (12). At the end of all these applications, the unsensitised pregnant women who have Rh incompatibility were given 300 microgram of anti-D immunoglobulin G. The samples taken for the cytogenetic studies were cultivated in proper methods and harvested. For the evaluation of the numeral and structural disorder of the chromosomes in all the cases, at least 20 metaphase plates were examined with the computerized chromosome analysis system.

## RESULTS

The indications and average ages at which the invasive procedures were performed and the gestation weeks of the pregnant women were shown in the Table 1. High risk in screenig test (*n*=1205), advanced maternal age (*n*=1106) and abnormal ultrasonographic examination (*n*=766) are the leading indications. The most frequent indication in the AS cases was high risk in screening test (*n*=1136), in the CS and CVS cases was the abnormal ultrasonographic examination. In 134 out of 3751 cases (3.57%) materials failed to grow because of infections or cell culture failure; 83 out of 3167 (2.6%) AS, 14 out of 394 (3.55%) CS, 37 out of 190 (19.47%) CVS cases. The culture success was 96.43%.

Chromosome anomaly was determined in 180 out of 3617 cases (4.98%) on whom cytogenetic studies were done for prenatal diagnosis and to whom the results were given. Also in 74 cases clinically insignificant chromosomal variants were determined. While 156 of these chromosome anomalies (4.36%) were numerical

anomalies (Table 2), 24 (0.65%) were structural anomalies (Table 3). While the most commonly karyotype seen among numerical anomalies is trisomy 21, the one among structural anomalies is translocations.

examination (10.84%), high risk in screening test (4.11%), and advanced maternal age (3.35%). In the group that formed the most common prenatal diagnosis indication (the high risk in the triple tests), the rate at which chromosome anomaly can be seen

Table 1. Indications, average age and gestation weeks of the pregnants that performed prenatal diagnosis.

| Indication of prenatal diagnosis | CVS | AS | CS | Total | % |
|---|---|---|---|---|---|
| **Double, Triple and Quadruple screen test** | 3 | 1136 | 66 | 1205 | 33,3149 |
| **Abnormal USG** | 110 | 494 | 162 | 766 | 21,17777 |
| **Maternal age risk** | 30 | 1012 | 64 | 1106 | 30,57783 |
| **Repeated pregnancy loss** | 0 | 26 | 0 | 26 | 0,718828 |
| **Inheritance risk*** | 9 | 385 | 11 | 405 | 11,19712 |
| **Others**** | 1 | 31 | 77 | 109 | 3,013547 |
| **TOTAL** | 153 | 3084 | 380 | 3617 | |
| **Mean mother age** | 28.13 | 30.15 | 27.21 | | |
| **Mean pregnancy week** | 12.51 | 19.41 | 25.5 | | |

* *Patients with the genetic disorders in the family history detectible with FISH or other molecular genetics techniques such as Di-George syndrome, Williams syndrome, SMA, DMD, and etc.*
** *IUGR, mother anxiety, child with chromosomal abnormality in the family history, toxoplasmosis, drug usage in the pregnancy, intrauterine transfusion, Rh incompatibility*

Table 2. Numerical chromosomal abnormalities.

| Karyotype | CVS | AS | CS | Total |
|---|---|---|---|---|
| 47,XY,+21 or 47,XX,+21 | 10 | 60 | 8 | 78 |
| 47,XY,+18 or 47,XX,+18 | 5 | 14 | 6 | 25 |
| 47,XY,+16 or 47,XX,+16 | 1 | | | 1 |
| 45,X | 6 | 11 | | 17 |
| 47,XXX | | 4 | 2 | 6 |
| 47,XY,+13 or 47,XX,+13 | 1 | 4 | 2 | 7 |
| 69,XXX | 1 | 3 | 1 | 5 |
| 46,XX[95]/47,XX,+18[5] | | | 1 | 1 |
| 47,XY,+mar | 1 | 1 | 1 | 3 |
| 49,XXXXX | | 1 | | 1 |
| 47,XYY | | 3 | 1 | 4 |
| 47XXX/45X | | | 1 | 1 |
| 47,XXY | | 3 | 1 | 4 |
| 46,XY[84]/47,XYY[16] | | 1 | | 1 |
| mos 46,XX[60]/46,XY[40] | | 1 | | 1 |
| mos 46,XY[80]/46,XX[20] | | 1 | | 1 |
| **Total** | 25 | 109 | 24 | 156 |

The three groups in which the most common chromosome anomaly was determined according to the indications were abnormal ultrasonographic

was determined as 4.75%. According to the indications of the prenatal diagnosis, the frequency of detected chromosome anomaly was shown in Table 4.

Table 3. Clinically significant structural abnormalities.

| Karyotype | CVS | AS | CS | Total |
|---|---|---|---|---|
| 46,XX,del(1)(p36) | 1 | | | 1 |
| 46,XX,t(1;3)(q23;p21) | | 1 | | 1 |
| 46,XX,t(1;16)(p13.3;p13) | | | 1 | 1 |
| 46,XY,t(2;8)(q37;q13) | | | 1 | 1 |
| 46,XY,t(2;12) (q31;q22) | | 1 | | 1 |
| 46,XY,t(3;8) (q13;q22) | | 1 | | 1 |
| 46,XY,t(4;9)(pter;q34) | | 1 | | 1 |
| 46,XY,t(4;22)(p12;p11.1) | | 1 | | 1 |
| 46,XY,t(6;16)(q25.3;p13.3) | | 1 | | 1 |
| 46,XY,t(7;8)(p22;q24.1) | | 1 | | 1 |
| 46,XY,t(7;15)(q11,2;q26.3) | | 1 | | 1 |
| 46,XY,der(18) t(10;18) (q25;q23)mat | | | 1 | 1 |
| 46,XX,t(12;22)(p11.2;p12) | | 1 | | 1 |
| 46,XX+13,t(13;14)(p13;q13),16qh+ | | 1 | | 1 |
| 46,XY,+21,rob(13;14)(q10;q10)* | | 1 | | 1 |
| 46,XX,t(13,14) / 46,XY,t(13,14) | | 2 | 1 | 3 |
| 46,XX,t(14;21)(p13;p13) | | 1 | | 1 |
| 46,XX,t(15;17)(q11.2;q25) | | 1 | | 1 |
| 46,XY,t(16;17)(q13;q23) | | 1 | | 1 |
| 46,XX,t(X;4)(q22.1;q34) | | 1 | | 1 |
| 46,XX,t(X;13)(q26; q22) | | 1 | | 1 |
| 45,XY,t(Y;21)(q12;q21) | | 1 | | 1 |
| **Total** | 1 | 19 | 4 | 24 |

** AS sample from 42 years old patient. Classic trisomy 21 Down syndrome with de novo balanced translocation.*

Table 4. Chromosomal abnormality ratio according to their indication.

| Indication of Prenatal Diagnosis | Number of pregnant women | Number of fetus with chromosomal abnormality | Percent of fetus with chromosomal abnormality (%) |
|---|---|---|---|
| **Double, Triple and Quadruple screen test** | 1242 | 51 | 4.11 |
| **Abnormal USG** | 766 | 83 | 10.84 |
| **Maternal age risk** | 1106 | 37 | 3.35 |
| **Recurrent pregnancy loss** | 39 | 0 | 0 |
| **Inheritance risk *** | 392 | 5 | 1.28 |
| **Others **** | 72 | 4 | 5.56 |
| **Total** | 3617 | 180 | 4.98 |

** Patients with the genetic disorders in the family history detectible with FISH or other molecular genetics techniques such as Di-George syndrome, Williams syndrome, SMA, DMD, and etc.*

*** IUGR, mother anxiety, child with chromosomal abnormality in the family history, toxoplasmosis, drug usage in the pregnancy, intrauterine transfusion, Rh incompatibility*

## DISCUSSION

During our work, the high risk in the triple test (33.31%), advanced maternal age (30.57%) and abnormal ultrasonographic examination (21.18%) are the most frquently seen indications for the pregnant mothers given a prenatal diagnosis. According to the literature, there are varied rates in the studies where the amniocentesis indications have been evaluated. The most frequent indication in the work of Sener et al. are the same as the ones in our work (13). While the first three indications in the work of Kose et al. are the advanced maternal age (42.3%), pathology in the second scanning test (28.3%) and pathologic ultrasound finding (8.6%) respectively, the first three indications in the work of Guven et al. are the triple test with a high risk, anomaly seen in the ultrasonogram and advanced maternal age (14,15). When the frequency of cordocentesis indications in the literature were studied, Guven et al. showed the advanced age and Yayla et al. showed the abnormal ultrasonographic examination as the most frequent indication (15,16). In our work, abnormal ultrasonographic examination has taken the first place.

When all the cases to which the prenatal diagnosis had been evaluated, 134 of 3617 cases couldn't be given a result. The culture success we obtained is 97.3% in AS, 96.31% in CS

and 75.8%in CVS; totally 96.42%. It has been stated in the literature that the AS culture success of Cengizoglu et al. is 99%, the amniocentesis culture success of Guven et al. and Yuce et al. is 98%; the AS culture success of Yayla et al. is 92.7%, their cordocentesis culture success is 85% (17,15,18,16). Their cordocentesis and fetal karyotyping success is approximately 90% (19). In the literature, the culture success in CVS samples of Türkyilmaz et al. is 88%. We think that the culture failure due to the contaminations of the amnion liquid during the material extraction, earlyp bleeding, insufficient material extraction, contamination, sample keeping and problems during the transport conditions. The chromosome anomaly rate seen in all our pregnant women who have been given prenatal procedures is 4.98%. The chromosome anomaly rate seen in AS cases in the literature is between 2-5.8% (the chromosome anomaly rate in AS series of Yayla et al. is 3.6%, that of Basaran et al. is 3.5%, that of Guven et al. is 2%, Karaoguz et al. is 3%.) (16,20,15,27). The chromosome anomaly rate seen in the cordocentesis cases is 8.2-15.25% (21,15,16). Turkyilmaz et al. determined that the chromosome anomaly rate in the chorion villus sampling is 8%. The frequency at which chromosome anomaly is seen in the pregnant women who have been given AS because of the abnormal ultrasonographic examination varies from 8.7% to 35.6% (22,23,16,24). The 12.79% rate determined in our work seems to comply with the literature. This also shows how important especially a detailed ultrasonogram scanning is. Karyotype anomaly was found in 4.75% cases of the patients who had been given amniocentesis and cordocentesis because of the triple test with a high risk. This rate varies between 1.5% and 10 in the literature (13,14,16). It is thought that this wide range is due to the threshold value and the standardization difference between the laboratories. As Sener et al. stated, the importance of a triple test must be questioned by the other centers.

The reason in 51-60% of the recurrent abortions is the chromosome anomaly (25,26). In our

work, the 39 pregnant women who had recurrent abortions were directly given AS, and the

karyotypes of these 39 women were found to be normal. Tissues cultures were successful in 96.43% from all samples (CVS, AS, CS). Gunduz et. al in their study showed culture succes of AS samples rate as 97.97% and 99.74% in different time periods (28). In our study from 3751 samples 3167 were AS material and in 83 of them culture was unsuccessful mostly because of maternal blood contamination, so succes rate for AS samples in our study is 97.37% which is lower than rates described in literature.

## CONCLUSION

The major indication of high risk in triple screening test (33.31%), advanced maternal age (30.58%), and abnormal ultrasonographic examination (21.17%) in all pregnants, respectively. Tissues cultures were successful in 96.43% of cases. Chromosome aberration were detected in 4.98% of cases.

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