PERINATAL JOURNAL

Research Article

Perinatal Journal 2013;21(3):101-106

The analysis of amniocentesis results of pregnants who are at 16-22 weeks of gestation and undergone genetic amniocentesis

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Abstract

Objective: It is aimed to evaluate the chromosome analysis results of cases who undergone genetic amniocentesis for prenatal diagnosis.

Methods: Amniocentesis indications, culture successes, karyotype results, screening ultrasounds and gestational prognoses of 311 amniocentesis cases referred to our perinatology clinic between November 2010 and April 2011 were evaluated retrospectively. Statistical analysis of the data was carried out by Predictive Analytics Software (PASW) package program.

Results: The mean age and gestational week of the cases who had amniocentesis procedure were found to be 32.72±7.49 and 17.98±6.56, respectively. The mean pregnancy number was 2.46±1.45, the mean delivery number was 1.32±1.21, the mean delivery week was 38.24±1.32, and the mean newborn weight was 3131±113 g. Chromosomal anomaly rate was found as 5.8%, while fetal loss rate was 0.9%. It was found that the most frequent amniocentesis indication was the risk increase at triple test (29.9%). Cell culture was successful in all 311 cases, except two cases (99.3%).

Conclusion: In this study, chromosomal anomaly rate was found as 5.8%. In our study, the increased risk at triple test was found as the most frequent amniocentesis indication.

Key words: Amniocentesis, prenatal diagnosis, karyotype.

Genetik amniyosentez yapılan 16-22 haftalık gebelerin amniyosentez sonuçlarının değerlendirilmesi

Amaç: Prenatal tanı amaçlı genetik amniyosentez yapılan olguların kromozom analizi sonuçlarını değerlendirmek.

Yöntem: Kasım 2010 - Nisan 2011 tarihleri arasında perinatoloji servisimizde yapılan 311 amniyosentez olgusunun amniyosentez endikasyonları, kültür başarıları, karyotip sonuçları ile tarama ultrasonları ve gebelik prognozları retrospektif olarak değerlendirildi. Verilerin istatistiksel analizi Predictive Analytics Software (PASW) paket programı ile yapıldı.

Bulgular: Amniyosentez işleminin yapıldığı olgularda ortalama yaş ve gebelik haftası sırasıyla 32.72±7.49 ve 17.98±6.56 olarak bulundu. Ortalama gebelik sayısı 2.46±1.45, ortalama doğum sayısı 1.32±1.21, ortalama doğum haftası 38.24±1.32 ve ortalama bebek ağırlığı ise 3131±113 gram olarak tespit edildi. Kromozom anomalisi oranı %5.8 bulundu. Fetal kayıp oranı %0.9 olarak saptandı. En sık amniyosentez endikasyonu üçlü testte risk artışı olarak tespit edildi (%29.9). Üç yüz onbir olgudan ikisi dışında hücre kültürü başarılı oldu (%99.3).

Sonuç: Bu çalışmada kromozom anomalisi oranı %5.8 olarak bulunmuştur. Çalışmamızda üçlü testte artmış risk, en sık amniyosentez endikasyonu olarak tespit edilmiştir.

Anahtar sözcükler: Amniyosentez, prenatal tanı, karyotip.

Introduction

Amniocentesis based on the examination of amniotic cells has been a significant invasive technique in prenatal diagnosis. It was first performed in 1950s for gender determination.[1] Steele and Breg started karyotype determination in a classic way by culturing the cells blended into amniotic fluid from fetal skin and urinary system.[2] Today, their major practice indications are

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Received: September 6, 2013; **Accepted:** November 25, 2013

Available online at:
www.perinataljournal.com/20130213001
doi:10.2399/prn.13.0213001
QR (Quick Response) Code:

abnormality in the screening tests applied for trisomies, advanced maternal age, structural anomalies at ultrasonography, delivery with chromosomal anomaly and chromosomal translocations known in one of spouses.

Amniocentesis is conventionally applied between 16 and 20 weeks of gestational for karyotype determination. At this period, the rate of living cells to the non-living cells in the amniotic fluid is higher compared to late (>20) weeks of gestation.[3] While there are studies reporting high fetal loss rates when applied at early weeks of gestation, there are also studies reporting that fetal loss for the procedure is increased when applied after 18 weeks of gestation.[4,5]

Markers detected in ultrasonographic examinations such as nuchal translucency, echogenic intestine, short femur, pyelectasis, lack of nasal bone, choroid plexus csyt, and echogenic intracardiac focus are associated with Down syndrome and other aneuploidies.[6] Prenatal screening tests conducted for Down syndrome diagnosis are more significant than the second trimester ultrasonographic screening tests. Amniocentesis requirement increases when ultrasonographic markers are detected when screening more chromosomal anomalies in structural abnormalities, and therefore this procedure increases abortus rate even a little.

Our aim in this study is to evaluate genetic amniocentesis results, screening ultrasound and gestational prognoses of 16-22 weeks pregnant cases who were followed up at our clinic, and undergone genetic amniocentesis.

Methods

Patients who referred to our perinatology clinic between November 2010 and April 2011 and undergone amniocentesis were included to the study. As inclusion criteria, patients who were between 16 and 22 weeks of gestation, found to have risk increase in the first or second trimester Down syndrome screening tests, or undergone amniocentesis for diagnosis purpose since they were 35 years old or above were chosen for the study (cut off value was determined as 1/270 for double and triple tests).[7] The amniocentesis results of the cases chosen for the study were retrospectively scanned for prenatal diagnosis.

At our hospital, genetic consultancy is provided to cases who are suggested amniocentesis. Before the procedure, informed consent forms were received from the couples who accept the intervention.

Before amniocentesis, each fetus is examined by USG in detail and the location of placenta, amount of amniotic fluid and procedure location are determined. Completed 35th age was accepted as advanced maternal age. It was expressed to cases who received or did not receive genetic consultancy that risk calculation might be performed by non-invasive methods (triple test, detailed USG). Cut off value as increased risk at triple was determined as 1/270; however, risk calculation was done amniocentesis option was offered to cases in which chromosomal anomaly markers were detected by ultrasonography among risky cases below 1/270.

All cases were called for control according to their karyotype result, and fetal losses after intervention, and delivery time and type, newborn findings and neonatal prognosis in cases followed up from post-procedure up to delivery were recorded.

Amniocentesis procedures of the cases included to our study were carried out between 16 and 22 weeks of gestation. Skin cleaning was done by povidone-iodine, and disposable 2, 5 or 10 ml injectors and 9 cm 20 or 22 G spinal needles were used for puncture and aspiration. Interventions are done by free hand technique with the help of USG. Incoming fluid is aspirated by applying slight negative pressure and amniotic fluid is collected as 1 ml per gestational week. For cases with Rh incompatibility risk, 300 µg anti-D IgG and post-procedure oral antibiotic and paracetamol are prescribed.

Collected fluids were sent to a private laboratory for analysis. Giemsa banding technique was used for evaluation after amniotic fluid culture. 20-50 metaphase plates which were accepted sufficient for each case were analyzed for numerical and structural abnormalities in chromosomes. Mean cell culture period was 14-20 days and the results were obtained averagely in 21 days.

Statistical analysis of the data was carried out by Predictive Analytics Software (PASW) package program. Definitive statistics were expressed as mean±standard deviation for continuous data, and as observation number and percentage (%) for categorical data. Significance levels and 95% confidence intervals for risk factors were calculated by chi-square test. P values less than 0.05 were accepted as statistically significant.

Results

Mean age and gestational week in cases who had amniocentesis procedure were 32.72±7.49 and 17.98±6.56, respectively. The mean pregnancy number was 2.46±1.45, the mean delivery number was 1.32±1.21, the mean delivery week was 38.24±1.32, and the mean newborn weight was 3131±113 g (**Table 1**).

Chromosomal anomaly rate was found as 5.8% (18/309) according to amniotic culture results, and detailed distribution was given in **Tables 2** and **3.** Except cases found to have anomalies, stable translocation was found in 2 cases [t (7,22)(p11,2; q11,2), t (2,10)(q31; q22)], and variant of normal was found in 6 cases [46 inv (9)(p11q12)]. In 291 of the pregnants (94.2%) fetal karyotype was found to be normal/variant of normal/stable translocation. The distribution of cytogenetic results obtained in the karyotyping according to amniocentesis indications are given in **Table 3.**

In our amniocentesis series, the success rate of achieving cell culture was 99.7% (309/311), and culture failure rate was 0.3% (2/311). The amniocentesis indication in two cases without any culture reproduction was risk increase in double test for one case, and anencephaly detection in anomaly USG screening for the other case. Pregnancy of the case found to have anencephaly was terminated at 20 weeks. Other case delivered a healthy baby (3250 g) at 38 weeks.

Table 1. Demographic data of the cases who undergone amniocentesis.

	Ortalama (±SD)
Age	32.72±7.49
Pregnancy number	2.46±1.45
Delivery number	1.32±1.21
Gestational weeks at delivery	38.24±1.32
Birth weight (gram)	3131±113

Table 2. Karyotype results.

Karyotype	Case number	Percentage (%)
Normal	291	94.2%
Trisomy 21	8	2.5%
Trisomy 18	3	0.9%
Turner syndrome	2	0.6%
69XXX	2	0.6%
Unstable karyotype	3	0.9%
Total	**309**	**100**

In the distribution of cases according to their amniocentesis indications, advanced maternal age was the biggest group with 152 cases (48.8%). However, 50 of these cases had triple test and 26 of them had double test, and their test results became compatible with increased biochemical risk except age risk. Amniocentesis was carried out in 76 cases (25.1%) only for advanced maternal age. Also, increased risk at triple test was found in 93 cases (29.9%) who were not at an advanced maternal age, fetal anomaly at USG was found in 37 cases (11.8%), and increased risk at double test was found in 24 cases (8.3%). Anomalies detected by ultrasonography were central nervous system anomalies in particular, cardiac anomalies, pelviectasis, cystic hygroma, hydrops fetalis, hyperechogenic intestine, choroid plexus cyst, and omphalocele. Beside these anomalies, two cases had baby with trisomy 21 history and one case had baby with trisomy 18 history. In these conditions, risk increase at triple test was the most frequent amniocentesis indication with 143 cases (93+50).

Pregnancy was terminated in 30 cases (9.6%) out of 311 amniocentesis cases. While the termination reason was chromosomal anomaly in 15 cases out of 30 cases, it was fetal anomalies found at US against normal karyotype in other 15 cases. The termination indications in 15 cases with normal karyotype and 2 cases with stable translocation and addition were central nervous system anomaly in 10 cases, cardiac anomaly in 2 cases, hydrops fetalis in 2 cases and multiple anomaly in one case. Anomalies found in 15 cases of whom pregnancies were terminated due to chromosomal anomaly were trisomy 21 in 8 cases, trisomy 18 in 3 cases, Turner syndrome in 2 cases, del(9)(p24) unstable translocation in 1 case and 69XXX karyotype in one case. One case who had triploid did not accept termination. Three out of four cases with stable translocation and addition received genetic consultancy and delivered healthy babies at term by cesarean section.

Abortus was seen in five cases and in utero mort fetalis in two cases among patients who had amniocentesis. While the reason for performing amniocentesis on one case that had normal fetal karyotype result was 'advanced maternal age' and abnormal USG, it was abnormal USG findings for four cases. In other two cases, chromosomal anomaly was found according to amniocentesis results. Abortus occurred within 30 days in four cases that had normal fetal karyotype result and undergone amniocentesis due to abnormal USG indi-

Table 3. The distribution of cytogenetic results obtained in the karyotyping according to amniocentesis indications.

	Delivery with chromosom al anomaly (n=3)	Advanced maternal age (n=76)	Fetal anomaly at USG (n=37)	Increased risk at triple test (n=143)	Increased risk at double test (n=50)	NT increase (n=1)
No reproduction (n=2	–	–	1	-	1	–
Normal karyotype (n=283)	3	72	29	133	45	1
Trisomy 21 (n=8)	–	–	2	4	2	–
Trisomy 18 (n=3)	–	1	1	–	1	–
45X (Turner syndrome) (n=2)	–	–	2	–	–	–
69XXX (n=2) add (15)(p13), add (21)(p13), del (9)(p24) [unstable karyotype] (n=3)	–	–	1	1	–	–
t(7,22) (p11,2;q11,2), t(2,10) (q31;q22) [stable translocation] (n=2)	–	1	–	1	–	–
46inv (9) (p11q12) [normal variant] (n=6)	–	3	–	2	1	–

cation. The amniocentesis indication was abnormal USG findings in another case who had abortion within one week after the procedure and found to have 69XXX.

Early fetal loss rate associated with amniocentesis due to the loss of 3 fetuses with normal fetal karyotype and no anomaly in the first 30 days after the procedure was found as 0.9%.

In utero mort fetalis developed 6 weeks later (24 weeks) in one case who had normal fetal karyotype result and undergone amniocentesis due to advanced maternal age indication. It was seen 5 weeks after the procedure (22 weeks) in another case who found to have trisomy 18 and undergone amniocentesis due to advanced maternal age.

Early membrane rupture was observed in two cases (0.6%) and preterm labor in one case (0.3%) within the amniocentesis group.

Abnormal karyotype was detected in 9 (19.5%) patients out of 46 patients who were found to have anomaly in ultrasonography. Only one (1.1%) case out of 89 cases, who found to have normal results in fetal anomaly USG, had abnormal karyotype. Accordingly, there was statistically significant relationship between having fetal anomaly in USG and having abnormal karyotype in amniocentesis (p=0.015).

Discussion

Amniocentesis which is the oldest prenatal diagnosis method is mostly performed at 16-18 weeks of gestation for genetic diagnosis purposes. The procedure indications are advanced maternal age in particular, increased risk at triple test, child history with chromosomal anomaly, or fetal anomaly detection at USG.

In our study, it was found that the most frequent intervention reason alone is increased risk at triple test with 93 (29.9%) cases, and advanced maternal age was the second one with 76 (25.1%) risk. Sjögren et al. found that the most frequent reason among amniocentesis cases was advanced maternal age with 57% of the cases.[8] This rate is 87% in the study of Milewczyk et al.[9] In the study of Bal et al., they found the rate of maternal age as 51%.[10] In various amniocentesis studies published in Turkey, advanced maternal age is reported as the most frequent intervention reason.[11-13]

In our amniocentesis series, chromosomal anomaly was found in 18 (5.8%) cases. This rate was found between 3.3% and 4.5% in other series published in Turkey.[11-14] Başaran et al. found chromosomal anomaly rate in 11 cases (3.5%) out of 301 cases.[14] While Sjögren et al. reported this rate as 2.5% in their study performed on 211 cases,[8] Milewczyk et al. found the rate as 5.4%.[9] We found chromosomal anomaly in 3 (3.84%) cases out

of 76 cases who undergone amniocentesis due to advanced maternal age. They were trisomy 18, t(7,22)(p11,2;q11,2), and add(15)(p13). Sjögren et al. reported this rate 2.2% for cases above 35 years old and as 5.3% for cases above 40 years old.[8] Nagel et al. found this rate as 4.7% for cases at 36 years old and above, and terminated 70.8% of pregnancies.[15] In the studies performed in Turkey, chromosomal anomaly rates were found between 1.2% and 13.3% in cases who undergone amniocentesis due to advanced maternal age indication.[10,13,16]

In our study, chromosomal anomaly was found in 6 (4.2%) out of 143 cases who undergone amniocentesis due to increased risk at triple test (≥1/270) Qi et al.,[7] reported in their multi-centered study that they found chromosomal anomaly in 22 (3%) cases out of 727 who had amniocentesis by considering cut-off value as ≥1/270. Four of detected chromosomal anomaly cases were trisomy 21, 1 case was 69XXX, 1 case was d(21)(p13), and 1 case was t(2,10)(q31;q22).

Yüce et al. found chromosomal anomaly rate as 3.7% in cases who undergone amniocentesis due to increased risk at triple test.[13] Wenstrom et al. detected 15 (2.9%) fetal karyotype anomalies in 516 cases who had triple test risk.[17] Bal et al. reported chromosomal anomaly rate as 3.9% in cases who had high risk for chromosomal anomaly at triple test.[10]

We found chromosomal anomaly in 3 (6%) cases out of 50 cases who undergone amniocenteses due to high risk at double test. Of detected chromosomal anomalies, 2 cases had trisomy 21 and 1 case had trisomy 18. The relationship between double test and amniocentesis is stronger than the relationship between triple test and amniocentesis. Today, double test is preferred more frequently as anomaly screening. Triple test is used most likely to screen the risk increase of spina bifida.

There are prominent differences among chromosomal anomaly detection rates in the amniocentesis series performed due to the detection of fetal anomaly at USG. This rate is reported between 4% and 27.1% in various series.[13,18-20] Stoll et al. found chromosomal anomaly at 8.9% after amniocentesis performed on 119 cases who had fetal USG anomaly.[20] Rizzo et al. reported chromosomal anomaly in 16.8% of 173 fetuses who found to have fetal anomaly at ultrasonography.[18] Hsieh et al. reported this rate as 20.27% in 148 cases with fetal USG anomaly.[21] In our case, we found chromosomal anomaly in 4 (10.8) cases among 37 cases who undergone amniocentesis due to fetal anomaly detection at USG. By these data, the possibility to detect chromosomal anomaly at amniocentesis increases in the presence of fetal anomaly (rather than maternal age and triple test). At experienced hands, fetal loss rates due to amniocentesis is not higher than 0.5-1%. While Eddlemann et al. found fetal loss rate as 0.15% in their series consisting of 1605 cases,[22] Armstrong et al. reported fetal loss rate as 0.2% in their series consisting of 28.163 cases.[23] Fetal loss rate in Lockwood's amniocentesis series consisting of 1375 cases is 0.40%.[21] Anderson et al. found this rate as 0.80% in their series consisting of 1200 cases.[24] Eydoux et al. found fetal loss rate 1.3%.[25] In Turkey, fetal loss rates were found to be between 0.6% and 3.3%.[10,11,14]

In our amniocentesis series, fetal loss occurred in 3 out of 311 cases within 30 days. Our loss rate is 0.9%, and it is consistent with the results reported in the literature. The patient should be informed in detail about the risks before the amniocentesis procedure. Informing patient about this matter is significant in terms of judicial and medical problems.

Cytogenetic analysis of amniotic cells indicates fetal genotype with accuracy level reaching 99%. According to our amniocentesis results, fetal cell reproduction was not occurred only 2 cases and culture success was found as 99.3%. Lack of culture reproduction of these cases was affiliated with the contamination by related laboratory. Similarly, culture success was found 98% by Güven et al. who sent amniotic fluids to an external center.[26] In the series published in 2006 by Müngen et al. and consisted of 2068 cases, culture success was reported 98.2%.[27] Tabor et al. found mosaicism 0.1% which is a significant problem in chromosomal analyses.[28] In such a case, cordocentesis is suggested instead of re-performance of amniocentesis. No mosaicism was found in our study.

In amniocentesis group, early membrane rupture was found in 2 cases (0.6%) and preterm labor was found in one case (0.3%). Early membrane rupture was reported 1-1.2% after amniocentesis in the study performed by Phubong et al.[29] In the study performed by Borrelli et al., preterm labor was reported in 6% of 1416 cases.[30]

Conclusion

Consequently, we found chromosomal anomaly rate 5.8% and fetal loss rate 0.9% in our study. Increased risk at triple test and advanced maternal age are the most frequent indications of amniocentesis.

Conflicts of Interest: No conflicts declared.

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