PERINATAL JOURNAL

Clinical Research Article

Perinatal Journal 2015;23(1):39–44

Evaluation of prenatal invasive procedures: analysis of retrospective cases

Aybike Tazegül Pekin[1], Özlem Seçilmiş Kerimoğlu[1], Setenay Arzu Yılmaz[1], Nadir Koçak[2], Feyza Nur İncesu[1], Ayşe Gül Kebapcılar[1], Çetin Çelik[1]

[1]*Department of Gynecology & Obstetrics, Faculty of Medicine, Selçuk University, Konya, Turkey*
[2]*Department of Medical Genetics, Faculty of Medicine, Selçuk University, Konya, Turkey*

Abstract

Objective: In this study, we aimed to present the results of prenatal invasive procedures carried out in our clinic.

Methods: The records of the prenatal invasive procedures carried out between April 2011 and 2014 were analyzed retrospectively, and the indications, complications and karyotype results of invasive procedures were evaluated.

Results: Prenatal invasive procedure was applied to 72 (23.4%) pregnant women who had only minor and/or major anomalies according to ultrasonography, 226 (73.3%) patients who referred for increased risk at screening tests, 5 (1.6%) patients with family history and 5 (1.6%) patients with advanced maternal age. Amniocentesis was carried out for 81.8% (n=252) of these patients, chorionic villus sampling for 11.7% (n=36) of them, and cordocentesis due to advanced week of gestation for 6.5% (n=20) of them. Karyotype analysis results were normal in 278 (90.2%) patients but no cytogenetic result was obtained in 11 (3.5%) patient, and aneuploidy was reported in 19 (6.2%) patients (trisomy in 2.9% and other genetic anomalies / variations in 3.3%). Two patients with karyotype results as 46XX+22p and 46XY,9qh were followed up. The results of the patients whose ultrasonography examination did not show any minor marker or major anomaly were considered as normal variants. Such pregnancies resulted in healthy live births. Karyotype anomalies also having ultrasonography findings were terminated.

Conclusion: Prenatal screening tests are still the major indications for prenatal invasive procedures. However, minor and/or major anomalies can be displayed in most of the aneuploidic fetuses; therefore, fetuses established with prenatal diagnosis indication should be evaluated carefully.

Keywords: Prenatal diagnosis, amniocentesis, chorionic villus sampling.

Özet: Prenatal invaziv girişimlerin değerlendirilmesi: Retrospektif olguların analizi

Amaç: Bu çalışmamızda amaç, kliniğimizde uygulanan prenatal invaziv girişimlerin sonuçlarını sunmaktır.

Yöntem: Nisan 2011–2014 tarihleri arasında uygulanan prenatal invaziv girişimlerin kayıtları retrospektif olarak tarandı, invaziv girişimlerin endikasyonları, komplikasyonları ve karyotip sonuçları değerlendirildi.

Bulgular: Ultrasonografide tespit edilen sadece minör ve/veya majör anomalisi olan 72 (%23.4) gebeye, tarama testlerinde artmış risk nedeniyle başvuran 226 (%73.3) hastaya, aile öyküsü olan 5 (%1.6) hastaya ve ileri anne yaşı nedeniyle 5 (%1.6) hastaya prenatal invaziv girişim uygulandı. Bu hastaların %81.8'ine (n=252) amniyosentez, %11.7'sine (n=36) koryon villus biyopsisi, %6.5'ine (n=20) ileri gebelik haftası nedeniyle kordosentez uygulandı. Karyotip analizi sonuçları 278 (%90.2) hastada normal, 11 (%3.5) hastada sitogenetik sonuç alınamadı ve 19 (%6.2) hastada anöploidi, (%2.9 trizomi ve %3.3 diğer genetik anormallikler/ varyasyonlar) olarak bildirildi. Karyotip sonucu, 46XX+22p ve 46XY,9qh olan 2 hasta takip edildi. Ultrasonografi değerlendirmesinde minör belirteç veya majör anomali saptanmayan hastaların sonuçları normal varyant olarak kabul edildi. Bu gebelikler sağlıklı canlı doğum ile sonuçlandı. Ultrasonografi bulguları da olan karyotip anomalileri termine edildi.

Sonuç: Prenatal tarama testleri halen prenatal invaziv girişimlerin ilk sıradaki endikasyonlarını oluşturmaktadır. Ancak minör ve/veya majör anomaliler anöploidik fetüslerin büyük kısmında görüntülenebilmektedir, bu nedenle prenatal tanı endikasyonu konulan fetüsler dikkatle değerlendirilmelidir.

Anahtar sözcükler: Prenatal tanı, amniyosentez, koryon villus biyopsisi.

Correspondence: Aybike Tazegül Pekin, MD. Selçuk Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Konya, Turkey. e-mail: aybiketzgl@hotmail.com

Received: October 18, 2014; **Accepted:** February 1, 2015

Please cite this article as: Tazegül Pekin A, Seçilmiş Kerimoğlu Ö, Yılmaz SA, Koçak N, İncesu FN, Kebapcılar AG, Çelik Ç. Evaluation of prenatal invasive procedures: analysis of retrospective cases. Perinatal Journal 2015;23(1):39–44.

Available online at:
www.perinataljournal.com/20150231009
doi:10.2399/prn.15.0231009
QR (Quick Response) Code:

deomed

Introduction

In pregnancies with the risk of fetal chromosomal anomaly, chorionic villus sampling (CVS) at the first trimester, amniocentesis at the second trimester and invasive prenatal diagnosis methods such as cordocentesis at further weeks may be carried out for diagnostic purposes. While all these prenatal invasive methods can be done mainly for fetal karyotype analysis, they also can be carried out to identify single gene diseases such as sickle cell anaemia or thalassemia major, and to investigate fetal infections, fetal blood type, hematocrit value, enzymes associated with metabolic diseases and lung maturation.[1] Fetal blood transfusion, amnioreduction, amnioinfusion, fetal shunt and laser practices can be can be listed as the other invasive procedures for fetal treatment purposes.[1] During a few decades, invasive procedure indications have become based on nuchal translucency and maternal serum biochemistry parameters rather than being based on advanced maternal age.[2,3] In this way, with the use of first trimester screening tests, CVS practices have become prevalent and they have enabled earlier diagnosis. Also, using maternal serum markers has increased the detection rates and decreased false positivity rates, thus decreased invasive procedure rates. With the tests analyzing cell-free fetal DNA (cfDNA) becoming popular recently, the decrease of false positivity and invasive procedure rates is expected.[4,5] Karyotype analysis can be done in case of advanced maternal age, trisomy in previous pregnancy or history of fetus with sex chromosome anomaly, presence of translocation, inversion or chromosomal anomaly in spouses, markers indicating aneuploidy or presence of major anomaly in the ultrasonography, positive prenatal test results, increased nuchal translucency and maternal anxiety.[6,1] Amniocentesis is considered to be the easiest method with the least risk for maternal and fetal morbidity among prenatal invasive diagnosis methods.[7] American College of Obstetricians and Gynaecologists (ACOG) reports the risk of pregnancy loss associated with the procedure during amniocentesis performed after 15 weeks of gestation as 1/300–500.[6] Also, it is reported in experienced centers that the risk of pregnancy loss with CVS is similar with amniocentesis.[6] Fetal loss risk after cordocentesis is shown as 1.4%.[8] In our study, we aimed to present the results of prenatal invasive procedures that we carried out with various indications in our clinic.

Methods

A total of 308 pregnant women were included in the study who were applied prenatal invasive procedures for the purpose of karyotype analysis between 2011 and 2014 in our clinic. The approval of Ethics Committee of the Selçuk University Hospital was obtained for the study. The consent forms were received from the patients in our clinic by informing them that their ultrasound images and genetic results can be used in the study before the examination and the procedure. The cases were evaluated retrospectively in terms of invasive procedure indications, cell culture success, genetic results and fetal prognosis. The pregnant women with risk rate over 1/250 according to the first trimester combined test result, the pregnant women with risk rate over 1/300 according to second trimester screening tests, pregnant women having major anomaly or ultrasonographic markers which may be associated with fetal karyotype anomaly, pregnant women who are above 40-year-old but did not have any prenatal screening test and pregnant women with karyotype anomaly risk in their obstetric history were recommended invasive procedures appropriate for their weeks of gestation. The patients and their spouses were informed about the indication related with the procedure, the technique to be applied, complications and the rates to accomplish result and their written consents were received. Before the procedure, blood type and HIV and hepatitis B serology of pregnant women were evaluated. CVS was carried out transabdominally between 11 and 14 weeks of gestation under sterile conditions with 18-Gauge (G) needle. Classical amniocentesis procedure at appropriate week of gestation was preferred in cases with retroverted uterus or posterior located placenta which were technically not suitable for transabdominal CVS procedure. Amniocentesis procedure was carried out between 15 and 20 weeks of gestation with 21-G needle under sterile conditions by entering through a distant zone from placenta and aspiring 1–2 ml fluid for each week of gestation. First 2 ml amniotic fluid was not examined in order to avoid maternal contamination. Cordocentesis procedure was carried out by using 22-G needle in pregnancies older than 21 weeks. By entering through the placental insertion zone or free floating area of umbilical cord, 2–3 ml fetal blood was collected from umbilical vein with an injector washed with heparin. Voluson 730 Expert (General Electric Healthcare, Milwaukee, WI, USA) and 3.5 MHz convex probe were used during the procedures. The procedure was carried out after fetus

and placenta were examined systematically. After the procedure, a single dose of 300 microgram anti-D immunoglobulin was administered intramuscularly to the pregnant women with Rh alloimmunization risk. Routine antibiotic prophylaxis was not applied. The patients were discharged in the same day. Fetal loss within three weeks following the procedure was considered as the complication of the procedure.

The samples collected for genetic analysis were cultured for 1 week for CVS, for 3 days for cordocentesis and for approximately 15–20 days for amniocentesis through the methods suitable for the samples, and culture extractions were done. Metaphase preparations obtained after the culture were stained by using Trypsin Giemsa banding method (GTG). In all cases, 25 metaphase plates were evaluated for structural irregularities and 50 metaphase plates were evaluated for numerical irregularities. Computerized analysis system was used in karyotyping analysis. Chromosomal anomalies were defined according to International System for Human Cytogenetic Nomenclature (ISCN) 2009.[9]

The statistical analysis of data was done by using SPSS software, version 16.0 (SPSS, Inc., Chicago, IL, USA). The data in parametric tests were provided as mean±standard deviation. Percentage values were used in groups.

Results

Of 308 pregnant women who undergone invasive procedures, mean age was 31.3±6.4 (range: 16 to 46) years, gravida was 2.4±1.1 (range: 1 to 7) and parity was 1.2±1.0 (range: 0 to 6). Prenatal invasive test was applied to 72 (23.4%) pregnant women who had only minor and/or major anomalies according to ultrasonography, 226 (73.3%) patients who referred for increased risk at screening tests, 5 (1.6%) patients with family history and 5 (1.6%) patients with advanced maternal age. The most frequent invasive procedure indications were increased risk at triple test (46%), major and/or minor anomalies (23.4%), increased risk at first trimester combined test (17%) and increased risk at quad test (10.3%) (**Fig. 1**). Increased nuchal thickness (2.9%) and increased nuchal translucency (2.3%) where the most frequent ultrasonographic findings among karyotype analysis indications (**Table 1**). Amniocentesis was carried out for 81.8% (252) of these patients, CVS for 11.7% (36) of them, and cordocentesis due to advanced week of gestation for 6.5% (20) of them. Karyotype analysis results were normal in 278 (90.2%) patients but no cytogenetic result was obtained in 11 (3.5%) patient, and aneuploidy was reported in 19 (6.2%) patients (trisomy in 2.9% and other genetic anomalies/variations in 3.3%) (**Table 2**). Cordocentesis was applied to one (0.3%) of the cases without cytogenetic result, CVS was applied to two (0.6%) of them and amniocentesis was applied to eight (2.5%) of them. There was ultrasonographic marker in 16 (84.2) of 19 fetuses found to have aneuploidy. The results of two patients, whose karyotype results were 46XX+22p and 46XY,9qh but there was no ultrasonographic finding, were considered as normal variant and followed up. Such pregnancies resulted in healthy live births. The follow-ups of two patients whose chromosomal analysis results were found as 46XX/47XX+ mar (live healthy delivery) and 46XY,inv(9) (intrauterine fetal death at 33 weeks) were discontinued. Gestational prognoses of these patients were learnt by contacting the patients. There was major anomaly (omphalocele) in the fetus whose chromosome structure was reported as 46XY,inv(9). Fifteen pregnancies which were found to have karyotype anomalies with ultrasonographic findings were terminated upon the requests of patients and families. Four of the terminated fetuses had minor markers and 11 fetuses had major anomalies. In this way, the results of three patients were considered as variation and the aneuploidy rate was calculated as 5.2% (16/308). The pregnancy of a patient, who undergone cordocentesis due to the diagnosis of non-immune hydrops fetalis at 20 weeks, was terminated due to the onset of the pains. Also, another pregnancy undergone CVS due to increased nuchal translucency at 11 weeks of gestation

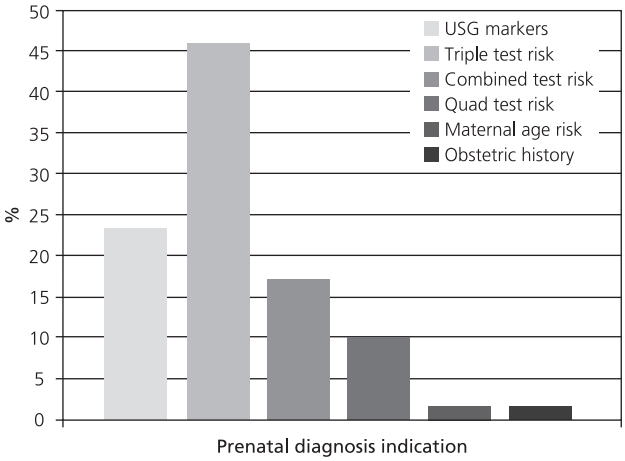

Fig. 1. The rates of invasive procedure indications.

Table 1. Invasive procedure indications according to ultrasonographic findings.

Ultrasonographic findings	n=308	%
Normal	236	76.6
Bilateral cleft palate/lip	1	0.3
Hypoplastic left heart + hydrops fetalis	1	0.3
AVSD	3	1
Hydrops fetalis	6	1.9
Cystic hygroma	5	1.6
Cystic hygroma + omphalocele	3	1
Omphalocele	2	0.6
Choroid plexus cyst >10 mm + SUA	2	0.6
Fallot's tetralogy	2	0.6
Dandy-Walker syndrome	2	0.6
Echogenic intestine grade 3 + ECF	2	0.6
Echogenic intestine grade3 + pyelectasis + increased nuchal thickness	1	0.3
Echogenic intestine grade 3 + pyelectasis + hypoplasic nasal bone	1	0.3
Holoprosencephaly + corpus callosum agenesis	2	0.6
ECF + pyelectasis	8	2.6
Ventriculomegaly/hydrocephaly	8	2.6
Ventriculomegaly + cleft palate-lip + hydrocephaly	1	0.3
VSD+ARSA	1	0.3
Ventriculomegaly + SUA	1	0.3
Absence/hypoplasia of nasal bone	3	1
Increased nuchal thickness	9	2.9
Increased nuchal translucency	7	2.3
Corpus callosum agenesis + ventriculomegaly + Fallot's tetralogy	1	0.3

AVSD: atrioventricular septal defect; **ARSA:** aberrant right sub-clavian artery; **ECF:** echogenic cardiac focus; **SUA:** single umbilical artery; **VSD:** ventricular septal defect.

was terminated at 13 weeks of gestation. The karyotype analysis of this fetus was 46,XY,inv(Y)(p11;q11). Procedure-related fetal loss rate was 0.6%.

Discussion

In our study, we found the most frequent invasive procedure indications as increased risk at triple test (46%) and major and/or minor anomalies detected by ultrasonography (23.4%) while various amniocentesis series published in Turkey reported advanced maternal age as the most frequent invasive procedure indication.[10,11] We found the invasive procedure rate due to advanced maternal age as 1.6%, and invasive procedures were recommended due to the advanced maternal age risk only to the patients who were over 40-year-old and did not undergo prenatal screening tests. Tongsong et al. reported advanced maternal age as the most frequent amniocentesis indication (86.3%), and found invasive procedure rate associated with anomalies found by ultrasonographically as 0.6%.[12] Tabor et al. also reported advanced maternal age as the most frequent indication and they reported invasive procedure rate with ultrasonography indication as 9%.[13] While previously the literature was reporting advanced maternal age as the 50–60% of amniocentesis indications,[13–15] it is not considered as an amniocentesis indication by itself today. In

Table 2. Karyotype analysis results.

Cytogenetic results	N=308	%
Normal	278	90.2
No cytogenetic result	11	3.5
46XY,t(16;22)(p13;q13)	1	0.32
46XY,inv(Y)(p11,q11)	1	0.32
Trisomy 13	1	0.32
46XY+15p	1	0.32
Trisomy 21	6	1.94
Trisomy 18	2	0.64
Triploidy 69 XXX	1	0.32
46XX/47XX+mar	1	0.32
46XX+22p	2	0.64
46XY,inv(9)	1	0.32
46XY,9qh	2	0.64

recent years, invasive procedure rates have decreased recommended due to only advanced maternal age risk[16] by the prevalent use of prenatal screening tests and extracellular DNA determination in maternal blood. By our study, we believe that the reason of the high rates of invasive procedure rates associated with major and/or minor anomalies detected by ultrasonography results from the high number of pregnant women with fetal anomalies and minor markers referred to our clinic since our clinic is a reference hospital.

In our study, increased nuchal thickness (2.9%), increased nuchal translucency (2.3%) were among the ultrasonographic findings of invasive procedure indications and there were ultrasonographic markers in 16 (84.2%) of 19 fetuses who had aneuploidy. Nyber and Souter analyzed 7 studies in their meta-analysis where genetic sonograms were evaluated, and they reported that nuchal thickness increase was the most frequent marker followed by choroid plexus cyst, echogenic cardiac focus, pyelectasis and humerus shortness.[17] On the other hand, choroid plexus cysts are not considered as a marker for trisomy 21 today. It has been shown that many ultrasonographic markers do not clearly increase previous trisomy 21 risk of pregnant women; however, it increases 3–4 times in the presence of ventriculomegaly, nuchal thickness increase and aberrant right sub-clavian artery, and 6–7 times in case of hypoplasia of nasal bone.[18]

In our study, we found the rate of detecting chromosomal anomaly in invasive procedures as 5.2%. Due to the non-existence of concomitant ultrasonographic findings in three patients, presence of similar chromosomal structure in paternal/maternal chromosomal analysis, completion of pregnancies with healthy live births and non-existence of anomaly in postnatal evaluations, cytogenetic changes were considered as variant. Our rate to detect chromosomal anomaly was higher than the rates reported in other regions of Turkey[19,20] and the rate of chromosomal anomalies found as 2.4% in risky group.[21] We believe that the reason results from the association of our invasive procedures with the indications and the wide use of screening tests. First trimester combined test is applied to all pregnant women in our clinic, and integrated test is carried out on patients if they have mid-level risk accordingly; however, we recommend second trimester quad screening test if the patient is considered not to be at appropriate week. Also, ultrasonography is performed for all pregnant women in order to evaluate fetal anomaly between 18 and 23 weeks of gestation.

In 11 (3.5%) of our cases which undergone amniocentesis, there was no reproduction in the culture. We attributed the reason to the laboratory errors associated with the period when the genetic laboratory of our hospital was established. In 7 of the patients without reproduction in the culture, analyses were run for 13, 18, 21 and X,Y chromosomes with fluorescence in situ hybridisation (FISH) method. The results evaluated as normal were confirmed by quantitative fluorescence polymerase chain reaction (QF-PCR). Four patients recommended cordocentesis refused the procedure. The literature reports the rate not obtaining reproduction in the culture after amniocentesis between 15 and 20 weeks as 0.6–1%.[22] However, these rates are reported higher in the studies performed in Turkey.[19,23]

In our study, we found procedure-related fetal loss rate as 0.6%. The pregnancy of a patient who undergone cordocentesis with the diagnosis of non-immune hydrops fetalis was lost at 21 weeks of gestation, and another pregnancy which undergone CVS due to increased nuchal translucency at 11 weeks was terminated at 13 weeks of gestation. The karyotype analysis of this fetus was 46,XY,inv(Y)(p11;q11). Also, we found that another fetus, which was found to have omphalocele with chromosome structure as 46XY,inv(9), was in utero ex at 33 weeks of gestation. However, this pregnancy was not deemed as procedure-related loss. In a study where pregnancy loss rates were compared in patients who undergone amniocentesis but no invasive procedure, it was reported that pregnancy loss risk increased 1% (95% CI, 0.3–1.5%) by amniocentesis.[7] Although differences were found among studies in a meta-analysis systematically evaluating complications associated with amniocentesis and CVS procedures, pregnancy loss rate before 24 weeks of gestation was reported as 0.9% after amniocentesis and as 1.3% after CVS.[24] Second trimester amniocentesis is considered as a safer method than early amniocentesis and transcervical CVS; however, transabdominal CVS for prenatal diagnosis purpose before 15 weeks of gestation is recommended as the first option.[25] In our study, we observed amniotic fluid leakage in 1 patient after amniocentesis at 16 weeks of gestation. The pregnancy of the patient whose fluid leakage stopped within 48 hours by strict bed rest resulted with healthy live birth at term. Amniotic fluid leakage is seen in 1–2% of the patients after amniocentesis and stops usually by itself; however, infection, oligohydramnios and fetal loss rate increase in case of persistent fluid leakage.[26]

Conclusion

Amniocentesis is the most easy-to-use invasive prenatal diagnosis method with the lowest complication rate, and also the procedure used most frequently in our study for prenatal diagnostic purposes. However, when first trimester combined test is preferred most frequently in screenings, the rate of CVS procedure with similar complication rates will increase and this method will offer earlier diagnosis opportunity. Also, together with the nuchal translucency measured according to the standards, wide use of first trimester combined tests which has lower false positivity rates will decrease unnecessary invasive procedure rates. Today, the indication of "advanced maternal age" which comes first in prenatal invasive procedures has been superseded by the indication of "increased risk at prenatal screening tests." Besides, together with the active use of ultrasonography devices with higher resolution beginning from the early weeks of gestation, viewable minor and/or major anomalies also become indications for invasive procedures more frequently. Despite all these practices, the rates of invasive procedures for fetal karyotyping purposes will decrease significantly as the tests evaluating extracellular free fetal DNA in maternal blood are used widely.

Conflicts of Interest: No conflicts declared.

References

1. Beksaç MS. Fetal Tıp; Prenetal Tanı. Ankara: Medical Network; 1996; p: 29–38.
2. Kagan KO, Etchegaray A, Zhou Y, Wright D, Nicolaides KH. Prospective validation of first-trimester combined screening for trisomy 21. Ultrasound Obstet Gynecol 2009; 34:14–8.
3. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn 2011;31:7–15.
4. Chiu RW, Akolekar R, Zheng YW, Leung TY, Sun H, Chan KC, et al. Noninvasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. BMJ 2011;342:c7401.
5. Gil MM, Akolekar R, Quezada MS, Bregant B, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: meta-analysis. Fetal Diagn Ther 2014; 35:156–73.
6. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. Obstet Gynecol 2007;110: 1459–67.
7. Tabor A, Philip J, Madsen M, Bang J, Obel EB, Norgaard-Petersen B. Randomized controlled trial of genetic amniocentesis in 4606 low-risk women. Lancet 1986;1(8493): 1287–93.
8. AU Ghidini A, Sepulveda W, Lockwood CJ, Romero R. Complications of fetal blood sampling. Am J Obstet Gynecol 1993;5:1339–44.
9. Shaffer LG, Slovak ML, Campbell LJ, editors. ISCN 2009: An international system for human cytogenetic nomenclature (2009) Basel: S. Karger; 2009.
10. Saatçi Ç, Özkul Y, Taşdemir Ş, Kiraz A, Müderris İ, Taşcıoğlu N ve ark. Retrospective analysis of 2295 cases with ınvasive prenatal diagnosis. Perinatal Journal 2007;15:120–6.
11. Kaplan Ö, Güney M, Yüksel M. 2. Trimester genetik tarama amniyosentez: 1586 olgunun değerlendirilmesi. Süleyman Demirel Üniversitesi Tıp Fakültesi Dergisi 2012;19:144–7.
12. Tongsong T, Wanapirak C, Sirivatanapa P, Piyamongkol W, Sirichotiyakul S, Yampochai A. Amniocentesis-related fetal loss: a cohort study. Obstet Gynecol 1998;92:64–7.
13. Tabor A, Vestergaard CHF, Lidegaard Ø. Fetal loss rate after chorionic villus sampling and amniocentesis: an 11-year national registry study. Ultrasound Obstet Gynecol 2009;34: 19–24.
14. Sjögren B, Uddenberg N. Decision making during the prenatal diagnostic procedure. A questionnaire and interview study of 211 women participating in prenatal diagnosis. Prenat Diagn 1989;9:263–73.
15. Lindemann CH, Theile U. Prenatal karyotyping in second trimester pregnancies. Prenat Diagn 1989;9:594–8.
16. American College of Obstetricians and Gynecologists Committee on Genetics, Committee opinion no. 545: noninvasive prenatal testing for fetal aneuploidy. Obstet Gynecol 2012;120:1532–4.
17. Nyberg DA, Souter VL. Use of genetic sonography for adjusting the risk of fetal Down syndrome. Semin Perinatol 2003;27:130–44.
18. Agathokleous M, Chaveeva P, Poon LCY, Kosinski P, Nicolaides KH. Meta-analysis of second trimester markers for trisomy 21. Ultrasound Obstet Gynecol 2013;41:247–61
19. Erdemoğlu M, Kale A. Genetik amaçlı amniyosentez uygulanan 183 olgunun prospektif analizi. Dicle Tıp Dergisi, 2007; 34:170–5.
20. Yayla M, Bayhan G, Yalınkaya A, Alp N. Yüksek riskli gebeliklerde 2. trimester genetik amniyosentez: 165 olgunun klinik değerlendirilmesi Perinatoloji Dergisi 1999;7:40–6.
21. Evans MI, O'Brien JE, Dvorin E, Johnson MP. Biochemical screening. Curr Opin Obstet Gynecol 1994;6:453–8.
22. Golbus MS, Loughman WD, Epstein CJ, Halbasch G, Stephens JD, Hall BD. Prenatal genetic diagnosis in 3000 amniocentesis. N Engl J Med 1979;300:157–63.
23. Pala HG, Artunç Ülkümen B, Eskicioğlu F, Uluçay S, Çam S, Bülbül Baytur Y, et al. Amniocentesis results of Manisa tertiary care in 2012. Perinatal Journal 2014;22:23–7
24. Mujezinovic F, Alfirevic Z. Procedure-related complications of amniocentesis and chorionic villus sampling. A systematic review. Obstet Gynecol 2007;110:687–94.
25. Alfirevic Z, Sundberg K, Brigham S. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev 2003;(3):CD003252.
26. Crane JP, Rohland BM. Clinical significance of persistant amniotic fluid leakage after genetic amniocentesis. Prenat Diagn 1986;6:6–25.