Indications, Results and Complications of Prenatal Genetic Diagnostic Testing at a Single Healthcare Center

Tek Bir Sağlık Merkezinde, Prenatal Genetik Tanı Testi Endikasyonları, Sonuçları ve Komplikasyonları

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ABSTRACT

Objectives: This study is intended to determine the relations between indications of prenatal diagnostic testing and fetal chromosomal abnormalities and evaluate the complications of invasive diagnostic tests.
Methods: Indications, results from karyotyping and complications were evaluated in pregnant women who preferred invasive diagnostic testing at a single healthcare centre between January 2018 and January 2020.
Results: 1232 pregnant women diagnosed with high risk in their aneuploidy screening and underwent prenatal diagnostic testing were investigated. Chorionic villus biopsy was administered on 235 (19.1%), amniocentesis on 969 (78.7%), and cordocentesis on 28 pregnant women (2.2%). The most common indication for prenatal diagnostic testing was the increased risk of trisomy 21 in the maternal serum. The indications most commonly associated with chromosomal abnormalities were fetuses with abnormal ultrasound results in the first trimester (34.2%). The most common chromosomal abnormality in fetuses with abnormal karyotype was trisomy 21. The procedure-induced complications were reported for 0.7%.
Conclusions: Prenatal ultrasound increases the rate of detection of fetal chromosomal disorders. Abnormal manifestations detected mainly in the first trimester ultrasonography are a strong indicator for the abnormal fetal karyotype.

Keywords: aneuploidy, karyotype, prenatal diagnosis, prenatal genetic screening

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ÖZET

Amaç: Prenatal tanı testlerinin endikasyonları ile fetal kromozomal anormallikler arasındaki ilişkileri belirlemek ve invaziv tanı testlerinin komplikasyonlarını değerlendirmektir.
Yöntemler: Ocak 2018 ile Ocak 2020 arasında tek bir sağlık merkezinde invaziv tanı testini tercih eden gebelerde endikasyonlar, karyotipleme sonuçları ve komplikasyonlar değerlendirildi.
Bulgular: Anöploidi taramasında yüksek risk saptanan ve prenatal tanı testi yapılan 1232 gebe incelendi. 235'ine (%19.1) koryon villus biyopsisi, 969'una (%78.7) amniyosentez ve 28 gebeye (%2.2) kordosentez uygulandı. Prenatal tanı testi için en yaygın endikasyon, maternal serum testinde trizomi 21 riskinin artmasıydı. Kromozomal anormalliklerle en sık ilişkili endikasyonlar, ilk trimesterde anormal ultrason bulguları olan fetüslerdi (%34.2). Anormal karyotipli fetüslerde en sık görülen kromozom anomalisi trizomi 21 idi. İşleme bağlı komplikasyonlar %0.7 olarak rapor edildi.
Sonuç: Prenatal ultrason, fetal kromozomal bozuklukların saptanma oranını artırmaktadır. Esas olarak ilk trimester ultrasonografisinde saptanan anormal bulgular, anormal fetal karyotip için güçlü bir göstergedir.

Anahtar Sözcükler: Anöploidi, karyotip, prenatal tanı, prenatal genetik tarama

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INTRODUCTION

About 3%–5% of pregnancies are complicated by congenital disabilities or genetic disorders (1). Chromosomal abnormalities are deviations in the number or structure of chromosomes. The most common abnormality of the number of chromosomes is aneuploidy, in which there is an extra or missing chromosome. Screening tests for aneuploidy include serological screening, cell-free DNA (cfDNA) and ultrasonographic screening (2). By comparing maternal serum levels of various analytes with the average values of the overall population, serum screening has long been used in identifying high-risk pregnancies. To calculate the risk of aneuploidy in the first trimester, the levels of human chorionic gonadotropin (hCG), pregnancy-associated plasma protein A and fetal nuchal translucency are tested (3,4). Triple-and quadruple-screening performed in the second trimester is based on the maternal serum measurements of hCG, alpha-fetoprotein, inhibin A and unconjugated estriol (triple screening does not include inhibin A) (5).

Second trimester ultrasonography is recommended between 18-22 weeks of gestation to investigate "soft markers" such as renal pelviectasis and hyperechogenic intestine suggesting aneuploidy and to detect fetal structural abnormalities (6).

There are several invasive methods used to obtain fetal cells for genetic diagnosis. Fetal specimens are usually retrieved through chorionic villus sampling (CVS) between the gestational weeks 11 to 14 or through amniocentesis or fetal blood sampling directly from the umbilical cord after the gestational week 16.

This study is intended to evaluate the indications for invasive diagnostic tests and assess the efficiency of prenatal genetic diagnosis and the frequency of complications because of invasive testing.

METHODS

Records of all patients undergoing prenatal genetic diagnostic tests at the University of Health Sciences Etlik Zübeyde Hanım Gynecology Training and Research Hospital between January 2018 and June 2020 were retrospectively reviewed. Ethics approvals for this study were provided (Decision Date-No: 09.07.2020-10/31). The study was not conducted on humans or animals. The archive records were used to obtain information about maternal age, test indications, type of the obtained sample (amniocentesis, CVS or cordocentesis) and performed test, gestational age, karyotype results, procedure-induced complications, and incidence of singleton and multiple pregnancies. A single record was created for women with a twin pregnancy and those who underwent re-testing during the same pregnancy.

The prenatal diagnostic test indications herein included advanced maternal age (those aged ≥35 with negative serum screening and normal ultrasound findings), presence of increased nuchal translucency (NT) (≥3mm), cystic hygroma, a structural anomaly in the ultrasound between the gestational weeks 11-14 or a high risk of trisomy 21 (>1/270) or trisomy 13/18 (>1/150) in maternal serum screening tests (combined screening in the first trimester or triple or quadruple screening in the second trimester) despite a normal ultrasound examination findings in the first trimester or low risk (<1/270) in the maternal serum screening tests but presence of aneuploidy markers (pyelectasia (≥4 mm), echogenic intestine, thick nuchal fold (≥6 mm), minor ventriculomegaly (10–15 mm), short femur (<2.5 percentile)) or presence of significant anomalies associated with aneuploidies (such as anomalies of the central nervous system and cardiac anomalies) in the second trimester ultrasound examination.

Those who have a history of genetic diseases in the family and were tested positive for cfDNA were excluded as they were in small numbers.

The samples obtained for the karyotype analysis were cultivated in three different flasks according to specific cell culturing conditions in appropriate media.

Harvesting of Cells

When the cells have reached the required amount colchicine added to the cell culture flask. After incubation and washing procedures, trypsin was added for the detachment of cultured cells. Fixative was added to pellet which were obtained via several steps of centrifuging and removing supernatant and resuspending cells. Cases with culture failure were excluded from the study.

Slide Preparation and G-banding

After centrifuging and resuspending the pellet, cell suspension was dropped from a distance onto a slide which is tilted which allowed the suspension to roll across the slide. After adding large amount of fresh fixative, the slide was put to sit out till completely dry. Trypsin treatment used before Giemsa staining (400-500 band resolution) air drying of slides.

Analyse

A computerised chromosome analysis system (metaphase finder) was used for evaluation of karyotypes in at least 20 metaphase plates. Results from karyotype analysis were categorized as normal or abnormal karyotype (numerical and structural chromosome abnormalities).

Information about complications that occurred within the one month after prenatal diagnostic sampling and during the whole pregnancy was also obtained.

Statistical analysis

Statistical analysis was performed using the IBM SPSS software v23 (IBM SPSS Statistics for Windows, Version 23, Armonk, NY, USA). Categorical data were expressed in count and percentages. Differences between groups in terms of categorical data were evaluated using the chi-squared test ($p<0.05$ was considered statistically significant).

RESULTS

A total of 1232 invasive test results that matched the criteria defined were obtained during the study period. Of the pregnant women, 1220 were singletons, and 12 were pregnant with twins.

The age range of the pregnant women was between 16 and 47, and the mean age was 31.71. Of the pregnant women, 744 (60.4%) were aged under 35, 488 (39.6%) were aged 35 and older.

For prenatal diagnostic purposes, CVS was performed on 235 pregnant women (19.1%), amniocentesis on 969 pregnant women (78.7%), and cordocentesis on 28 pregnant women (2.2%). The mean pregnancy weeks for the invasive procedures, CVS, amniocentesis and cordocentesis were 12.57 (11-14), 18.07 (15-23) and 25.43 (23-34), respectively. The success rate of cytogenetic analyses was 99.3% (1232/1240) as only eight cultures failed due to microbial contaminations (5 CVS and 3 AS samples).

In maternal serum testing, the diagnostic testing was performed on 506 pregnant women (41.0%) with a high risk of trisomy 21, 193 pregnant women (15.7%) with abnormal ultrasound findings in the first-trimester ultrasound, 347 pregnant women (28.2%) with abnormal ultrasound findings in the second-trimester ultrasound, 166 pregnant women (13.5%) because of advanced maternal age, and 20 pregnant women (1.6%) with increased risk of trisomy 13/18 (Table 1).

Table 1. Indications for prenatal diagnosis

Indications	Number (%)
Increased risk of trisomy 21	506 (41.0)
First trimester abnormal ultrasound	193 (15.7)
Second trimester abnormal ultrasound	347 (28.2)
Advanced maternal age	166 (13.5)
Increased risk of trisomy13/18	20 (1.6)
Total	1232 (100.0)

In 128 out of 1232 fetuses, an abnormal karyotype was detected (10.4%). The most common abnormal karyotype results were trisomy 21 (35.9%), trisomy 18 (11.7%), and trisomy 13 (3.9%), which rendered the trisomy the most common chromosomal abnormality with a 51.5% ratio. Monosomy X accounted for 14.1%, while 34.4% were chromosomal disorders (Table 2). Furthermore, 94.0% of the total number of 506 fetuses that were performed diagnostic testing because of increased risk of trisomy 21 in maternal serum were found to have a normal karyotype (n=476), while 5.9% of them had abnormal karyotype (n=30); moreover, 65.8% (n=127) of 193 fetuses with abnormal findings in their first-trimester ultrasound had a normal karyotype, while 34.2% (n=66) of them had abnormal karyotype.

Note that 92.2% (n=320) of 347 fetuses with abnormal results in their second-trimester ultrasound had a normal karyotype, while 7.8% (n=27) of them had abnormal karyotype. 97.6% of the total number of 166 fetuses that were performed diagnostic testing because of advanced maternal age had a normal karyotype (n=162), while 2.4% of them had abnormal karyotype (n=4). Furthermore, 95.0% of the total number of 20 fetuses that were performed diagnostic testing because of increased risk of trisomy 13/18 had a normal karyotype (n=19), while 5.0% of them had abnormal karyotype (n=1). Details of the karyotype results by indication are shown in Table 3.

Table 2. Results of fetal abnormal karyotype (n=128)

Abnormal karyotype	Number (%)
Trisomy 21	46 (35.9)
Trisomy 13	5 (3.9)
Trisomy 18	15 (11.7)
Monosomy X	18 (14.1)
Structural abnormality	44 (34.4)
Total	128 (100.0)

Table 3. Detail of fetal karyotype results according to indications

Indications	Fetal karyotype						
	Normal N (%)	Trisomy 21 N (%)	Trisomy 13 N (%)	Trisomy 18 N (%)	Monosomy N (%)	Structural abnormality N (%)	Total N (%)
Increased risk of trisomy 21	476 (94.0)	13 (2.6)	0 (0)	1 (0.2)	3 (0.6)	13 (2.6)	506 (100)
First trimester abnormal ultrasound	127 (65.8)	25 (12.9)	2 (1.0)	10 (5.2)	14 (7.3)	15 (7.8)	193 (100)
Second trimester abnormal ultrasound	320 (92.2)	7 (2.0)	3 (0.9)	3 (0.9)	1 (0.3)	13 (3.7)	347 (100)
Advanced maternal age	162 (97.6)	1 (0.6)	0 (0)	0 (0)	0 (0)	3 (1.8)	166 (100)
Increased risk of trisomy13/18	19 (95.0)	0 (0)	0 (0)	1 (5.0)	0 (0)	0 (0)	20 (100)
Total	1104 (89.6)	46 (3.7)	5 (0.4)	15 (1.2)	18 (1.5)	44 (3.6)	1232 (100)

Compared to other indication groups, those with abnormal findings in the first-trimester ultrasound had the highest rate of abnormal karyotype (34.2%) ($p<0.001$, chi-squared test). Of a total number of 1169 pregnant women whose results from their first-trimester ultrasounds were obtained, 976 had a normal ultrasound finding, while 6.6% of them had chromosomal abnormalities (n=64). Among the first trimester ultrasound findings, the most common abnormal karyotype was detected in fetuses with cystic hygroma (55.9%), and the rate of abnormal karyotype detection was higher than other findings ($p<0.001$). The rate of abnormal karyotype detection in the second-trimester ultrasound is 18.2% for the cardiac anomaly, 16.7% for multiple soft marker findings, 8.8% for intestinal echogenicity increase, 7.7% for renal pyelectasis, 6.5% for central nervous system anomalies, and 3.0% for choroid plexus cyst. There was no significant difference in abnormal karyotype rates based on the abnormal ultrasound findings during the second trimester ($p=0.225$). According to the abnormal ultrasound findings of the first and second trimesters, the prevalence of the abnormal fetal karyotype is shown in Tables 4 and 5.

Table 4. First trimester abnormal ultrasound findings and fetal karyotype results

First trimester abnormal ultrasound findings	Fetal karyotype		
	Normal karyotype N (%)	Abnormal karyotype N (%)	Total N
Increased NT	54 (75.0)	18 (25.0)	72
Cystic hygroma	30 (44.1)	38 (55.9)	68
Structural abnormalities	43 (81.1)	10 (18.9)	53
Total	127 (65.8)	66 (34.2)	193

Table 5. Second trimester abnormal ultrasound findings and fetal karyotype results

Second trimester abnormal ultrasound findings	Fetal karyotype		
	Normal karyotype N (%)	Abnormal karyotype N (%)	Total N
Hyperechogenic bowel	156 (91.2)	15 (8.8)	171
Pyelectasis	24 (92.3)	2 (7.7)	26
Echogenic intracardiac focus	8 (100)	0 (0)	8
Choroid plexus cysts	32 (97.0)	1 (3.0)	33
Increased NF	5 (100)	0 (0)	5
Short femur	1 (100)	0 (0)	1
Cardiac defects	9 (81.8)	2 (18.2)	11
CNS abnormality	29 (93.5)	2 (6.5)	31
Multiple soft markers	10 (83.3)	2 (16.7)	12
Other abnormalities	46 (93.9)	3 (6.1)	49
Total	320 (92.2)	27 (7.8)	347

The prevalence of trisomy 21 in women aged 35 and over (5.3%) was higher than in women under 35 (2.7%) (p=0.035). The prevalence of monosomy X in the fetuses of women aged under 35 (2.2%) was higher than in women aged 35 and over (0.4%) (p=0.035) (Table 6). Furthermore, 1223 (99.3%) of 1232 pregnant women had no complications, while 9 (0.7%) had complications (Table 7). Of all the pregnant women, 7 (0.5%) had amniotic fluid leakage, 2 (0.2%) had intrauterine death, which is estimated to be due to the procedure. Complications appeared within one week after the procedure. All pregnant women who had an amniotic fluid leakage were observed to have developed this complication after the amniocentesis procedure, while intrauterine death occurred after CVS in one patient and after amniocentesis in another. There was no statistically significant difference between the prenatal testing techniques regarding complication rates (p=0.531). Pregnancy outcomes of 700 cases out of a total number of 1232 pregnant women who were performed prenatal diagnostic tests due to being of high risk in the aneuploidy screening were accessed. Of these cases, 516 (73.7%) had a live birth, while 151 (21.6%) were terminated because of structural or chromosomal abnormalities, and 33 (4.7%) resulted in intrauterine death (Table 8). Three of the cases of amniotic fluid leakage resulted in a live birth, while one case was terminated because of anhydramnios and another because of corpus callosum agenesis. One case whose karyotype was tested positive for trisomy 13 and another case with normal karyotype resulted in intrauterine death in the third trimester.

Table 6. Maternal age and fetal karyotype results

Fetal karyotype	Maternal age		Total N (%)
	<35 N (%)	>35 N (%)	
Normal	670 (90.0)	434 (89.0)	1104 (89.6)
Trisomy 21	20 (2.7)	26 (5.3)	46 (3.7)
Trisomy 13	3 (0.4)	2 (0.4)	5 (0.4)
Trisomy 18	8 (1.1)	7 (1.4)	15 (1.2)
Monosomy X	16 (2.2)	2 (0.4)	18 (1.5)
Structural abnormality	27 (3.6)	17 (3.5)	44 (3.6)
Total	744 (100)	488 (100)	1232 (100)

Table 7. Complications following prenatal diagnostic test

Complications	Number	Percent
No	1223	99.3
Leakage of amniotic fluid	7	0.5
Intrauterine death	2	0.2
Total	1232	100.0

Table 8. Pregnancy outcomes following prenatal diagnostic test

Pregnancy outcome	Number (%)
Termination	151 (21.6)
Intrauterine death	33 (4.7)
Live birth	516 (73.7)
Total	700 (100)

DISCUSSION

Maternal serum and ultrasound screenings identify high-risk pregnancies for trisomy 21, 18, 13 and other chromosomal abnormalities, and therefore, pregnancies at such a high risk require invasive diagnostic testing (7). Studies report that the incidence of abnormal chromosomes varies between 3.3% and 27.2% (8-12). Consistent with the literature, we identified that abnormal karyotype in 10.4% of high-risk pregnancies. Again, consistent with the literature, trisomies were the most common anomaly reported in prenatal diagnostic testing, and the most common trisomy was trisomy 21 (12,13). Yakut et al.(14) reported 99.33%, Saatçi et al.(15) reported 96.4% success rate of culture in their study which shows that success rate reported in this study (99.3%) is in accordance with literature.

Among the indications, abnormal karyotypes most frequently detected in prenatal testing due to the first trimester abnormal ultrasound findings (33.0%), followed by the second trimester abnormal ultrasound findings (8.8%), and high risk of trisomy 21 in maternal serum test (6.1%), respectively. Among the most common indications were high risk of trisomy 21 in maternal serum testing (41.0%), abnormal findings in the second-trimester ultrasound (28.2%), and abnormal findings in the first-trimester ultrasound (15.7%), respectively. There was an inverse correlation between the prevalence of indications and the rate of abnormal karyotype detection.

The prevalence of chromosomal abnormalities in pregnancy is 1 out of about 150 live births (16). According to current study results, the prevalence of abnormal karyotype among the pregnant women who underwent prenatal screening and had a high risk of chromosomal abnormalities increased to 10.4%, and screening test positivity increased the risk of chromosomal abnormalities approximately 15 times. Certain similar studies have obtained different results. In a study conducted in Turkey in the past years, chromosomal anomaly was found only in 4.98% of patients who underwent invasive procedures for prenatal diagnosis (15). Zhang et al. (13) detected chromosomal abnormalities in 111 (3.99%) of 2782 samples and reported that the highest chromosomal abnormality rate (67.86%) is due to the presence of parental balanced chromosomal abnormality. Dai et al. (17) examined 4952 amniocentesis results for genetic diagnosis and reported that fetal chromosomal abnormalities were detected in 204 (4.12%) cases. They reported that half of the cases with fetal chromosomal abnormalities had a positive serological screening, and the highest predictionary indication was positive serological screening. In their study where Lostchuck et al. (18) examined changes in prenatal diagnosis from past to present, the researchers reported that the rate of diagnostic tests performed due to the ultrasound abnormality increased from 13% to 29.4% over time and that the most common indication for diagnostic tests is ultrasound abnormalities. In our study, while the most common indication for testing regarding chromosomal abnormalities was the high risk of trisomy 21 in maternal serum test, the best indicator for chromosomal abnormalities is ultrasonographic abnormalities, especially abnormal findings in the first-trimester ultrasound. This can be explained by the differences in ultrasound performing experiences of specialists or data reporting centres being reference centres.

In their study with a large number of samples where Vičić et al. (19) investigated prenatal diagnosis of Down syndrome, they observed an abnormal first/second trimester ultrasound scan in 59.8% of the fetuses with Down syndrome. In our study, abnormal ultrasound findings were present in the first-trimester ultrasound in 50% (n=23) of the 46 fetuses with Down syndrome and the second-trimester ultrasound in 17.4%; thus, it is 67.4% in total and more than Vičić et al. (19) reported. This result shows the importance of ultrasound in aneuploidy screening. Moreover, this result may be related to running ultrasound scans on those cases which tested negative in maternal serum screening for detection of aneuploidy in our centre.

As the maternal age increases, the likelihood of the fetus to have an additional chromosome (21, 18, 13) increases (20). The risk of Down syndrome at the maternal age of 30 is approximately 1/1000, it is about 1/400 at the age of 35 and reaches to 1/100 ratio at the age of 40 (21). In previous studies, advanced maternal age is the most common indication (8,22). However, using multiple biochemical markers and ultrasound rather than screening only by maternal age has significantly improved detection rate in all age groups and greatly reduced the false positivity ratio (23). Therefore, it is recommended that additional screening tests consisting of maternal serum markers and ultrasound evaluation should be used in combination, rather than solely resorting according to maternal age in the screening (7,20). There is now a decline in the rate of invasive testing performed due to the indication of advanced maternal age (24). In our study, advanced maternal age accounted for 13.5% of the indications (n=166); this group is over 35, has been tested negative in serum screening with normal ultrasound findings, but underwent invasive prenatal testing due to maternal anxiety. The prevalence of abnormal karyotype in this group was 2.4% (n=5). This result is lower than the rate of 4.51% previously reported by Zhang et al. (13) and the rate of 6.17% reported by Dai et al. (17). This difference may be related to excluding pregnant women aged over 35 who had an additional indication from the group of advanced maternal age in our study.

In previous studies, the complication rates of prenatal diagnostic tests show significant heterogeneity. Sean et al. (8) reported the total rate of complications in their study at 0.6%, while Jummaat et al. (12) reported a complication rate of 14.0% in their study. In our study, 9 out of 1232 cases (0.7%) had complications related to the procedure and was similar to the number reported by Sean et al. (8). Different rates of pregnancy loss have been reported in the literature depending on the type of prenatal diagnostic tests.

The risk of pregnancy loss is reported to be 0.22% for CVS (25) and to be between 0.11% and 1.75% for amniocentesis (12, 26-28). In our results, the rate of procedure-related pregnancy loss was 0.2%, which is consistent with the literature. Amniotic fluid leakage was reported in 1-3% (12, 29, 30) of cases. Our results were found to be 0.5% for amniotic fluid leakage and were lower than those reported in the literature. As stated by Ghi et al. (31), we think it is related to familiarity and experience.

cfDNA test, known as a noninvasive prenatal test (NIPT) or screening, is now a popular screening test, especially for aneuploidy syndromes such as trisomy 21, 13, and 18. After its launch in 2013, it became a widespread test. NIPT is the most sensitive and specific screening test for common fetal aneuploidies. However, it has the potential of false positivity and false negativity; therefore, it should not be considered equivalent to a diagnostic test (6). Ultrasound and serum marker assessments should not be replaced by cfDNA because these techniques can detect fetal structural defects such as anencephaly and gastroschisis (32). Among all the pregnant women admitted by our centre, those who tested positive in cfDNA could not be included in the study as they were in a very small number.

Prenatal ultrasound increases the rate of detection of fetal chromosomal disorders. Abnormal findings detected in the first-trimester ultrasonography are robust indicators for abnormal karyotype in fetuses. Rates of pregnancy loss are low in prenatal diagnostic testing, and these tests can be considered safe. Given the false negativity of prenatal screening tests, all pregnant women should be informed about the reliability of prenatal screening and diagnostic tests.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Centers for Disease Control and Prevention (CDC) : Update on overall prevalence of major birth defects–Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep 2008; 57: 1-5.

2. Sheth F, Rahman M, Liehr T, Desai M, Patel B, Modi C, et al. Prenatal screening of cytogenetic anomalies-a Western Indian experience. BMC Pregnancy Childbirth. 2015;15:90.

3. Nicolaides KH, Azar G, Snijders RJ, Gosden CM. Fetal nuchal oedema: associated malformations and chromosomal defects. Fetal Diagn Ther. 1992;7:123–31.

4. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. Fetal Medicine Foundation First Trimester Screening Group. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. Lancet 1998;352:343–6.

5. Wald NJ, Cuckle HS, Densem JW, Nanchahal K, Royston P, Chard T, et al. Maternal serum screening for Down's syndrome in early pregnancy. BMJ. 1988;297:883–7.

6. Rose NC, Kaimal AJ, Dugoff L, Norton ME. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: Obstet Gynecol. 2020;136:48-69.

7. Practice Bulletin No. 163: Screening for Fetal Aneuploidy. Obstet Gynecol. 2016; 127(5): 123-137

8. Sean CB, Margot GA, Paul CN. Five-year experience with midtrimester amniocentesis performed by a single group of obstetriciansgynaecologist at a community hospital. Am J Obstet Gynecol 2002; 186: 1130–1132.

9. Ercan Ö, Köstü B, Arslan G, Bakacak M, Özer A, Arıkan D. Does amniocentesis increase the rates of fetal loss and poor pregnancy outcomes? J Clin Anal Med 2016; 7: 197–200.

10. Christine AP, Mary MS, Mary-Fraces G, Marisa L, Janice MS. Early amniocentesis: report of 407 cases with neonatal follow-up. Obstet Gynecol 1990; 76: 1032–1036.

11. El Din SM, Ismail NA, Ramy AR. Fetal chromosome abnormalities and congenital malformations: an Egyptian study. Egypt J Hum Genet 2007; 8: 131–145.

12. Jummaat F, Ahmad S, Mohamed Ismail NA. 5-Year review on amniocentesis and its maternal fetal complications. Horm Mol Biol Clin Investig. 2019; 40(2):/j/hmbci.2019.40.issue-2/hmbci-2019-0006/hmbci-2019-0006.xml.

13. Zhang L, Zhang XH, Liang MY, Ren MH. Prenatal cytogenetic diagnosis study of 2782 cases of high-risk pregnant women. Chin Med J 2010; 123: 423-430.

14. Yakut, S., Cetin, Z., Şİmşek, M., Mendilcioğlu, I. I., Toru, H. S., Karaüzüm, S. B., & Lüleci, G. (2015). Rare structural chromosomal abnormalities in prenatal diagnosis; clinical and cytogenetic findings on 10125 prenatal cases. Turk Patoloji Derg, 31(1), 36-44.)

15. Saatçi Ç, Bayramov R, Başbuğ M, Güneş MC, Dündar M. Retrospective evaluation of results of 3617 invasive prenatal diagnosis cases applied between 1997-2015 years. Journal of Health Sciences. 2016;25: 120-125.

16. Nussbaum RL, McInnes RR, Willard HF. Principles of clinical cytogenetics and genome analysis. In: Thompson & Thompson genetics in medicine. 8th edn. Philadelphia: Elsevier; 2016; 57–74.

17. Dai R, Yu Y, Xi Q, Hu X, Zhu H, Liu R, Wang R. Prenatal diagnosis of 4953 pregnant women with indications for genetic amniocentesis in Northeast China. Mol Cytogenet. 2019;12:45.

18. E Lostchuck , A Poulton , J Halliday , L Hui. Population-based trends in invasive prenatal diagnosis for ultrasound-based indications: two decades of change from 1994 to 2016. Ultrasound Obstet Gynecol 2019; 53: 503-511.

19. Vičić A, Hafner T, Bekavac Vlatković I, Korać P, Habek D, Stipoljev F. Prenatal diagnosis of Down syndrome: a 13-year retrospective study. Taiwan J Obstet Gynecol 2017; 56: 731–735

20. Chitayat D, Langlois S, Wilson RD. No.261-Prenatal Screening for Fetal Aneuploidy in Singleton Pregnancies. J Obstet Gynaecol Can 2017; 39: 380-394.

21. Savva GM, Morris JK, Mutton DE, Alberman E. Maternal age-specific fetal loss rates in Down syndrome pregnancies. PrenatDiagn 2006; 26: 499.

22. Pathompanitrat S, Choochuay P, Wannawat N. Second trimester genetic amniocentesis at secondery center hospital in Southern Thailand. Thai J Obstet Gynecol 2013; 21: 134–140.

23. Resta RG. Changing demographics of advanced maternal age (AMA) and the impact on the predicted incidence of Down syndrome in the United States: implications for prenatal screening and genetic counseling. Am J Med Genet A 2005; 133: 31-36.

24. Awomolo A, Palomares K, Garcia GH, Rosen T, Duzyj C, Ashkinadze E. Trends in invasive prenatal diagnostic testing ata single institution. Prenat Diagn 2018; 38: 735-739.

25. Wapner RJ, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med 2012; 367: 2175–2184.

26. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2015; 45: 16–26

27. Caughey AB, Hopkins LM, Norton ME. Chorionic villus sampling compared with amniocentesis and the difference in the rate of pregnancy loss. Obstet Gynecol 2006; 108: 612–616.

28. Odibo AO, Gray DL, Dicke JM, Stamilio DM, Macones GA, Crane JP. Revisiting the fetal loss rate after second-trimester genetic amniocentesis: a single center's 16-year experience. Obstet Gynecol 2008; 111: 589–595.

29. Philip J, Silver RK, Wilson RD, Thom EA, Zachary JM, Mohide P, et al. Late first-trimester invasive prenatal diagnosis: results of an international randomized trial; NICHD EATA Trial Group. Obstet Gynecol 2004; 103: 1164–1173.

30. Reid KP, Gurrin LC, Dickinson JE, Newnham JP, Philips JM. Pregnancy loss rates following second trimester genetic amniocentesis. Aust N Z J Obstet Gynaecol 1999; 39: 281–285.

31. Ghi T, Sotiriadis A, Calda P, Da Silva Costa F, Raine-Fenning N, Alfirevic Z. ISUOG Practice Guidelines: invasive procedures for prenatal diagnosis. Ultrasound Obstet Gynecol 2016; 48: 256–268.

32. Wojcik MH, Reimers R, Poorvu T, Agrawal PB. Genetic diagnosis in the fetus. J Perinatol 2020; 40: 997-1006.