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Evaluation of the incidence of anomaly in fetus and neonates of prenatal aneuploidy screening

Salih Demir[1], Mustafa Törehan Aslan[2], İlke Özer Aslan[1]
[1] Department of Obstetrics and Gynecology
[2] Department of Pediatrics, Division of Neonatology, Faculty of Medicine, Tekirdağ Namık Kemal University, Tekirdağ, Turkey

Abstract

Aim: Our study aimed to investigate the frequency of anomalies and related maternal and neonatal outcomes in pregnant women who were admitted in our clinic in the last five years and underwent prenatal aneuploidy screening.

Materials and Methods: The prenatal fetal aneuploidy screening results of the pregnant women who participated in the study, the pregnant and maternal outcomes of the pregnant women who underwent amniocentesis according to these results, and the detection rates of chromosomal aneuploidy in infants were retrospectively analyzed.

Results: According to the first-trimester screening test, 22.4% of the cases (n=121); According to the second-trimester screening test, 11.8% (n=6) of the patients were found to be at high risk for chromosomal aneuploidy. Amniocentesis was recommended to 199 participating in the study, and 17.6% (n=35) of these cases were accepted. Chromosomal aneuploidy was found in 1.8% (n=3) of those who underwent amniocentesis. Two pregnancies with aneuploidy were terminated at the request of the families. The anxiety levels of the pregnant women who had prenatal screening tests were higher in the studies.

Discussion: Fetal aneuploidy screening tests may give false positive results at high rates, adversely affecting maternal anxiety and, thus, pregnancy outcomes. To increase the prenatal diagnosis rates cost-effectively, it is helpful to perform combined tests to increase the sensitivity or more sensitive tests are needed.

Keywords

Amniocentesis, Aneuploidy, First Trimester Screening, Second Trimester Screening, Prenatal Screening.

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Corresponding Author: İlke Özer Aslan, Department of Obstetrics and Gynecology, Faculty of Medicine, Tekirdağ Namık Kemal University, Tekirdağ, Turkey.
E-mail: ilkeozeraslan@nku.edu.tr P: +90 505 389 48 00
Corresponding Author ORCID ID: https://orcid.org/0000-0002-3175-8354
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Introduction

Considering that newborns with congenital anomalies cause problems for families and society, screening tests for chromosomal abnormalities are recommended for pregnant women in our country, as in many countries. The purpose of prenatal screening tests is to identify pregnant women with a high risk for chromosomal aneuploidy in the early weeks of pregnancy and to inform each pregnant woman by considering their current troubles and preferences.

Prenatal diagnosis can be made through invasive and non-invasive testing (NIPT). The American Society of Obstetricians and Gynecologists (ACOG) and the Maternal-Fetal Medicine Association (SMFM) recommend that prenatal genetic screening tests be offered to all pregnant women, regardless of age or risk for chromosomal abnormality [1].

Screening tests from maternal blood, free human chorionic gonadotropin (free β-hCG) and pregnancy-associated protein A (PAPP-A) in the first trimester, a triple screening test (alpha-fetoprotein (AFP), free β-hCG and unconjugated protein A (PAPP-A) in the second trimester) estriol (uE3). The detection rate for Trisomy 21 with the first-trimester screening test varies between 82-87%, using a 5% positive screening rate depending on the laboratory [2]. The advantage of this test is that the test can be performed in the early stages of pregnancy (10-13 weeks of pregnancy) [3,4]. Patients who agree to have a diagnostic test at 10-13. Chorionic villus sampling (CVS) may be recommended during gestational weeks or amniocentesis from the 15th gestational week (26). 16-18. It is known that the triple screening test (AFP, β-hCG, E3) performed during gestational weeks has an accuracy rate of 60% with a false positive rate of 5% [5,6]. The most important expectation from screening tests is a high congenital anomaly detection rate and low false positivity. However, screening at an early gestational week allows for earlier prenatal diagnosis by calculating the possible increased risk earlier. With the detection of chromosomal anomalies by diagnostic tests, a termination option can be offered in the early weeks.

When the results of the screening tests are received, negative or positive results should be communicated to the family promptly. Even if the screening test result is negative or low-risk, the patient should be advised that an abnormality may still exist. In case of a high-risk outcome, the family should be informed about additional diagnostic testing options, if desired [1,7].

It is aimed to investigate whether diagnostic tests are performed and what their results are and to examine the contribution of prenatal screening tests to patients and physicians in a versatile way.

Material and Methods

Among the pregnant women who applied to the Tekirdağ Namık Kemal University, Faculty of Medicine Health Practice and Research Hospital Gynecology and Obstetrics Polyclinic between 01.07.2017 and 01.07.2022, the pregnant women who were screened for fetal aneuploidy in a different clinic gave birth in a different clinic under the age of 18. This is a retrospective cross-sectional study in which a total of 542 pregnant women and their newborns were examined, excluding those with twin pregnancies, those whose screening results were not reported, and those whose screening results were not reported. Patient data and examination results were obtained through the hospital automation system, outpatient follow-up forms and phone calls. This data includes patients' name, surname, age, comorbidities, smoking, weight, gravida, parity, abortion, number of living children, number of curettages, and family history were questioned. PAPP-A, β-hCG, NT, uE3, AFP test results, Trisomy 21 (T21) risk score, Trisomy 13 and Trisomy 18 (T13-18) risk score, NTD risk score, according to results of double screening and triple screening. The pregnant women who underwent amniocentesis and their genetic influences, the week of the birth of the pregnant women who were born in our hospital, the birth weight of the newborn, the mode of delivery, the Apgar score of the newborn at birth, whether there was a need for neonatal intensive care after delivery, and the results of the neonates whose postpartum chromosomal analysis was performed from peripheral blood were recorded. In any of the prenatal screening tests, those with a cut-off value greater than 1/250 were considered high-risk, and those that were small were considered low-risk. Those with NT greater than 2.5 mm were considered high-risk, and those with undersized NT were deemed low-risk.

Statistical analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Independent groups t-test was used to compare two groups of normally distributed quantitative variables. Fisher's exact test was used to compare qualitative data. Spearman correlation analysis was used to evaluate the relationships between quantitative variables. Statistical significance was accepted at $p < 0.05$.

Ethical Approval

The current study was approved by the ethics committee of Tekirdağ Namık Kemal University (Date: 26.07.2022 / No: 2022.145.07.12). The study was conducted in accordance with the Helsinki Declaration rules.

Results

Our study was conducted with 542 cases, all women, who were admitted to our hospital between 01.07.2017 and 01.07.2022. The age of the study's subjects ranged from 18 to 45, and the mean age was 28.91±5.37.

It was observed that 1.3% (n=7) of the cases participating in the study had a family history. The chromosomal anomaly was found in 0.54% (n=3) of the genetic results of the neonates.

When the dual screening test results of the subjects participating in the study were examined, 19.8% (n=107) had an age-related risk, 4.1% (n=22) had a T21 risk, and 0.6% (n=3). T13-18 risk was observed in 0.6% (n=3) of NT-related risk. It was determined that there was a risk in first-trimester screening test results in 22.4% (n=121) of the cases.

The second-trimester screening test was performed in 9.4% (n=51) of the cases in the study. In the test results of the cases, it was determined that 8.3% (n=3) had an age-related

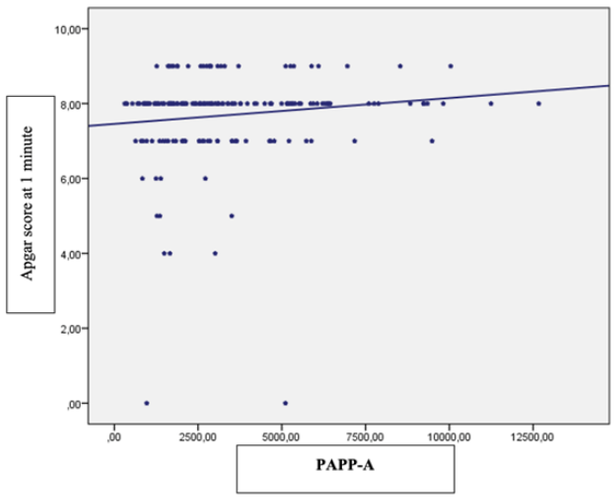

Figure 1. Relationship between PAPP-A and Apgar score at 1 minute.

Table 1. Distribution of results of first and second-trimester screening tests

		n (%)
Dual Screening Test		
Age-Related Risk	Low-risk	433 (80.2)
	High-risk	107 (19.8)
T21 Risk	Low-risk	515 (95.9)
	High-risk	22 (4.1)
T13-18 Risk	Low-risk	533 (99.4)
	High-risk	3 (0.6)
Risk due to NT	Low-risk	533 (99.4)
	High-risk	3 (0.6)
Dual screening test result	Low-risk	419 (77.6)
	High-risk	121 (22.4)
Triple Screening Test		
Status of taking the test	No	491 (90.6)
	Yes	51 (9.4)
Age-Related Risk	Low-risk	33 (91.7)
	High-risk	3 (8.3)
NTD Risk	Low-risk	31 (96.9)
	High-risk	1 (3.1)
T21 Risk	Low-risk	46 (95.8)
	High-risk	2 (4.2)
T13-18 Risk	Low-risk	29 (100.0)
	High-risk	0 (0,0)
Triple screening test result	Low-risk	45 (88.2)
	High-risk	6 (11.8)

risk, 3.1% (n=1) had an NTD risk, and 4.2% (n=2) had a T21 risk. T13-18 risk was not detected in any of the cases. It was determined that there was a risk in 11.8% (n=6) of the issues due to the triple screening test. While chromosomal aneuploidy was detected in one of the neonates of three pregnant women who were found to be risky for fetal aneuploidy, according to NT, chromosomal aneuploidy was not detected in two neonates. Amniocentesis was recommended for 199 cases participating in the study. It was determined that 17.6% (n=35) of the cases who were recommended to perform amniocentesis accepted the amniocentesis procedure, and 1.8% (n=3) had positive

Table 2. Distribution of the characteristics of the cases

Characteristics		
PAPP-A	Mean±Sd	3276.00±2485.86
	Median (Min-Max)	2630 (310-20003)
ß-hCG	Mean±Sd	40.13±40.04
	Median (Min-Max)	30 (4-512)
Gravity (n=538)	Mean±Sd	2.35±1.42
	Median (Min-Max)	2 (1-8)
Parity (n=321)	Mean±Sd	1.44±0.69
	Median (Min-Max)	1 (1-4)
Abort (n=120)	Mean±Sd	1.66±1.00
	Median (Min-Max)	1 (1-6)
Curettage (n=47)	Mean±Sd	1.30±0.55
	Median (Min-Max)	1 (1-3)
Family history	No	535 (98.7)
	Yes	7 (1.3)
Birth (external center)	Training and Research Hospital	186 (34.3)
	Other hospitals	356 (65.7)
Apgar score at 1 minute (n=186)	Mean±Sd	7.67±1.22
	Median (Min-Max)	8 (0-9)
Apgar score at 5 minutes (n=186)	Mean±Sd	8.67±1.12
	Median (Min-Max)	9 (0-10)
Gestational age	Mean±Sd	36.96±5.32
	Median (Min-Max)	38 (4-41)
Type of birth (n=18)	Vaginal delivery	50 (26.9)
	Cesarean section delivery	136 (73.1)
Birth weight	Mean±Sd	3149.08±587.85
	Median (Min-Max)	3197.5 (500-4905)
Admission to the NICU	No	515 (95.0)
	Yes	27 (0.5)
Level 2 antenatal ultrasonography	No	515 (95.0)
	Yes	27 (5.0)
Cff-DNA (n=3)	Low risk	1 (33.3)
	High risk	2 (66.7)

Table 3. Comparison of the presence of chromosomal aneuploidy according to screening tests

		Chromosome Anomaly		p
		Chromosomal aneuploidy (-) Chromosomal	Chromosomal aneuploidy (-) Chromosomal	
First trimester screening test result	Low-risk	417 (99.5)	2 (0.5)	[a]0.534
	High-risk	120 (99.2)	1 (0.8)	
Second trimester screening test result	Low-risk	45 (88.2)	-	1.000
	High-risk	6 (11.8)		

[a]Fisher's exact test

test results. Two pregnancies with positive test results were terminated at the family's request.

According to the double screening test results, no statistically significant difference was found between the chromosomal anomaly results of the cases ($p>0.05$). Since only one of the three cases with chromosomal abnormality had a risk in the double screening test, the test's sensitivity was 33.3%, and the specificity was 77.6%. Its positive predictive value was 82.6%, and its negative predictive value was 99.5%.

There was a very weak statistically significant correlation between the ß-hCG measurement values of the subjects and the 1st minute Apgar scores ($r=0.160$; $p=0.022$; $p<0.05$) in the negative direction (As ß-hCG increases, Apgar score decreases). There was a very weak statistically significant correlation between the PAPP-A measurement values of the cases and the 1st minute Apgar scores ($r=0.160$; $p=0.030$; $p<0.05$).

In addition, the weights of cases with high risk in the first-trimester screening test were statistically significantly higher than those without risk ($p=0.001$; $p<0.01$). The consequences of patients with increased risk in the first or second-trimester screening test were statistically significantly higher than those without risk ($p=0.001$; $p<0.01$). The risk rate in smokers' first or second-trimester screening test was statistically significantly higher than that of non-smokers ($p=0.049$; $p<0.05$).

Discussion

Prenatal screening tests have been developed to detect fetal aneuploidies. These tests and their combinations applied in the first and second trimesters have different detection rates for chromosomal aneuploidies. Screening tests for chromosomal aneuploidies do not definitively tell whether the fetus is abnormal; instead, they can tell whether the fetus has a low or high probability of having the condition [8].

According to Kaya et al., a risk group of 5.75% was determined according to the results of the second-trimester screening test in a study conducted on 1841 pregnant women [9]. In their study, Atak et al. found a high risk of Down syndrome in 1.5% (n=78) of those who underwent the first-trimester screening test and in 5.9% (n=353) of those who experienced the second-trimester screening test [10]. Similarly, in our study, the risk of Down syndrome was high in 4.1% (n=22) of those who underwent the first-trimester screening test and 4.2% (n=2) of those who experienced the second-trimester screening test. In addiition, the high-risk rate for the anomaly in the first-trimester screening test was 22.4% (n=121), and the high-risk rate in the second-trimester screening test was 11.8% (n=6). In our study, only 51 cases also had the second-trimester screening test. Since the first-trimester screening test showed a risk in only one of the three cases with the chromosomal anomaly, the test's sensitivity was 33.3%, and the specificity was 77.6%. Its positive predictive value was 82.6%, and its negative predictive value was 99.5%. It is known that there are differences in the sensitivity of screening tests. When the studies in the literature are examined, we see that prenatal screening tests recommend using contingency screening and fully integrated screening strategies that combine first and second-trimester screening tests to increase the rate of catching chromosomal aneuploidy [11,12].

Screening tests require a blood sample from the mother and a fetal ultrasonographic evaluation, so there is no increased risk of losing the pregnancy. Diagnostic testing for chromosomal abnormalities requires sampling fetal or placental fluid or tissue. There is a slight increase in the risk of losing the pregnancy (about 1/200 for chorionic villus sampling (CVS) and 1/300-1/600 for amniocentesis) [13]. Chromosomal aneuploidy was detected in three of the patients who underwent amniocentesis. In two of them, the family terminated the pregnancy, and the fate of the third woman's pregnancy is unknown since she continued her follow-up in an external center. The benefits of screening programs should be more pronounced than the adverse physical and psychological effects that may occur from participating in the screening program. It is essential to inform society adequately about the screening test, considering the anxiety that the screening tests may cause to pregnant women in our study, in which the rates of patients found to be at high risk as a result of screening tests are also examined. This is one of our study's most critical clinical results.

When the literature is examined in detail, it has been shown in studies that although screening tests have benefits, the obtained risk estimation significantly increases the anxiety level of pregnant women [14]. If an increased risk is detected in terms of chromosomal anomaly in the screening test, performing these screening tests in cases that will not go to the diagnostic test or terminate the pregnancy does not mean anything other than unnecessary cost and an increase in the anxiety rate in patients. Similar to our study, in the study of Kömül et al. concluded that it is essential that prenatal screening tests can be used more effectively by informing families about Down syndrome in detail. Thus, the expenditures made for screening tests for cases that do not want termination are used to solve the health problems of live-born Down syndrome cases, increase the quality of life, and reintegrate them into society. Kömül et al. stated that it will be more effective [15]. Therefore, some studies stated that these high-risk cases should be followed carefully throughout pregnancy [16,17]. The idea that maternal serum PAPP-A and ß-hCG values may also be significant in predicting complications in the advancing gestational weeks, apart from determining the risk of chromosomal anomaly prompted researchers to conduct numerous studies on this subject [18,19]. In other studies, significant correlations were found between pregnancy complications such as gestational diabetes, low birth weight, high birth weight, intrauterine growth restriction and preterm labor, and maternal serum PAPP-A and ß-hCG values [20,21]. On the other hand, Morssink et al. also stated that first-trimester PAPP-A and ß-hCG values were not significantly associated with preterm labor [22]. While examining the results of the cases in our study, we also investigated whether there is a relationship between PAPP-A and ß-hCG values of pregnant women who need admission to the neonatal intensive care unit (NICU) for their babies. However, it did not detect a statistically significant association. In addition, there is no statistically significant relationship between the birth weight of newborns and PAPP-A measurement values and ß-hCG values in pregnant women ($p>0.05$).

The body weights of the cases with risk in the first-trimester screening test were statistically significantly higher than those

without risk (p=0.001; p<0.01). In addition, the risk rate in the double or triple screening test of smokers was statistically significantly higher than that of non-smokers (p=0.049; p<0.05). Our findings, in line with the literature, support that maternal body weight and smoking effectively increase the risk of chromosomal anomalies [23]. We think the relationship of some pregnancy-related biochemical markers with pregnancy complications and possible complications in the newborn in the postnatal period will be revealed in different studies, including more extensive case series.

In conclusion, the aim of prenatal diagnosis applications is not only to detect anomalies in fetal life but to terminate such pregnancies. To provide necessary counseling on many issues, such as ensuring the preparation of the required conditions for postnatal care and enabling prenatal treatment of the affected fetus. Screening tests for chromosomal aneuploidies do not definitively say whether the fetus is abnormal. It can only tell whether the fetus has a low or high probability of having this condition.

Conversely, a diagnostic test can definitively tell if the fetus is abnormal. In this regard, it can be said that counseling for pregnant women is not sufficient. Accurate and effective prenatal screening tests are vital for adequate prenatal diagnosis. We emphasize the importance of these prenatal tests and reporting the patients correctly.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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