

# Comparing the First Trimester and Second Trimester Screening Programmes for the Screening of Down's Syndrome

## DOWN SENDROMU TARAMASINDA İLK TRİMESTER TARAMA TESTİ İLE ÜÇLÜ TESTİN KARŞILAŞTIRILMASI

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### Summary

**Objective:** To compare the first trimester screening test and the triple test for sensitivity, specificity, false positive and negative rates in the screening for Down's Syndrome. The two tests are also compared for the detection of other fetal complications like neural tube defects, in utero exitus, gastroschisis, hydronephrosis, and etc.

**Setting:** Marmara University Hospital Department of Obstetrics and Gynecology, Fetal – Maternal Unit

**Material and Method:** 122 patients with gestational ages between 11 weeks and 13 weeks and 6 days who had given consent for the study have been enrolled. Both the first trimester screening test and the triple test have been applied to all these pregnancies and amniocentesis is performed when there was an indication for a diagnostic test as a result of increased risk due to one or both of the tests or due to patient's anxiety. All the pregnancies were followed till birth.

**Results:** Among the 122 patients enrolled into the study there was one trisomy 21 fetus and there were 6 fetuses with different complications as holoprosencephaly in one, hydronephrosis in two, gastroschisis in one and in utero exitus in two. First trimester screening programme had high-risk for 4 and triple test had high-risk for 12 of the 122 pregnancies. A total of 23 amniocentesis were performed leading to a total of 18.8% invasive test rate; 3.3% for first trimester screening test, 8.2% for triple test and 7.4% for the anxiety of patients. For Down's Syndrome first trimester screening test had 100% sensitivity and 97.52% specificity while triple test had 100% sensitivity and 90.90% specificity. For other fetal abnormalities, sensitivity and specificity of first trimester screening were 33.3% and 98.3% respectively. Sensitivity and specificity of the triple test were 100% and 94.8% for these other fetal abnormalities.

**Conclusion:** The increased sensitivity of the triple test for picking up the other fetal abnormalities was thought to be the result of AFP measurement. It seems wise to screen for Down's syndrome with the first trimester screening programme and then screen for other fetal abnormalities during the second trimester by measuring maternal serum AFP level only. However, these findings should be validated by randomized large series, in multi-centre studies.

**Key Words:** First trimester screening programme, Triple test, Trisomy 21

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### Özet

**Amaç:** Bu çalışmanın amacı Down Sendromu taraması için kullanılan ilk trimester tarama testi ve üçlü testin sensitivite, spesifisite, yalancı pozitif ve negatif oranlarının karşılaştırılmasıdır. Ayrıca her iki test nöral tüp defektleri, in utero ölümler, gastrosizis ve hidronefroz gibi diğer fetal anomalilerin risklerini tespit edebilme açısından da karşılaştırılmıştır.

**Çalışmanın Yapıldığı Merkez:** Marmara Üniversitesi Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum AD, Fetal – Maternal Tıp Ünitesi

**Materyal ve Metod:** Gestasyonel yaşları 11 hafta ile 13 hafta 6 gün arasında olan ve çalışma için onay veren 122 hasta çalışmaya alınmıştır. Gebelere hem ilk trimester tarama testi hem de üçlü test uygulanmış ve bir veya her iki testte de riski yüksek çıktığı için endikasyonu olan veya tamsal test isteği bulunan hastalara amniyosentez yapılmıştır. Tüm gebeler doğuma kadar izlenmiştir.

**Bulgular:** Çalışmaya alınan 122 gebeden birinde Down Sendromlu fetus saptanmıştır. Ayrıca bir holoprozensefali, iki hidronefroz, bir gastrosizis ve iki in utero ölüm olmak üzere toplam altı tanede diğer fetal anomali mevcuttur. Bu 122 hastanın tarama testlerinin sonucunda ilk trimester tarama testi 4 gebede ve üçlü test de 12 gebede yüksek riskli olarak tespit edilmiştir. Toplam 23 amniyosentez yapılmış olup, bu %18.8'lik bir girişimsel test oranı oluşturmaktadır. İlk trimester tarama testi sonucu riski yüksek çıktığı için %3.3, üçlü test sonucu riski yüksek çıktığı için %8.2 ve hasta isteği nedeniyle de %7.4 oranlarında girişimsel test uygulanmıştır. Down Sendromu için ilk trimester tarama testi %100 sensitivite ve %97.52 spesifisiteye sahipken, üçlü test için sensitivite yine %100 ve spesifisite de %90.90 olarak tespit edilmiştir. Diğer fetal anomaliler için ise ilk trimester tarama testinin sensitivitesi %33.3 ve spesifisitesi %98.3; üçlü testin sensitivitesi %100 ve spesifisitesi de %94.8 olarak bulunmuştur.

**Sonuç:** Diğer fetal anomalilerin riskini üçlü testin daha iyi tespit edebilmesi AFP ölçümüne bağlanmıştır. Down Sendromu taramasının ilk trimester tarama testi ile yapılması ve takiben diğer fetal anomaliler için tarama amaçlı ikinci trimesterde sadece AFP bakılması uygun bir yaklaşım gibi görünmektedir. Ancak bu bulguların geniş serili randomize ve çok merkezli çalışmalarda teyit edilmesi gerekmektedir.

**Anahtar Kelimeler:** İlk trimester tarama testi, Üçlü test, Trizomi 21

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All pregnant women, no matter what age they are, face the risk of giving birth to a physically or mentally handicapped baby to some extent. In some cases this handicap is due to a chromosomal abnormality like Down's Syndrome. It is well clear now that the risk of having a chromosomally abnormal fetus increases with age. As a result, increased maternal age was the first screening method used in identifying the high-risk population for chromosomal defects. If the cut-off point for age is taken to be 35 then 5% of the population would be considered as having high-risk and 30% of the Down's babies would be detected (1).

During 1980s, a screening programme called triple test is introduced for the screening of Down's Syndrome which incorporates maternal serum levels of unconjugated estriol (uE3), alpha-feto protein (AFP), and human chorionic gonadotrophin (HCG) levels at 16<sup>th</sup> weeks of gestation. Triple test was sure a better screening test than maternal age alone for the screening of Down's Syndrome with a 60% detection rate (1).

Then during the 1990s first trimester screening test which incorporates the age of the mother, the ultrasonographically measured nuchal translucency of the fetus and the maternal serum levels of pregnancy associated plasma protein A (PAPP-A), and beta-human chorionic gonadotrophin ( $\beta$ -HCG) during 11-14 weeks of gestation is introduced. In different studies the detection rate for Down's Syndrome has been stated to be 46% for maternal age and  $\beta$ -HCG combination, 48% for maternal age and PAPP-A combination, 73% for maternal age and nuchal translucency combination and 67% for maternal age,  $\beta$ -HCG and PAPP – A combination. However, the detection rate reaches 90% when maternal age, fetal nuchal translucency, maternal serum  $\beta$ -HCG and PAPP-A levels are used in combination for the calculation of Down's risk (1-4).

An effective screening test with a high sensitivity and specificity and a low false positive rate is needed because the only diagnostic test is either amniocentesis or chorion villus sampling which each has a 1% risk of miscarriage (5). Using an effective screening test would enable us to select high-risk patients more efficiently and would decrease the miscarriage rates due to invasive tests.

The objective of this study is to compare the first trimester screening test and the triple test for sensitivity, specificity, false positive and negative rates in the screening for Down's Syndrome. The two tests are also compared for the detection of other fetal complications like neural tube defects, in utero exitus, gastroschisis, hydronephrosis, and etc.

### Material and Method

122 patients with gestational ages between 11 weeks and 13 weeks and 6 days who had been admitted to Mar-

mara University Hospital Obstetrics Clinic, and who had given consent for the study have been enrolled into the study. Both the first trimester screening test and the triple test have been applied to all these pregnancies and amniocentesis is performed when there was an indication for a diagnostic test as a result of increased risk due to one or both of the tests or due to the patient's anxiety.

The nuchal translucency is measured by using a 3.5 MHz multi-frequency (between 2-5) broad convex probe of a Logic 500 Pro real-time Doppler ultrasonography machine. Maternal serum AFP and HCG levels are measured by using electro-chemiluminescence immunoassay (ECLIA), free  $\beta$ -HCG is measured by using two site immunoradiometric assay (IRMA), uE3 level is measured by using radioimmunoassay (RIA) and PAPP-A is measured by using ELISA sandwich type method.

The first trimester risk is calculated by using the First Trimester Screening Programme of the Fetal Medicine Foundation which incorporated the maternal background risk and age, fetal nuchal translucency measurement and the maternal serum  $\beta$ -HCG and PAPP-A levels. This test is performed between the gestational ages of 11 weeks and 13 weeks and 6 days. Triple test risk is calculated by using the maternal background risk and age and serum levels of  $\beta$ -HCG, AFP and uE3 between 16 weeks and 17 weeks and 6 days of gestation by a computerized programme.

A risk of more than 1 in 300 is considered to be high risk for both tests. And in those who had indications, an ultrasonography-guided amniocentesis is done by using a 20 G 12 cm needle and amnion fluid is cultured according to normal amniocyte culture techniques. The results are obtained within 15-20 days of the amniocentesis.

All the pregnancies were followed till birth and any fetal abnormality at birth is noted. Fetal karyotype is obtained for those who have been suspected of a chromosomal abnormality at birth if amniocentesis had not been performed. Sensitivity, specificity, positive and negative predictive values for each test is calculated and the results are then compared.

### Results

Among the 122 patients enrolled into the study there was one trisomy 21 fetus and the patient was detected by both the first trimester screening programme and the triple test. Since the patient was 33 years of age, if age was used for screening this patient would not have been detected. Other than this there were 6 fetuses with different complications as holoprosencephaly in one, hydronephrosis in two, gastroschisis in one and in utero exitus in two.

First trimester screening programme had high-risk for 4 of the 122 and triple test had high-risk for 12 of the 122 pregnancies. In 2 of the patients who had high-risk in the

triple test, AFP was elevated and therefore the risk for neural tube defects was increased. All the high-risk patients in the first trimester screening programme agreed to have an amniocentesis while only 10 of the 12 high-risk patients in the triple test did so. Other than these, amniocentesis has been done to 9 other patients because they were anxious about their age and their risk for having a Down's baby. Therefore a total of 23 amniocentesis were performed leading to a total of 18.8% invasive test rate; 3.3% for first trimester screening test, 8.2% for triple test and 7.4% for the anxiety of patients.

The sensitivity, specificity, positive and negative predictive values of each test for Down's Syndrome is shown in Table 1. As can be seen both tests are 100% sensitive for detecting Down's Syndrome. However, the specificity of first trimester screening programme is better than triple test's with a 97.52% to 90.90%. As a result it can be concluded that both can detect the real Down's patients while first trimester screening programme is better than triple test in detecting the ones that are not Down's. As a result of this it is obvious that when first trimester screening programme is used, less invasive tests would be necessary for at least the same sensitivity. Also the positive predictive value of first trimester screening programme is better than triple test's while the negative predictive values seem to be the same. Overall the accuracy of first trimester screening test is better than triple test's (Table 1).

When the other pregnancy complications like holoprosencephaly, hydronephrosis, gastroschisis and in utero excitus is taken into account then the sensitivity of the triple test becomes much better than the sensitivity of the first trimester screening programme by 100% to 33.3%. As was the case in our study and is known maternal serum AFP levels are increased in holoprosencephaly, gastroschisis and hydronephrosis. From these results it can be concluded that triple test is more sensitive for other fetal abnormalities most probably due to its maternal AFP level component. The sensitivity, specificity, positive and negative predictive values and accuracies of the two tests for other fetal abnormalities are presented in Table 2.

### Discussion

Down's Syndrome or Trizomy 21 as the optional name, is the presence of a segment or the whole of the 21<sup>st</sup> chromosome in triple copies instead of the normal double. This can be a result of non-disjunction (as in 95 % of the cases), translocation or mosaism (6). In 1966, it became possible to prenatally diagnose this syndrome with the introduction of karyotyping of the amniotic fluid cell cultures (7,8). However prenatal diagnosis had a 1% miscarriage risk (5) and was an expensive method; therefore, it was not going to be cost-effective to offer this prenatal diagnostic test to every pregnant women. Then the question

**Table 1.** The sensitivity, specificity, positive and negative predictive values and accuracy of the first trimester screening programme and the triple test for detecting Down's Syndrome are presented.

For Down's Syndrome	First Trimester Screening	
	Programme	Triple Test
Sensitivity	100 %	100 %
Specificity	97.52%	90.90 %
Positive Predictive Value	25 %	8.3 %
Negative Predictive Value	100 %	100 %
Accuracy	97.53 %	91 %

**Table 2.** The sensitivity, specificity, positive and negative predictive values and accuracy of the first trimester screening programme and the triple test for detecting fetal abnormalities like holoprosencephaly, gastroschisis, hydronephrosis and in utero exitus are presented.

For Other Fetal Abnormalities	First Trimester	
	Screening Programme	Triple Test
Sensitivity	33.3 %	100 %
Specificity	98.3 %	94.8 %
Positive Predictive Value	50 %	50 %
Negative Predictive Value	96.6 %	100 %
Accuracy	95.1 %	95.1 %

of who should be karyotyped prenatally is raised and from that time on screening methods to identify high-risk pregnancies for Down's Syndrome is being sought.

In 1970s, Shuttleworth realized the association between increased maternal age and Down's Syndrome. When first described, 40 years was the cut-off point and every pregnant woman more than 40 years of age were offered prenatal diagnostic test. Then this cut-off was defined to be 35 years. The pregnant women who were older than 35 years of age made up 5% of all the pregnancies; however, only 30% of Down's babies were born from this age group (1). Moreover, over the years especially in the more developed countries, 35 year or older pregnant women started to increase, making up nearly 10% of the population. This meant losing more normal babies as a result of miscarriage due to invasive tests. Therefore, a more sensitive and specific screening method is sought. And in 1980s triple test was introduced, which incorporated the maternal background risk and age along with three serum markers as uE3, HCG and AFP. By using this test for a screening method 60% of Down's pregnancies could be detected for a 5% invasive test rate (1). 1990s was a new era for the screening for Down's Syndrome with first the introduction of fetal nuchal translucency measurement and incorporating this with maternal background

risk and age produced a 75% detection rate for a 5% invasive test rate and then adding maternal serum markers as PAPP-A and  $\beta$ -HCG, further increased the detection rate to 90% for the same 5% invasive test rate (1-4,9).

In our study, increased risk for Down's Syndrome was observed in 4 of the first trimester screening tests and in 12 of the triple tests. All 4 high risk ones in the first trimester screening agreed for an invasive test while only 10 of the high risk ones in the triple test agreed for it. As a result of the invasive tests performed, only one Down's baby was found. And no additional Down's Syndrome was detected at birth. This meant a 100% sensitivity for both tests, but the invasive test rate was 3.3% for first trimester screening test and 8.2% for triple test. And it would have been even higher, 9.8% if all of the high-risk patients on the triple test have agreed for an invasive diagnostic test. It should be noted that the patient was 33 years of age, so if screening was done according to maternal age alone, this Down's baby would not have been prenatally diagnosed.

Pajkrt E., et al. published their results of 1473 low risk pregnancies whom have been screened by using nuchal translucency measurement (10). They presented a 78% detection rate for a 8.1% invasive test rate when the cut-off was taken to be 1 in 100 and the detection rate increased to 100% for a 19.1% invasive test rate if the cut off is increased to 1 in 300. If maternal age was used for screening in this same study, 67% detection rate would have been reached for a 24% invasive test rate. So they concluded that the nuchal translucency screening between 11-14 weeks of gestation was an efficient way of screening for Down's Syndrome in the low-risk pregnancies. In our study, we would not have been able to detect the Down's baby for a 39% invasive test rate if we had used maternal age for screening. And first trimester screening programme produced the same result as triple test for a less invasive test rate.

Michailidis GD, et al. presented their data of 7447 pregnancies and stated a 87% prenatal detection rate for a 8.5% invasive test rate. 74% of the affected fetuses were recognized by first trimester ultrasonography and half of those missed by it could be picked up by the second trimester biochemistry screening. This further increased the sensitivity of the combination of first trimester ultrasonography and triple test to 90.5% for a 4.2% invasive test rate. Karyotyping those older than 35 years of age with a negative screen resulted in the identification of no more affected fetuses. As a result they concluded that first trimester nuchal translucency screening is an effective screening method and when triple test is combined with it the effectiveness further increases but delay in diagnosis till the second trimester is an important handicap of this method.

So they proposed biochemical screening in the first trimester at the time of ultrasound scan for the nuchal translucency (11). Likewise, sensitivities for nuchal translucency, triple test and combining the nuchal of the first trimester and triple test of the second were reported to be 75%, 60% and 90% respectively in a study of 4130 pregnant patients who were older than 38 years (12). Our data supports the idea of combining the biochemical markers and nuchal translucency in the first trimester for the screening of Down's being more effective than waiting for the second trimester and doing a triple test.

We also tried to find out if there was any difference between the two screening programmes for other fetal abnormalities like holoprosencephaly, gastroschisis, hydronephrosis, etc. The sensitivity of first trimester screening test for these abnormalities was found to be 33% which was very low when compared to the 100% of the triple test's. Specificities, positive and negative predictive values and the accuracies were similar for both tests. The increased sensitivity of the triple test for picking up these other fetal abnormalities was thought to be the result of AFP measurement. It seems wise to screen for Down's syndrome in the first trimester with a combination of fetal nuchal thickness, maternal serum PAPP-A and  $\beta$ -HCG and then screen for other fetal abnormalities during the second trimester by measuring maternal serum AFP level only. However, these findings should be validated by randomized large series, multi-centre studies.

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