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Positive Predictive Value of Screening Tests in the First and Second Trimester of Pregnancy in the Diagnosis of Trisomy 21, 18, and 13 Using Amniocentesis

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ABSTRACT

Background: The aim of this study is to analyze the positive predictive value (PPV) of trisomies 21, 18 and 13 at first and second trimester using amniocentesis for clinical practice.

Methods: : This is a descriptive cross-sectional study in which data were extracted from a cohort project of mother and infant conducted between March 2016 and February 2021 among 3110 pregnant women in Yazd city.

Results: Out of 3110 pregnant women, 84 mothers were at high risk in the screening tests of the first and second trimesters of pregnancy and therefore were candidates for amniocentesis. None of them were detected by the positive amniocentesis method. The mean age of mothers was 33.2 years. The causes of amniocentesis included old age (45.9%), positive results of Down syndrome screening (23%), high NT ultrasound (4.9%), and pathological results of anomaly scan sonography (3.8%).

Conclusion: In this study, the PPV was zero and the number of false positives in screening tests was 84 (100%). This may be because our population was normal and had no history of genetic abnormalities or other special conditions.

Introduction

The most common chromosomal abnormalities are trisomy 21, also referred to as Down's Syndrome (DS), trisomy 18, which is also known as Edwards' syndrome (ES), and trisomy 13.[1] The incidence of trisomy 21 increases with the age of the mother. Therefore, trisomy 21 screening and diagnosis for the fetus is an important subject for pregnant women over 35 years old and other high-risk mothers.[2]

First-trimester screening (FTS) is a valid screening method for major chromosomal aneuploidies.[3] FTS considers a combination of maternal age, Nuchal translucency (NT) Scan, and maternal serum. This maternal serum screening is done by a combination of two biochemical markers including serum free β-human chorionic gonadotrophin (free β-hCG) and pregnancy- associated plasma protein A (PAPP-A).[2] FTS is performed at 11 to 13 weeks of pregnancy; using ultrasound to scan the fetal neck for enlarged NT. Increased NT is associated with not only trisomy 21 but also with other chromosomal abnormalities.

Second-trimester screening with quadruple marker test or quad screen has been replaced by FTS due to earlier diagnosis of chromosomal abnormalities, higher detection rates, and use of increased NT as a marker of cardiac abnormalities and other structural defects.[4] The main objectives of the second trimester are as follows: To identify the relationship between quad test or second-trimester serum markers, consisting of alpha-fetoprotein (AFP), unconjugated estriol (uE3), free β-human chorionic gonadotrophin (β-hCG) and inhibin-A (IHA).[5,6] Ultrasound (USG) has become an important part of obstetrics and gynecology care for the health of the fetus and the diagnosis of prenatal abnormalities.[7]

Women at high risk may receive genetic counseling or more invasive testing.[2] Identification of any of these findings warrants further counseling and possible referral to a prenatal diagnostic center with the option of invasive testing for fetal karyotyping.[7]

Invasive prenatal diagnosis for fetal trisomy is usually based on high-risk mothers, abnormal FTS, abnormal ultrasound findings, or second-trimester abnormalities. However, data on the PPV of these screening modalities and the resulting incidence of termination of pregnancy (TOP) in case of a positive result are scattered.[8] Although sensitivity and specificity are important performance metrics, PPV and negative predictive value (NPV) become more clinically relevant after results have returned.[9] The PPV analysis showed that the more the number of indications is more; the PPV tends to be maximized.[10]

Invasive prenatal diagnosis tests obtain the sampling of fetal genetic material through amniocentesis or chorionic villus sampling (CVS).[11] The invasive procedures may still result in intrauterine infection or miscarriage. Therefore, the invasive prenatal diagnosis is not accepted by some pregnant women. Non-invasive prenatal screening (NIPS) is the alternative for these women.[11,12] Diagnosing the chromosomal abnormalities and fetal disorders in the early stages of pregnancy can prevent future adverse conditions for the infant and his/her family.[13]

We performed a retrospective cohort study and screened key maternal serum biomarkers in 3110 pregnant women with old age and other risk factors. Then we analyzed the PPV of trisomy 21, 18, and 13 in high risk pregnant women of Yazd. The PPV of first and second screening tests was not investigated in Yazd so in this study we aimed to evaluate the PPV of the first and second-trimester screening tests for identifying high-risk mothers and fetal chromosomal disorders in pregnant women. On the other hand, our aim was to investigate the reliability of maternal serum screening for high-risk pregnant women in the first and second trimesters of pregnancy.

Materials and Methods

This cross-sectional descriptive study was

conducted between 2016 and 2021 in Yazd city. The data were extracted from the mother and infant cohort study (MICS) in Yazd conducted by Shahid Sadougi University of Medical Sciences and registered in the relevant system. Data included demographic information, screening results, and maternal ultrasound. Then, the data were analyzed by descriptive statistics.

Research Methods: The data needed for the research was obtained from the information recorded in the Yazd mother and baby cohort system. In this cohort, the mothers were informed about the work process by experts in a briefing session. Each participant read and signed the informed consent form. They were examined by a gynecologist. Questionnaires of pregnant mothers were completed. Their blood samples were used for preliminary tests. The results of the tests requested by the specialist (including screening tests of the first and second trimesters of pregnancy for trisomy 21, 18 and 13) and ultrasound were recorded in the system. If any of the tests were positive (high-risk mother), the patient was recommended for amniocentesis by a specialist and the results were recorded in the system, and these results were used in this research.

Subjects: A total of 3110 pregnant women who were referred to participating hospitals after 12 weeks of pregnancy, participated in our cohort study. The inclusion criteria were: Gestational age more than 12 weeks, singleton pregnancy and participation in the Yazd cohort study. The exclusion criteria included: Mothers who were visited after the 20th week, non-Iranian women, and mothers who migrated to other cities.

Results

This study was carried out with the special purpose of positive predictive value of screening tests in the first or second trimester of pregnancy; that the amount of positive predictive value was zero and the number of false positive cases was 84. In this study, among the 3110 pregnant mothers who were examined in the cohort, 84 people underwent amniocentesis, and all of them had a negative amniocentesis (normal karyotype).

Patient characteristics: The maternal age ranged from 19 to 40 years of age with a median of 32.3, and 33 cases were older than 35 years. The average weight of the mothers was 64.74 with a minimum of 39 and a maximum of 92 kg, and their average height was 160.79 with a range of 146 to 175 cm. None of the mothers had diabetes and were non-smokers; one of the mothers had twins. None of the mothers had children with congenital anomalies or Down syndrome. The mean NT of mothers was 1.82 mm with a range of variation of 0.5 to 3.2. None of the mothers used assisted reproductive methods to conceive.

Frequency of mothers based on age: According to Table 1, from the total information of 75 pregnant mothers, the number of mothers with high-risk age was 33 (44%) and the number of mothers with low-risk age was 42 (56%). So half of the mothers in the age group were high risk and half of them were in the low risk group.

Number of pregnancies: According to Table 1, the information of 75 pregnant mothers is available. The number of first and second time mothers were 14 (18.7%) and 23 (30.7%), respectively. The number of third time mothers was 27 (36%). Nine participants (12%) were fourth time mothers, and 2 mothers (2.7%) became pregnant 5 times. Therefore, most of the mothers were in their third pregnancy, which is not a high number.

History of abortion: Of the total of 73 people whose information is available, the number of mothers who have not had a history of previous abortion was 55 (75.3%), the number of mothers who have had a history of 1 previous abortion was 13 (17.8%), the frequency of mothers who have had a history of 2 previous abortion was 4 (5.5%). The number of mothers who had a history of 4 previous abortions was 1.4%. Most mothers had a history of 1 abortion, which is not a large number (Table 1).

Table 1. Characteristics of Mothers (Age, Number of pregnancies and Previous Abortions)

Frequency of mothers based on age	Number of mothers	Percentage of mothers
Old age (≥ 35)	33	44
Young age (< 35)	42	56
Total	75	100
Number of pregnancies	Frequency of mothers	Percentage of mothers
1	14	18.7
2	23	30.7
3	27	36
4	9	12
5	2	2.7
Total	75	100
Number of previous abortions	Frequency of mothers	Percentage of mothers
0	55	75.3
1	13	17.8
2	4	5.5
3	1	1.4
Total	73	100

Causes of amniocentesis in mothers: According to Figure 1, the reason for amniocentesis of the mothers was as follows: 28 people (45.9%) due to old age, 14 people (23%) at high risk of Down syndrome in the screening test, and 7 people (11.5%) average risk of Down syndrome in screening test, 5 people (8.2%) simultaneously with risk of Down syndrome and old age, 3 people (5 %) NT measurement ≥ 3mm, 1 person (1.6%) high risk of trisomy 18 and 13 in the screening test, 1 person (1.6%) due to thalassemia minor of the mother, 1 person (1.6%) due to the swelling of the fetal kidney in the ultrasound and 1 person (1.6%) due to the short nasal bone of the fetus in the ultrasound scan. Amniocentesis was performed to diagnose genetic disorders. The reason for amniocentesis was not available in 22 cases. Therefore, the most common reason was related to old age and high risk of Down syndrome in the screenings.

Risk of trisomies in the screening of the first and second trimester screening: According to the table 2, among the people who have performed FTS *(First trimester screening)* screening, 11 people (24.4%) had high risk, 26 people (57.8%) had moderate risk, and 8 people (17.8%) had low risk of Down syndrome (trisomy 21). Some mothers at moderate risk of Down syndrome were referred for amniocentesis with a doctor's diagnosis, and others had amniocentesis for other reasons. For trisomy 18, one person (2.2) was at high risk, 3 (6.7) were at moderate risk, and 41 (1.91) were at low risk. For trisomy 13, one person (2.2%) had high risk, 4 people (8.9%) had moderate risk, and 40 people (88.9%) had low risk. Among the people who performed the quad test, 5 people (83.3%) were at high risk, 1 person (16.7%) was at moderate risk of Down syndrome. Among mothers who had the test and were available, none were at low risk.

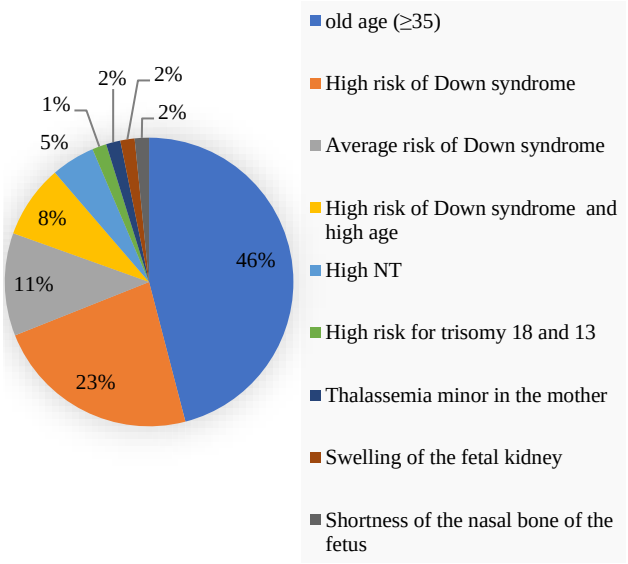

Figure 1. Causes of amniocentesis in mothers

Table 2. Prevalence of the Risk of Trisomies in the Screening of the First and Second Trimester

Screening risk		First combined test			Second combined test		
		T 21	T18	T13	T21	T18	T13
High risk (≥1.250)	N (%)	11 (24.4)	1 (2.2)	1 (2.2)	5 (83.3)	0	-
Moderate risk (1.250-1.1500)	N (%)	26 (57.8)	3 (6.7)	4 (8.9)	1 (16.7)	1 (16.7)	-
low risk (<1.2500)	N (%)	8 (17.8)	41 (91.1)	40 (88.9)	0 (0)	5 (83.3)	-
Total		45 (100)	45	45	6	6	-

For trisomy 18, one person (16.7) showed moderate risk and 5 people (83.3) showed low risk for this trisomy, and the high-risk number was zero. Therefore, the number of subjects with a high risk of trisomy was small.

FTS: According to Table 3, from the total of 55 mothers whose NT values are available, 4 cases (7.27% of mothers) had an NT value greater than 3 mm (high risk) and 52 cases (92.72%) were at low risk. More Mothers were in the low- risk group in terms of NT. As can be seen in Table 3, of the 46 subjects who had β-hCG and PAPP_A tests registered, the multiple of the median (MoM) value for high-risk hCG-β, i.e. more than 1.5, was observed in 24 subjects (52.17%), and MoM was less than 1.5 in 22 mothers (47.82%). The MoM value for PAPP_A ≤ 0.5 was considered high risk and seen in 17 mothers (36.95%). Twenty nine mothers (63.04%) had PAPP_A level more than 0.5. Therefore, according to β-hCG, about half of the mothers were in the high-risk group, and according to PAPP_A, most of the mothers were in the low-risk group.

QUAD TEST in second trimester screening: According to Table 4, quadruple data for AFP are available from 7 mothers, one mother (16%) had a minimum AFP MoM value of 0.53. The protein results of the other five mothers include values of 0.55, 0.56, 0.67, 0.78, and 0.81. One mother had a maximum MoM AFP value of 1.01. The mean AFP was 0.67 and all mothers had AFP MoM less than 2 and screened negative.

Table 3. NT Amount in NT Ultrasound and B-hCG and PAPP-A Values in FTS

Biomarker amount	Frequency	Percentage
NT amount		
NT < 3mm	51	92.72
NT ≥ 3mm	4	7.27
Total	55	100
β_hCG < 1.5	22	47.82
β_hCG ≥ 1.5	24	52.17
Total	46	100
PAPP_A ≤ 0.5	17	36.95
PAPP_A > 0.5	29	63.04
Total	46	100

According to Table 4, the average βhCG was 1.67. Five mothers had βhCG MoM below 2 and were negative in screening. One mother had a βhCG MoM of 3.55 and was at high risk. Also, the average uE3 MOM was 2 and the uE3 MOM of five mothers was normal and above 0.5 but one mother's uE3 MOM was 0.35 and at high risk. The average inh-A MOM was 2 and most mothers had normal levels of inh-A MOM, just one mother's inh-A MOM was more than two.

According to Table 5, the ultrasound information of 27 people was available. Those sonographic markers were normal for all of these people except for one person whose fetal nasal bone length was shorter than normal.

Table 4. The Amount of AFP, βhCG, uE3 and inh-A in the Quad Test of Mothers

Marker	Mean ± SD	Median	Maximum	Minimum	Number of mothers	Total
AFP	0.70 ± 0.17	0.67	1.01	0.53	7	100
βhCG	1.91 ± 0.83	1.67	3.55	1.21	6	100
uE3	0.80 ± 0.34	0.83	1.34	0.35	6	100
inh-A	1.58 ± 0.456	1.63	2.12	0.97	6	100

Table 5. Risk of aneuploidy depending on the soft marker detected on ultrasound

Soft marker	Number of mothers with normal markers	Number of mothers with abnormal markers
Nuchal fold thickness	27	0
Nasal bone length	26	1
Ventriculomegaly	27	0
Hyperechogenic bowel	27	0
Echogenic intracardiac	27	0
Choroid plexus cyst	27	0
Pyelectasis	27	0
Short femur & amp; humerus	27	0

Discussion

In the present study, we combined the data from 5 years of screening in the Yazd cohort study after the first and second prenatal screening policies by evaluating the PPV of different referral categories after invasive testing. Previous studies evaluating trisomy screening showed that the risks of T18 and T13 were small as part of a combination trial, but the combination trial nevertheless picked up more cases of T21.[8] According to previous studies, the probability of positive FTS is directly influenced by many factors, including maternal age and gestation. Amniocentesis is necessary for all FTS-positive mothers and will almost always detect chromosomal abnormalities.[14]

The results of our study on the causes of amniocentesis showed that the most common indications were older age, more than 35 years (46%), high risk of Down syndrome (23%) and average risk of Down syndrome (11.5%) in the screening test. The positive result of maternal serum screening, which accounts for more than half of the amniocentesis cases in our population (42%). In our study, the PPV for aneuploidies at karyotyping following amniocentesis after referral for abnormal screening findings was zero for all screening tests.

The most similar study to ours is Siljee and et al. They evaluated PPV for detection of trisomies 21, 18 and 13 and termination of pregnancy rates after referral for advanced maternal age. They showed that for referral from advanced maternal age (AMA), the PPV for T21 was 1.0% for amniocentesis and 1.8% for chorionic villus biopsy (CVB); for the combined test at a maternal age ≥ 36 years, these percentages were 4.9% and 12.5%, respectively and for maternal age < 36 years, 4.4% and 8.1%, respectively.[8]

According Li, et al., FTS is an effective means of screening for trisomy 21 in Southeast Asian populations. The PPV of FTS in detecting trisomies 21, 18 and 13 at 1:1,000 selected risk cut‐offs was 5.64%.[3] In another study that was performed in Iran by Heidari et al., predictive value of FTS markers for Down Syndrome (DS) in Iranian Pregnancies was evaluated. The PPV for PAPP-A, β-hCG, NT, and NB were 60.99%, 46.51%, 55%, and 100%, respectively. They concluded the novel decision-tree model base on serum markers revealed a better predictive value to achieve high sensitivity and specificity of first trimester DS screening in Iranian population.[15] Yassaee et al., in a comparative study evaluated amniocentesis following positive first trimester combined screening. Only 17.1% cases out of 70 (mothers with positive FTS) showed positive amniocentesis, which had a significant relationship with chromosomal abnormality. First trimester combined screening has very high accuracy (94.6%) in prediction of genetic abnormalities.[14] Abib et al. in Brazil evaluated first-trimester combined screening test for aneuploidies. The results of 2,748 patients were analyzed. The first trimester combined test achieved PPV of 6.91% and negative predictive value (NPV) of 99.76%. They concluded the combined test of

aneuploidy screening showed a detection rate inferior to those described in the literature for a higher FP rate.[16]

However according to Shirazi et al., the sensitivity of the first-trimester test was more than sensitivity of second- trimester screening but specificity of the second-trimester test more than sensitivity of first -trimester screening.[13] Ali Akbari et al., analyzed indications of amniocentesis and PPV of cytogenetic findings of chromosomal abnormalities. In their work the PPV analysis showed that the more the number of indications; the PPV tends to be maximized. Investigating indications and results of embryonic amniocentesis samples in the present study indicates the importance of genetic screening for the identification of chromosomal abnormalities in 5.5% of pregnant women.[10] Dar et al., said PPVs are more valuable to clinicians than detection rates. When the detection rate is close to 100% (as in the case for trisomy 21), it may provide a misleading view on noninvasive prenatal testing (NIPT) and suggest that it is actually a diagnostic test.[17]

Most studies evaluated PPV of non – invasive prenatal screening (NIPS) and few study assessed PPV of invasive prenatal screening such as amniocentesis. The studies evaluated PPV of NIPS reported range of 1 to 93 percent. Petersen AK et al. evaluated PPV estimates for cell-free NIPS from data of a large referral genetic diagnostic laboratory. Their results showed the PPV for trisomy 13, 18, and 21 were consistent with previous reports at 45%, 76%, and 84%, respectively.[12]

Neufeld-Kaiser et al., evaluated PPV of NIPS for fetal chromosome disorders. They reported the PPV for all conditions included in the screen was 77.4 % (95 % CI, 63.4-87.3).[9] Zhu and et al. evaluated efficiency of NIPS in pregnant women at advanced maternal age. Their results indicated the PPV of NIPS for detecting fetal trisomy 21 were 90.98. The PPV parameter for detecting fetal trisomy 18 was 67.92, and for detecting trisomy 13 was 27.78. The prevalence of fetal trisomy 21 increased exponentially with maternal age. The high-risk percentage incidence rate of fetal trisomy 21 was significantly higher in the pregnant women at 37 years old or above than that in pregnant women at 35 to 37 years old.[11] Meck et al., evaluated PPV of NIPS for Aneuploidy. They showed The PPV for NIPS were as follows: 93% for trisomy 21, 58% for trisomy 18, 45% for trisomy 13 and 23% for monosomy X.[18] Cell-free fetal DNA-based NIPS has been proven to be of high sensitivity and specificity for detecting common chromosomal aneuploidies (trisomies 21, 18 and 13), with low false positive and false negative rates. [11] It seems that NIPS had a higher sensitivity specificity and PPV than Invasive prenatal diagnosis, for detecting fetal trisomies 21, 18 and 13 in pregnant women.[11]

In this paper, we investigated the PPV of trisomies 21, 18, and 13 in mothers who referred to our cohort study after a combined first-trimester test or ultrasound and second-trimester findings, but we found that the PPV is very low and zero. Therefore, there is a need for more studies to analyze PPV and suggest improvements for clinical practice.

Conclusion

According to the results, the most common reason for introducing patients to amniocentesis was old age. The results of screening tests and various studies showed that the PPV of screening tests was very low and their false positive rate was very high. It is necessary to significantly decrease the number of unnecessary prenatal interventional diagnoses and improve the efficiency of prenatal screening.

Conflict of Interest

The authors have no conflict of interest.

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The present study was approved by the Ethics Committee of Islamic Azad University/ Yazd Branch (IR.IAU.YAZD.REC.1400.018).

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