Original Article

Relationship between False Positive Screening Results of Down Syndrome and Adverse Pregnancy Outcomes

Abstract

Background: Maternal serum sample screening in the first and second trimesters has been commonly used to identify women who are at risk of fetal trisomy 21. In addition, these serum markers are associated with adverse perinatal outcomes. Hence, the present study was conducted to determine the relationship between false positive screening results of Down syndrome and adverse pregnancy outcomes. **Material and Methods:** This prospective, two-group, cohort study was conducted on 608 pregnant women who had undergone fetal contingent screening. They were selected through convenience sampling in the twentieth week of pregnancy and were followed up until delivery. The raw Odd Ratios (OR), Relative Risk (RR), and adjusted OR of adverse pregnancy outcomes were calculated in the false positive and true negative groups. **Results:** The adjusted OR of developing preeclampsia was 1.98 (95% CI: 1.14–3.42), and its RR was 2.13 (95% CI: 1.34–3.38) times higher in the false positive group. Moreover, the adjusted OR of Small for Gestational Age (SGA) was 2.80 (95% CI: 1.76–4.47), and its RR was 2.28 (95% CI: 1.54–3.36) times higher in the false positive group. The adjusted OR of Low Birth Weight (LBW) was 3.34 (95% CI: 1.97–5.64), and its RR was 2.65 (95% CI: 1.72–4.11) times higher in the false positive group. In addition, no significant difference was observed between false positive and true negative groups in terms of preterm birth. **Conclusions:** Women with a false positive fetal screening test result are more likely to suffer from preeclampsia, SGA, and LBW and require planned prenatal care.

Keywords: *Adverse pregnancy outcomes, Down syndrome screening, low birth weight, small for gestational age*

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Introduction

Multiple maternal serum markers in the first and second-trimester screening are the basis of the prenatal diagnosis of Down syndrome and other genetic conditions. All women should be screened before the twentieth gestational week, regardless of maternal age.[1,2]

The first trimester combined test is a combination of Nuchal Translucency (NT) screening and serum levels of Pregnancy-Associated Plasma Protein A and β-human Chorionic Gonadotrophic Hormone measurement at weeks 11–14 of gestation. This protocol increases the detection rate by 79–88% and the false positive rate by 5%.[1,3–6]

Based on these screening results, women are divided into low-risk, intermediate-risk, and high-risk groups. Diagnostic tests [amniocentesis and Chorionic Villus Sampling (CVS)] are recommended in high-risk individuals. Women in the intermediate-risk group (15–20%) are screened again in the second trimester, and the remaining (80–85%) with a risk of equal to or less than 1 per 1000 have low-risk screening results.

The second-trimester screening includes triple testing, namely, Alpha-Fetoprotein (AFP), Unconjugated Estriol (uE3), and Human Chorionic Gonadotropin (HCG) measurement, with a diagnostic power of 31–70%. By adding a fourth marker called dimeric inhibin-A to the triple test, the quad test is performed at 15–20 weeks of gestation and the detection rate reaches 80% with a false positive of 5%.[1] In individuals with abnormal analytic or positive Down syndrome screening, CVS or amniocentesis is recommended for the detection of chromosome abnormalities.[7,8]

In addition to the main role of these screening methods in predicting aneuploidy,

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several studies showed an association between abnormal screening results with an increased risk of adverse perinatal outcomes.[8–12]

Earlier studies have shown that false positive results of Down syndrome screening are connected with increased risk of preterm birth, hypertensive disorders in pregnancy, Small for Gestational Age (SGA), and Intrauterine Fetal Death (IUFD),[6] but other studies have reported controversial results. Moreover, race has been reported as an important and independent risk factor for adverse outcomes. Despite the availability of Down syndrome, trisomy 18, and neural tube defects screening tests, there is little information on the association of the false positive results of these tests with pregnancy outcomes in Iran.[13] Therefore, the present study was conducted to determine the relationship between false positive results of Down syndrome screening and adverse pregnancy outcomes.

Material and Methods

The present study was a two-group prospective cohort study. All women in the twentieth week of pregnancy, who had undergone random contingent sequential screening according to the national protocol, and referred to the prenatal clinic of Al-Zahra and Beheshti Hospitals in Isfahan, Iran, during the year 2018 were selected through convenience sampling and were followed until delivery.

Pregnant women who had a singleton pregnancy, did not use any drugs, narcotics, cigarettes, or alcohol, had no fetal abnormalities or any diseases affecting the pregnancy process, such as lupus, and no structural defects, such as abdominal wall defects, neural tube defects, or fetal abnormality, in the ultrasound anomaly scan in the second-trimester screening, were included in the study voluntarily. Moreover, women who had a home delivery or a neonate born with Down syndrome or visible anomaly were excluded from the study. Then, the gestational age for screening and amniocentesis was calculated based on the first day of the Last Menstrual Period or the Crown-Rump Length in the ultrasound performed in the first trimester. Moreover, the serum levels were converted to Multiples of the Median by adjusting the gestational age, ethnicity, Body Mass Index (BMI), and diabetes and smoking status based on local references.

Fetal NT of above 95% percentile or NT ≥3 mm according to the first-trimester ultrasound report or national cutoff point <250 were considered as high-risk screening test results and diagnostic amniocentesis was performed in these cases. However, in cases with medium risk, second-trimester prenatal aneuploidy screening was performed with quad tests including AFP, uE3, and dimeric inhibin-A in weeks 15–18. Diagnostic test including amniocentesis was performed for high-risk screening results.

Pregnant women with high-risk (positive) screening results, no chromosomal abnormalities in amniocentesis, and lack of Down syndrome in the newborn were considered as the false positive group (n = 304), and they were compared with women who had low-risk screening results in the contingent test, as the true negative group (n = 304), in terms of pregnancy outcomes such as preeclampsia, preterm birth, SGA, and LBW.

Preeclampsia was defined according to the guidelines of the American College of Obstetricians and Gynecologists, based on systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two recordings at least 4 hours apart, with the presence of proteinuria 300 mg in 24 hours or ≥+1 protein on dipstick analysis after 20 weeks of gestation in a woman with previously normal blood pressure. Preterm birth was defined as delivery before 37 weeks of gestation, LBW was considered as neonate weight of less than 2500 g at birth, SGA was defined as fetal weight of less than the tenth percentile according to gestational age at ultrasound, and IUGR was considered as postnatal birth weight of less than the tenth percentile of gestational age under the supervision of a perinatologist.

The necessary data were collected in information forms after obtaining consent from pregnant women with clinical examination, and their prenatal and delivery records, ultrasound, and computerized documentation systems were studied. Statistical analyses were performed using SPSS software (version 20; IBM Corp., Armonk, NY, USA). $p < 0.05$ was considered significant.

The reproductive and demographic characteristics were evaluated in false positive and true negative groups. Then, these characteristics were assessed regarding pregnancy outcome. Frequency distribution, and central and distribution indices of variables were calculated and independent samples t-test and Chi-square test (χ^2) were used. A variable that was significantly related to both screening test results and pregnancy outcomes was considered as a confounding variable. The incidence of the adverse outcome in the two groups was calculated, and raw Odds Ratio (OR) and relative risk with a 95% Confidence Interval (CI) were evaluated based on the calculated incidence. Finally, logistic regression was used to assess the relationship between the independent variable and adverse pregnancy outcomes by removing the confounding variable effect.

Ethical considerations

The present study was approved by the Regional Medical and Biological Research Committee of Isfahan University of Medical Sciences, Iran (Code of Ethics: IR.MUI.REC.1395.2.160) at 2016. The research aims and methods were thoroughly explicated to the participants, and then, written informed consent was obtained from the volunteer women. Confidentiality was observed in all stages of the research. Additionally, they were allowed to withdraw from the study at any stage of research.

Results

The present study was conducted on 608 pregnant women with a SD age of 29.97 (5.81) years, and SD BMI of 25.03 (4.41) kg/m^2. Based on the screening results, 304 women were assigned to the false positive group and 304 to the true negative group.

The reproductive and demographic characteristics were compared between false positive and true negative groups [Table 1]. The confounding variables for each outcome were calculated separately. Thus, variables that were significantly related to both screening test results and pregnancy outcomes were considered confounding variables. Therefore, age, exposure to cigarette smoke, average number of pregnancies, and BMI were considered as confounding variables for preeclampsia, and age, BMI, average number of pregnancies, previous birth weight of less than 2500 grams, and urinary tract infection were considered as confounding variables for preterm birth. Nuchal Translucency was considered as a confounding variable for SGA and age, NT, and average number of pregnancies were considered as confounding variables for LBW.

As shown in Table 2, raw OR of developing preeclampsia was 2.36 (95% CI: 1.40–3.98) and its RR was 2.13 (95% CI: 1.34–3.38) times higher in the false positive group, raw OR of SGA was 2.69 (95% CI: 1.70–4.25) and its RR was 2.28 (95% CI: 1.54–3.36) times higher, raw OR of LBW was 3.12 (95% CI: 1.90–5.15) and its RR was 2.65 (95% CI: 1.72–4.11) times higher in the false positive group, and raw OR of preterm birth was 2.76 (95% CI: 1.82–4.15) and its RR was 2.20 (95% CI: 1.58–3.05) times higher.

Finally, adjusted OR from logistic regression analysis of factors associated with each pregnancy outcome was calculated separately by removing the confounding variable effect. As shown in Table 3, OR of developing preeclampsia was 1.98 (95% CI: 1.14–3.42) times higher in the false positive group, SGA was 2.80 (95%CI: 1.76–4.47) times higher, and LBW was 3.34 (95% CI: 1.97–5.64) times higher. The OR of preterm birth was 1.48 (95% CI: 0.78–2.81), and showed no significant differences between false positive and true negative groups.

Discussion

The present prospective cohort study was conducted in Iranian women to determine the relationship between false positive results of contingent screening test and adverse pregnancy outcomes in 608 women. The two groups of mothers were similar in terms of most reproductive characteristics. Logistic regression was used to control the confounding factors. The adjusted OR of preeclampsia was 1.98 times higher in the false positive group, the OR

Table 1: Comparison of the reproductive and demographic characteristics of the false positive and true negative groups at the beginning of the study

Group Parameter	True negative *n*=304	False positive *n*=304	*t*-test or chi-square	df*	*p***
Age (years)	31.41 (5.98)	28.54 (5.26)	6.27	606	0.001
Number of pregnancies	2.02 (1.07)	1.82 (0.96)	2.42	606	0.016
Number of deliveries	0.83 (0.89)	0.63 (0.75)	3.09	605	0.002
BMI***	25.62 (4.57)	24.45 (4.17)	3.29	606	0.001
NT****	1.60 (0.65)	1.35 (0.34)	5.71	606	0.001
Weight gain during pregnancy (kg)	11.56 (4.05)	12.80 (4.01)	0.42	602	0.510
Interval of less than 18 months with older child	7 (4.00%)	2 (1.40%)	2.069	1	0.150
Previous birth weight of less than 2500 grams	53 (30.60%)	20 (13.70%)	12.871	1	0.001
Past history of IUFD*****	5 (1.60%)	2 (0.70%)	1.30	1	0.450
Chronic hypertension	3 (1.00%)	0 (0%)	3.01	1	0.240
Iron deficiency anemia in pregnancy	1 (0.40%)	2 (0.70%)	0.23	1	0.540
Gestational diabetes	29 (10.10)	25 (4.00%)	0.62	1	0.250
Exposure to cigarette smoke	18 (5.90%)	8 (2.60%)	4.01	1	0.045
Prenatal care	199 (65.50%)	169 (55.60%)	6.196	1	0.013
Urinary tract infection	29 (9.50%)	16 (5.30%)	4.056	1	0.044

*df: degrees of freedom; **p: *p*-value; ***BMI: Body Mass Index; ****NT: Nuchal Translucency; ***** IUFD: Intrauterine Fetal Death

Table 2: Raw odds ratio and risk ratio for adverse pregnancy outcomes in the two groups

Adverse pregnancy outcomes	OR*	95% CI	*p***	RR***	95% CI****	*p*
Preeclampsia	2.36	1.40-3.98	0.001	2.13	1.34-3.38	0.001
Small for gestational age	2.69	1.70-4.25	0.001	2.28	1.54-3.36	0.001
Low birth weight	3.12	1.90-5.15	0.001	2.65	1.72-4.11	0.001
Preterm birth	2.76	1.82-4.15	0.001	2.20	1.58-3.05	0.001

*OR: Raw Odds Ratio; **p=*p*-value; ***RR=Relative Risk; **** CI=Confidence Interval

Table 3: Adjusted odds ratio with adverse pregnancy outcomes in the two groups

Adverse pregnancy outcomes	Adjusted OR*	95% CI**	*p****
Preeclampsia	1.98	1.14-3.42	0.015
Small for gestational age	2.80	1.76-4.47	0.001
Low birth weight	3.34	1.97-5.64	0.001
Preterm birth	1.48	0.78-2.81	0.230

*Adjusted OR: Adjusted Odds Ratio; **CI: Confidence Interval; ***p: *p*-value

of SGA was 2.80 times higher, and the OR of LBW was 3.34 times higher, and the two groups differed significantly in terms of these outcomes. The OR of preterm birth was 1.48 times higher in the false positive group, but no significant difference was observed between the two groups in this respect. A systematic review and meta-analysis showed an association between false positive results, Down syndrome screening, and increased odds of preeclampsia and stillbirth. However, there was no significant association between these variables and growth restriction and preterm birth.[2] Yazdani *et al*.[13] conducted a cohort study on 300 pregnant women and found a higher rate of preeclampsia (p = 0.008), SGA (p = 0.028), and premature rupture of membrane (p = 0.004) among those who had positive quad test results.

Baer *et al*.[14] indicated a higher prevalence of preeclampsia, placenta previa, and placental abruption among pregnant women with positive screening test results in comparison with those with negative results. Preeclampsia increased by 1.7 times and fetal loss by 3.5 times in the false positive group. The women who had positive screening results in both tests of the first and second stages were significantly at higher risk of fetal death (CI: 95%, 21.8–194.4; RR = 33.6–156.7).

Several studies have indicated that false positive results of Down syndrome screening were correlated with an increased risk of preterm birth, SGA, hypertensive disorders, and intrauterine death.[15–18] However, Yee *et al*.[6] indicated that the prevalence of adverse pregnancy outcomes such as preeclampsia (p = 0.63), preterm labor (p = 0.20), and LBW (p = 0.28) was not higher in women with positive screening results.

Furthermore, Sritippayawan and Vachirasrisoontra conducted a case control study and found no significant increase in adverse pregnancy outcomes such as preterm delivery, LBW, SGA, preeclampsia, placenta previa, and fetal death in women with false positive results of Down syndrome screening.[18]

Perhaps, the difference between the results of the above study and the present study is in the method of study and control of confounding factors, race, and type of study.

The present study has several strengths such as the prospective nature of the cohort study, which involved the consideration of the inclusion and exclusion criteria and all the reproductive and demographic variables, the long-term follow-up of samples until delivery, and the controlling of the confounding variables using logistic regression.

Participants of this study were selected through convenience sampling only among pregnant women who referred to governmental centers (prenatal clinic of Al-Zahra and Beheshti Hospitals), which can be considered as a limitation of this study.

Conclusion

The present study indicated that women with false positive results in fetal contingent screening were at approximately 2, 3, and 3.5 times higher risk of preeclampsia, SGA, and LBW, respectively. Therefore, the false positive results of these screening tests can predict risks for the mother and fetus, and help prenatal care providers plan intensive care for these women in early pregnancy to protect them from adverse pregnancy outcomes like preeclampsia, SGA, and LBW.

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Conflicts of interest

Nothing to declare.

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