Evaluating the association between first trimester screening tests and adverse perinatal outcomes

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ABSTRACT

Prenatal screening tests are not diagnostic and only show and determine the risk of fetal abnormalities. This study aimed to evaluate the association between the results of double marker test and nuchal translucency (NT) in first trimester with adverse perinatal outcomes (Low-Birth-Weight, Small for Gestational Age, Intrauterine Growth Restriction, Aneuploidy, and fetal abnormalities) in pregnant women. This nested case control study was conducted on two groups of pregnant women. In case group (n=46) the result of double test in first trimester was positive (more than 1.50) and nuchal translucency was also positive (more than 3 mm). In control group (n = 77) the result of double test and nuchal translucency was negative. For each woman, data including demographic data, gestational age, gravidity, parity, number of abortion, weight and height of pregnant women, and the results of double screening test and nuchal translucency were recorded in a check list. For women who had positive test, amniocentesis (in 16 weeks of pregnancy) was performed. Borderline cases were followed using cell free fetal DNA or quadruple screening test. All women were followed during pregnancy until delivery. The prevalence of Down syndrome, intrauterine growth restriction and fetal abnormality in case group was more than the control group and difference was significant statistically (P = .001). Trisomy 18 and 13 were not found in the two groups. In terms of the frequency of spinal cord defects, respiratory distress, SGA, LBW and infant mortality there was no significant difference between the two groups. Conclusion: Our findings showed that adverse perinatal outcomes in screening positive cases were higher. Therefore the double marker test could be helpful in detecting fetal outcomes such as intrauterine growth restriction and fetal structural abnormalities.

Keywords: Screening Test, Fetal Outcomes, Trisomy, Spinal Cord Defects

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INTRODUCTION

The first trimester Down syndrome screening based on nuchal translucency measurement was introduced firstly by the Fetal Medicine Foundation (FMF), London, in the late 1990s and it was performed in Germany by German branch of FMF in 2002 [1]. The first trimester screening tests are nuchal translucency and double marker test (fβ-hCG and PAPP-A) and quadruple screening test (Alpha phetoprotein, Unconjugated estriol, hCG,inhibin-A) which performed in 11 to

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13 and 15 to 20 weeks of pregnancy respectively [2].Double marker test predict the risk of congenital defects. The quad marker screen can predict approximately 75% to 80% of the problems related to the development of fetus`s brain and spinal cord. NT which measures the nape of fetal neck would be performed from the beginning of the end of week 11 to week 13 of pregnancy. The nape of neck of a fetus with Down syndrome is increased [3].In terms of the risk, screening tests put pregnant women in three groups. The first group is high risk women (<1/50), they are recommended to perform invasive diagnostic tests such as amniocentesis, chorionic villus biopsy and fetal tissues karyotyping. The second group is low-risk women (> 1/1500) who do not need another test and the third group are women with moderate risk (1/50 – 1/1500), which the second trimester screening tests [4] or noninvasive prenatal testing (NIPT) such as cell free fetal DNA should be carried out for them [5].Different findings have been reported about above mentioned tests in various previous studies. A study reported that high level of hCG is associated with more fetal abnormalities such as intrauterine growth restriction (IUGR), fetal death and stillbirth [6]. Another study reported that AFP, UE3 and HCG as markers with MOM> 2 have a good predictive value for problems in a singleton pregnancy such as intrauterine fetal death, IUGR and miscarriage [7]. In a study in Iran no significant relationship between the triple screening test results with perinatal outcomes was found [8].Despite significant correlation between abnormal serum markers with fetal outcomes, yet there is no a screening test with high sensitivity and specificity for the diagnosis of miscarriage, fetal distress, intrauterine growth restriction, fetal abnormality, fetal mortality, Down syndrome and spinal cord disorders .Therefore the aim of this study was to evaluate the association between the results of double marker test and nuchal translucency (NT) in first trimester with adverse perinatal outcomes in pregnant women.

MATERIALS AND METHODS

This nested case control study was conducted on 123 pregnant women referred to Besat hospital, Sanandaj, Iran during the second quarter of 2016.In case group (n=46) the result of double marker test in first trimester was positive (more than 1.50) and nuchal translucency was also positive (more than 3 mm). In control group (n = 77) the result of double marker test and nuchal translucency was negative. Inclusion criteria included; pregnant women living in Sanandaj and desire to do the first and second trimester screening tests and NT and exclusion criteria included: BMI higher than 30 and less than 20, multiple pregnancies, vaginal bleeding, steroid therapy, hyperthyroidism and hypothyroidism, chronic hypertension, gestational diabetes, chronic liver disease and legal abortion due to maternal disease. For each woman, data including demographic data, gestational age, gravidity, parity, number of abortion, weight and height of pregnant women, and the results of double screening test and nuchal translucency were recorded in a check list. Informed consent was taken from all participants. Fetal outcomes including; fetal distress, abortion, intrauterine growth restriction, stillbirth, SGA, Down syndrome, trisomy 18 and 13, NTD and LBW were controlled and recorded. All women were followed during pregnancy until delivery. After birth; infants were examined clinically by a neonatologist. For women who had screening positive test, amniocentesis was performed in 16 weeks of pregnancy. Borderline cases were followed using cell free fetal DNA or quadruple screening test. Data were analyzed using SPSS Ver.18. Descriptive statistics, including absolute and relative frequency also analytical statistics, Chi-square test and Fisher's exact test were used to find the relationship between case and control groups with fetal outcomes. This study was approved by the ethics committee of Kurdistan University of Medical Sciences.

RESULTS

The results showed that there was no statistically significant between the two groups in terms of maternal age (P = 0.65), parity (P = 0.26) and gravidity (P = 0.86).(Table 1)Based on the t-test there was a significant difference in the mean of double marker test for two groups. PAPP-A in case group was lower than the control group (P = .001) and fβ- hCG in case group was significantly higher than the control group (P = .0001). (Table 2)In case group the frequency of abnormal levels of PAPP-A was 54.3% and the abnormal level of fβ-HCG was 67.4%. Results showed that one woman in case group and two in the control group had IUFD. In the case group three women (7/7%) had abnormal level of amniocentesis. Trisomy 18 and

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Table 1: The quantitative variables in the two groups

Variables	Group	No.	Mean and SD	t	P value
Maternal Age	Case	46	31.59±6.38	.44	.65
	Control	77	32.06±5.44		
Parity	Case	46	.70±.69	1.12	.26
	Control	77	.55±.73		
Gravidity	Case	46	2.02±1.08	.18	.86
	Control	77	1.99±1.04		

Table 2: Comparing the mean of marker`s level in the two groups

Markers	Group	No.	Mean and SD (MOM)	t	P value
PAPP-A	Case	46	.67±.62	3.57	.001
	Control	77	1.18±.81		
fβ HCG	Case	46	2.20±1.08	8.2	.0001
	Control	77	1.04±.45		

PAPPA= pregnancy-associated plasma protein-A
fβ HCG=free beta human chorionic gonadotropin

Table 3: Comparing the fetal outcomes in the two groups

Outcomes	Group	Abnormal No(. %)	NormalNo.(%)	P value	OR	CI 95%
Down syndrome	Case	3(6.5)	43(93.5)	.05**	-	-
	Control	0	77(100)			
Spinal cord defects	Case	4(8.7)	42(91.3)	.06**	7.2	.8-66.9
	Control	1(1.3)	76(98.7)			
Abortion	Case	9(19.6)	37(80.4)	.001*	18.5	2.3-151.4
	Control	1(1.3)	76(98.7)			
Intrauterine growth restriction	Case	4(8.7)	42(91.3)	.19**	3.5	.6-20.3
	Control	2(2.6)	75(97.4)			
LBW	Case	4(8.7)	42(91.3)	.72**	1.4	.4-5.4
	Control	4.(6.5)	73(93.5)			
SGA	Case	1(2)	45(98)	.19**	-	-
	Control	0	77(100)			
Respiratory distress	Case	5(10.9)	41(89.1)	.75*	1.2	.4-4.1
	Control	7(9.1)	70(90.9)			
Neonatal death	Case	1(2)	45(98)	.19**	-	-
	Control	0	77(100)			
fetal structural abnormalities	Case	9(19.6)	37(80.4)	.27	3.5	1.1-11.2
	Control	5(6.5)	72(93.5)			

*Pearson Chi-Square   ** Fisher's Exact Test   OR: Odds Ratio   CI: Confidence Interval

Table 4: The frequency of type of fetal structural abnormalities in two groups

Type of fetal structural abnormalities		Case	Control	Identification
Digestive disorders	Diaphragmatic hernia	1	0	High freeBHCG
	Gastroschisis	1	0	High freeBHCG nad High PAPP-A
	Omphalocele	1	0	Ultrasound and low PAPP-A
	Cleft lip	1	0	Examination after birth
	Cleft palate	0	1	Examination after birth
Renal disorders	Kidney Hydronephrosis	0	1	sonography
	Polyhydraminos	0	1	sonography
Cardiac disorders	Fetal heart arrhythmias during pregnancy	1	0	Fetal heart echo , High freeBHCG, high and low PAPP_A
	hydrops fetalis	1	0	Low PAPP-A
Other disorders	Choroid plexus cysts	0	1	sonography
	Hypospadias	0	1	Examination after birth
	Ventriculomegaly	1	0	sonography
	Smith–Lemli–Opitz syndrome	1	0	sonography
	cystic hygroma	1	0	High freeBHCG

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13 was not found in the two groups. Comparing fetal and neonatal outcomes in two groups showed that there was significant difference between the two groups in terms of abortion (P = .001), Down's syndrome (P = .05) and fetal structural abnormalities (P = .027).But in terms of spinal cord defects, intrauterine growth restriction, LBW, SGA and respiratory distress there was no significantly different between the groups (P> .05). (Table 3)The frequency distributions of fetal structural abnormalities in two groups are presented in table 4.

DISCUSSION

Prenatal diagnosis is the only way to prevent the birth of infants with anomalies. Screening for chromosomal aneuploidy by measuring biochemical markers have been used in recent years. With increasing age maternal serum markers increased in the first and second trimester of pregnancy [9].Social, cultural and economic factors, attitude to Down syndrome and other disorders, consulting, the cost and awareness for screening during pregnancy are important elements and should be considered.

In this study there was a significant difference between the mean double marker test (PAPP-A and fβ hCG) in the two groups. In a study by Wald et al the mean free beta-hCG level in affected pregnancies was 1.79 times the mean level for unaffected pregnancies, and the mean PAPP-A level was 0.43 times the normal mean [10]. This finding is inconsistent with our findings that in case group the frequency of abnormal levels of PAPP-A was 54.3% and the abnormal level of fβ HCG was 67.4%. A study by Godbole et al [11] showed that the abnormal level of PAPP-A and fβ HCG were 73.3% and 66.3% respectively which was not inconsistent with our findings. The difference may be due to differences in study population, the time of screening and considered cut off levels for biomarkers. Results showed that one woman in case group and two in the control group had IUFD. Feyzbakhsh et al found a significant association between intrauterine fetal death (IUFD) and screening tests [9].

Although the prevalence of Down syndrome and spinal cord defects in the two groups had no significant difference, but all cases of Down syndrome and the majority of spinal cord defects cases were in infants who their mother`s

screening test results were positive. In the present study Trisomy 18 (Edward syndrome), Trisomy 13 (Patau syndrome) was not found in the two groups. In a study by Hassanzadeh et al amniocentesis results showed that there were 11(9.1%) cases of aneuploidy that among them 4.1% were Down syndrome, 2.5% were Trisomy and 2.5% had spinal cord defects [12].Brizot in a study showed that in fetuses with trisomy 21, total hCG and fβ-hCG level were significantly higher, whereas in trisomies 18 and 13 levels of total hCG and fβ-hCG were lower than in chromosomally normal controls. There was also no significant association between hCG and nuchal translucency thickness in either the chromosomally normal or abnormal group [2].In this study the prevalence of intrauterine growth restriction in case group was more than the control group and difference was significant statistically. In a study by Huang, women with deceased first trimester maternal serum pregnancy-associated plasma protein A (PAPP-A) were at greater risk of developing adverse pregnancy outcomes including intrauterine growth restriction [13] which is similar to our findings.

In our study the frequency of infants with low birth weight (LBW) in the control group was more than case group, but the difference was not significant. In a study by Godbole et al there was also no significant difference between the two groups in terms of LBW [11]. This study was inconsistent with our study. In the present study there was no difference between the two groups in terms of SGA (Small for Gestational Age). In a systemic review study by Morris et al which was conducted to determine the accuracy of five serum analytes used in Down's serum screening for prediction of preeclampsia and small for gestational age, the results showed that predictive accuracy was low generally. They showed that the best predictor for SGA was AFP>2.0MoM [6].Hui et al in another systemic review study concluded that, currently there is no identifiable combination of serum markers performs well as a screening test for preeclampsia, small for gestational age, and stillbirth beyond 24 weeks .Therefore they suggested large cohort studies with standardized screening test parameters and outcomes [14].In terms of the frequency of respiratory distress there was no significant difference between the two groups. In a study by Godbole in double and triple test there was no difference between the two groups in terms of respiratory distress [11].

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Therefore it can be said that abnormal levels of screening tests in first trimester was not associated with the occurrence of respiratory distress and cannot predict it.

In this study, infant mortality in the two groups showed no significant difference. Huang showed that reducing PAPP-A in first trimester and reducing unconjugated estriol (uE3), increasing serum alpha fetoprotein (AFP) and total human chorionic gonadotrophin (hCG) in second trimester put women at greater risk of developing adverse pregnancy outcomes, and combinations of these markers predicted at best 33.3% of fetal loss and 31.5% of preterm births (PTB) before 32 weeks of gestation [13].The frequency distribution of fetal structural abnormalities in the case group that had performed double marker test was higher. Several previous studies have shown that maternal serum markers in first and second trimester significantly associated with increased adverse pregnancy outcomes [14-16], but in a study by Dugoff et al there was no statistically significant association between abnormal levels of maternal serum markers in the first and second trimester of pregnancy for a number of outcomes such as fetal aneuploidy and systematic malformations. These markers alone were not effective for screening the adverse pregnancy outcomes and their sensitivity and positive predictive value was low [17].Future studies should focus on tests and new markers management strategies for early detection of adverse outcomes in pregnant women who are at risk. Closer monitoring on at risk women and identifying them to perform screening tests not only identify outcomes such as IUFD and IUGR but also may lead to further insight into the mechanism of these diseases [18].

CONCLUSION

The results of this study showed that adverse perinatal outcomes in screening positive cases were higher. Therefore the double marker test could be helpful in detecting fetal outcomes such as intrauterine growth restriction and fetal structural abnormalities.

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