ORIGINAL REPORT

The Association between Second-Trimester Maternal Serum Alpha-Fetoprotein in 14-22 Weeks and Adverse Pregnancy Outcome

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Abstract- Aim of this study is to determine the risk of adverse pregnancy outcome by maternal serum alpha-fetoprotein (MSAFP) level. We followed 295 pregnant women from MSAFP screening in the 14th to 22th week of gestation until the end of pregnancy and information on pregnancy outcome have been recorded in questionnaires. Of 295 pregnant women, 270 had term labor and 25 had preterm labor. The frequencies of pregnancy outcomes were as following: 3 (1.01%) stillbirths, 25(8.47%) preterm labor, and 10 (3.4%) preterm rupture of membranous (PROM), 15 (5.1%) pre-eclampsia, 23 (7.8%) oligohydramnious, and 1 (0.33%) miscarriage. The mean of preterm labor was significantly associated with the higher level of MSAFP (P =0.021). The mean was 55.1 ng/cc in preterm labor and 41.1 ng/cc in term labor. Also, second trimester MSAFP levels were higher in women with pre-eclampsia (P <0.001). The significant association was found between higher level of MSAFP with oligohydramnious (P <0.001) and low birth weight (P <0.001). Pregnancies with an elevated MSAFP level are associated with adverse obstetric outcomes and need more prenatal care.

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Key words: Alpha- fetoproteins; pregnancy outcomes; mothers

Introduction

A major goal of antenatal care is to intervene in high risk pregnancies. It has been suggested that maternal serum alpha-fetoprotein (MSAFP) screening, apart from identifying fetuses with open neural tube defects and chromosomal abnormalities, could also identify pregnancies at high risk of adverse outcomes (1). Unexplained high levels of MSAFP have been associated with an increased risk of adverse pregnancy outcomes, such as fetal death before the 28th week, perinatal death, low birth weight (LBW), preterm labor, and other obstetric complication (2-4). Also, a raised maternal serum level of AFP during the second trimester of pregnancy is one of the best biochemical predictors of the risk of unexplained stillbirth (5). Previous studies have suggested similarities between unexplained stillbirth and sudden infant death syndrome (SIDS) with respect to clinical and pathological findings, suggesting that the two conditions may be related. As a result there might be a direct association between maternal serum AFP levels and the risk of SIDS (6-7). Subsequent investigation has clarified that in a significant proportion of women, elevated MSAFP "initially" unexplained is associated with a higher frequency of adverse pregnancy outcomes at later gestations. Such adverse outcomes included hypertensive disorders, intrauterine growth restriction (IUGR), anteparum bleeding, and preterm labor (8).

A hypertensive disorder such as pre-eclampsia is a multi-system disorder specific to pregnant women. It remains one of the most important causes of maternal and fetal mortality and morbidity in developed countries (9). Pre-eclampsia has also been associated with an elevation of AFP in maternal serum (10-11). Using a threshold value of two multiples of the median (MOM), elevated AFP in the mid-trimester has been shown to be associated with a 2.3 to 3.8 fold increased risk of developing pre-eclampsia (12-13).

In addition to, AFP is a valued screening test for both neural tube defects and biochemical screening for Down's syndrome (14-15). In fact, low MSAFP values

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are associated with an increased risk for fetal chromosome anomalies including Down syndrome and trisomy 18, but high MSAFP values are associated with neural tube defects (16).

Some studies have reported that unexplained low levels of MSAFP have been associated primarily with an increased risk of fetal death, including spontaneous abortions and stillbirths (17-19).

The aim of this study was to determine the association between the second trimester MSAFP and adverse pregnancy outcomes such as preterm labor, pre-eclampsia, oligohydramnious, stillbirths, abortion and low birth weight.

Patients and Methods

295 pregnancies women were reviewed by the maternal serum alpha-fetoprotein screening program. This study was restricted to live-singletons pregnant women referred to shahid sadoughi hospital and Mother Hospital, Yazd, Iran between September 1, 2006, until August 31, 2007. In this study, the age and weight of all pregnant women were 20-30 years old at conceptions and 55-70kg respectively. Participants are ideally screened between 14-22 weeks' gestation.

All screened women gave informed consent to data acquisition and review as part of their participation in the MSAFP program. Gestational age of patients is ascertained by last menstrual period (LMP) or early ultrasound dating when dating is uncertain.

The MSAFP levels are reported in ng/cc by a single central reference laboratory and an experienced person.

Demographic characteristics of these women were maternal age, birth weight, and gestational age at the time of MSAFP draw.

Weight of the fetus was estimated by the Honarvar 2 equation and compared with real weight (20).

SPSS software was used for statistical analysis of data. The appropriate statistical tests including student's T Test, chi- square, ANOVA and exact test were used to compare the results. The differences were considered statistically significant if P value was less than 0.05.

Results

In this study, 295 pregnant women between the 14th and 22th weeks of gestation were evaluated.

The mean age of the participants was 23.7±3.02 years .The mean of the birth weight was 3056±511 gram (1700-4340gram). The mean maternal serum Alpha-fetoprotein was 43.56±39.1 ng/cc (2.3-250 ng/cc). The median MSAFP was 34 ng/cc.

Of 295 pregnant women, 270 had term labor and 25 had preterm labor .The frequency of pregnant outcomes were as following: 3 (1.01%) stillbirths, 25(8.47%) preterm labor, 10(3.4%) PROM, 15(5.1%) pre-eclampsia, 23(7.8%) oligohydramnious, 1(0.33%) miscarriage. There was a correlation between preterm labor and higher MSAFP. The mean was 55.1 ng/cc in preterm labor and 41.1 ng/cc in term labor (P-value~0.021). With respect to compare these mean, the mean of MSAFP in preterm labor was significantly associated with higher level of MSAFP than term labor.

Table 1: Risk of pre-eclampsia, preterm labor, PROM, oligohydramnious, stillbirth and miscarriage by mean level of maternal serum alpha-fetoprotein.

Variable	Number	MSAFP (n/cc)	P-value	Variable	Number	MSAFP (ng/cc)	P
Pre-eclmpasia	15	77.16±70.5	0.001	Oligohydramnious	23	78.39±60.3	0.000
Without pre-eclampsia	280	41.76±36.01		Without oligohydramnious	272	40.61±35.3	
Preterm labor	25	55.16±32.5	0.021	Stillbirth	3	36.13±10.5	0.74
Without preterm labor	270	41.19±39.9		Without Stillbirth	292	43.63±39.27	
PROM	10	42.3±15.12	0.91	miscarriage	1	40.3±11.12	1.000
Without PROM	285	43.6±39.68		Without miscarriage	294	43.5±28.42	

The mean MSAFP was 77.1 ng/cc in pre-eclamptic women while it was 41.7 ng/cc in pregnant women without pre-eclampsia. Therefore, second trimester MSAFP levels were significantly higher in women with pre-eclampsia (P <0.001). Also, an association was found between level of MSAFP and oligohydramnious. It was higher in pregnancy women with oligohydramnious compared with normal women (78.4 ng/cc vs. 40.6 ng/cc) (P <0.001). The association between low birth weight and the levels of MSAFP was significant. With increasing MSAFP between 14-22 weeks' gestation, birth weight decreased (P <0.001).

There was no relation between preterm rupture of membranous (PROM), stillbirth and miscarriage with the level of MSAFP (P =0.91, P =0.74, P =1 respectively) (Table 1). However, the number of patients with stillbirth and miscarriage was not enough for decision.

Discussion

alpha-fetoprotein(AFP) is produced in the fetal liver and yolk sac, and secreted into the fetal circulation and amniotic fluid, passed into the maternal circulation via the placenta and its concentration is 100 fold increase in the first third trimester of pregnancy compared with non pregnant women. The use of AFP as a serum marker in cancer actually predates its employment in the detection of congenital defects, but the latter use of AFP as a fetal defect marker has propelled its clinical utilization. Although the serum –marker capacity of AFP has long been exploited, less is known of the biological activities of this oncofetal protein during fetal and perinatal development (21). In our study, unexplained high levels of MSAFP have been associated with pre-eclampsia, preterm labor, oligohydramnios and LBW.

Bernstein *et al* (1992) reported that women with elevated MSAFP level had an increases incidence of preterm labor, fetal growth retardation and fetal death (22) .in our research, high level of MSAFP was in correlation with increasing preterm labor too.

Neggers *et al* (2000) evaluated the relationship of MSAFP to preterm labor. They stated that MSAFP levels greater than the 90th percentile significantly increased the risk of preterm labor (23).Our findings are the same with them. Kuo *et al* (2003) investigated the association between elevation of MSAFP and pregnancy outcomes on 168 singleton pregnancies. They suggested that screening for pregnancies with elevated MSAFP and pregnancy outcomes included preterm labor, preeclampsia, intrauterine fetal death would help to identify the low-risk cases and facilitate cost-effective management (24). Another study showed that increases risk of pregnancy-induced hypertension, preterm labor, oligohydramnious and abruption placenta are associated with elevated MSAFP levels (25).

Our findings are consistent with the study by Tikkanen *et al* (2007), Waller *et al* (1996) and Williams *et al* (1992) about the correlation of preeclampsia and MSAFP (26-27-13) while Khoo's study (1978) showed, in preeclamptic women; significantly lower mean AFP values were obtained (28). Wald *et al* (2006) identified in the pregnancies that went on to develop pre-eclampsia, early second trimester inhibin-A and hCG values were significantly raised and uE3 values were significantly lowered, while AFP values were not significantly altered (29). Kiran *et al* (2005), Brock *et al* (1982), Haddaw *et al* (1987), Mariona *et al* (1984) and Morssink *et al* (1997) revealed an association between low birth weights with abnormal unexplained high levels of second trimester MSAFP levels (30-34). Their finding was paralled our result. In our study, the significant associations were not found between levels of MSAFP and miscarriage and stillbirth because the number of cases with miscarriage and stillbirth was not enough to evaluate the relationship between MSAFP level and them; whereas another study has found significant associations between elevated MSAFP and stillbirth and miscarriage (35). On the other hand, Burton (1988) and Baschat *et al* (2002) reported patients with unexplained low levels of MSAFP had a significantly greater risk of fetal loss (3, 36).

Also, Simpson *et al* (1991) suggested that women with PROM showed elevated second trimester MSAFP (37) while there was no association between MSAFP and PROM in our study. In conclusion, however, in pregnancies with an unexplained elevated second-trimester MSAFP, the rate of adverse pregnancy outcomes such as Oligohydramnious, Preterm labor, Pre-eclmpasia and low birth weight increased but screening for MSAFP in the second trimester seems to be of no value in predicting PROM.

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