Mid-trimester maternal serum AFP levels in predicting adverse pregnancy outcome

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Summary

Objective: In this prospective study, we investigated the association between mid-trimester maternal serum alpha-fetoprotein AFP (MSAFP) levels and adverse pregnancy outcome in a South-Western Greek population. *Materials and Methods:* 110 healthy Greek women with spontaneous pregnancies, investigated for MSAFP levels between the 13th and 24th week of gestation and followed for adverse pregnancy outcome. AFP levels > 2.0 multiples of the median value for gestation were considered abnormal. Statistical analysis was performed by Pearson's chi-square test. *Results:* Elevated MSAFP levels were detected in a total of 27 of the 110 women studied (24.5%). Among them, only four women (14.8%) developed pregnancy complications. *Conclusion:* Multiparameter testing of placental function in the mid-trimester (uterine artery Doppler, placental morphology and MSAFP screening) may allow us to identify women with increased risk of developing severe placental insufficiency and pregnancy complications.

Key words: Maternal serum AFP levels; Adverse pregnancy outcome.

Introduction

Maternal serum alpha fetal protein (MSAFP) was originally introduced for the detection of neural tube defects [1]. However, increased ultrasound machine quality, and sonographer expertise have greatly reduced the need for MSAFP screening in mid- trimester [2].

Pregnancies with unexplained mid-trimester elevation of MSAFP are at increased risk of pregnancy complications [intrauterine growth restriction (IUGR), intrauterine fetal death (IUFD), and preeclampsia (PE)] resulting from placental insufficiency [3-5].

In our prospective study, we investigated the association between mid-trimester MSAFP levels and adverse pregnancy outcome in a South-Western Greek population.

Material and Methods

Between February 2005 and February 2007, about 110 women with spontaneous pregnancies were referred to the Outpatient Clinic of the Obstetrics and Gynaecology Department of the University of Patras Medical School. All women were investigated for MS AFP between the 13th and 24th week of gestation and followed for adverse pregnancy outcome.

Gestational age was estimated from the last menstrual period for women with regular (21-35 days) menstrual cycles or confirmed from ultrasonographic scan in the first trimester for women with irregular menstrual cycles. Women with multiple pregnancies, diabetes mellitus, pregnancy with chromosomal or structural abnormality, hypertension diagnosed before the 20th week of gestation, or history of PE in a previous pregnancy were excluded from the study.

All women had a dated ultrasound examination at their first visit, followed by a detailed examination at the 18th-22nd week of gestation. The study was approved by the Ethical Committee of the Hospital. Written informed consent was obtained from each woman.

Serum samples were collected from all women between the 13th and 24th week of gestation and were stored at -20°C. AFP levels were measured with immunoradiometric assay using two highly specific monoclonal antibodies for coating of the solid phase and the tracer. The tracer antibody and the coated antibody react simultaneously with the AFP present in patient samples or standards. Excess tracer is removed by a washing step and the radioactivity bound to the tube wall is measured in a gamma scintillation counter (IRMA-mat AFP, DiaSorin Inc). MSAFP levels > 2.0 multiples of the median value for gestation (MoM) were considered as abnormal.

Adverse pregnancy outcomes were considered as all gestational complications with fetomaternal circulatory disturbances (PA), IUGR, IUFD, PE.

Placental abruption (PA) was defined as the separation of the placenta from its site of implantation before delivery of the fetus [6].

Intrauterine growth retardation (IUGR) was defined as a birth weight below the 5th percentile for gestational age [7].

Intrauterine death (IUFD) was defined as fetal loss after 24 weeks' gestation.

Preeclampsia (PE) was defined by a blood pressure above140/90 mmHg after 20 weeks' gestation, proteinuria > 300 mg/24 hours or persistent 30 mg/dl (1+ dipstick) in random urine samples. The term severe preeclampsia is used when blood pressure above 160/110 mmHg is recorded at least six hours apart, and proteinuria of more than 5 g during 24 h occurs [8].

Statistical analyses were performed using the SPSS-12 for Windows. The chi-square test was used to assess the association between categoric variables.

Results

Serum samples were collected at a median gestation of 19 weeks (range 13-24). The median weight of the women at the time of serum sampling was 70 kg (range

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50-105). The median age at the estimated delivery date was 31 years (range 17-50).

From the 110 women included in the study, ten (9.1%) developed gestational complications during the follow-up of the current pregnancy. The demographics of women with gestational complications compared to those without are shown in Table 1.

Table 1. — *Women's demographics (n=110).*

		Women with complications (n = 10)	Women without complications (n = 100)
No. of pregnancies	1 pregnancy	10 (100%)	85 (85%)
	≥ 2 pregnancies	0 (0%)	15 (15%)
Age of women	< 25	0	17 (17%)
	25-35	6 (60%)	60 (60%)
	> 35	4 (40%)	23 (23%)
Complications in previous pregnancies	No	7 (70%)	89 (89%)
	Yes	3 (30%)	11 (11%)
Smoking	No	8 (80%)	90 (90%)
	Yes	2 (20%)	10 (10%)

Abnormal MSAFP levels were detected in a total of 27 of the 110 women studied (24.5%). Among them, only four women (14.8%) developed gestational complications in the current pregnancy. These data are shown in Tables 2 and 3.

Table 2. — *MSAFP levels in women with and without gestational complications.*

MSAFP levels	Women with complications (n = 10)	Women without complications (n = 100)	p value
MSAFP > 2 MoM (n = 27)	4	23	ns
MSAFP ≤ 2 MoM (n = 83)	6	77	

p value was calculated by the chi-square test.

Table 3. — *MSAFP levels in women with specific gestational complications in the current pregnancy (n = 10).*

MSAFP levels	PA	IUGR	PE	IUFD
MSAFP > 2 MoM (n = 27)	2	1	0	1
MSAFP ≤ 2 MoM (n = 83)	1	5	0	0
Total	3	6	0	1

PA = placental abruption; IUGR = intrauterine growth restriction; PE = pre-eclampsia; IUFD = intrauterine fetal death.

Discussion

AFP is initially synthesized by the yolk sac, followed shortly thereafter by the fetal liver. Because the human yolk sac involutes at the 9th week, the fetal liver is responsible for most of the AFP production during development [9, 10]. AFP synthesis by the proliferating fetal liver actually increases through the 20th week of gestation, after which it remains fairly constant until the 32nd week [9-11].

Despite the decrease in fetal serum AFP throughout the mid-trimester, MSAFP levels continue to rise until the 32nd week [9-11]. In fact, MSAFP continues to rise well into the third trimester of gestation, with an approximate doubling of maximal values for each trimester [11, 12]. After the 32nd week, MSAFP begins to decline until parturition. Decreasing MSAFP in the third trimester is already related to advancing gestational age [11, 13].

Elevated MSAFP levels have been strongly associated with congenital abnormalities, placental dysfunction and preterm birth [11, 14]. When the fetus is structurally normal, mid-trimester high MSAFP levels are thought to reflect a defect in placentation and are associated with an increased risk of complications in later pregnancy, including severe PE, IUGR and IUFD [11, 14-16]. In our study mid-trimester elevated MSAFP levels were detected in a total of 27 of the 110 women studied (24.5%). Among them, only four women (14.8%) developed pregnancy complications (2 PA, 1 IUGR and 1 IUFD).

In many instances elevated MSAFP levels have been associated with a breakdown in the fetal-maternal placental barrier [17, 18]. It was proposed that an abnormality of the placenta predisposes the pregnant woman to complications, and that this abnormality is initiated early in pregnancy (when MSAFP level is normally measured). Thus, mid-trimester MSAFP was thought to be useful in predicting PE in women who were at high risk for adverse pregnancy outcome and who would require careful monitoring [11].

Hypertensive disorders during pregnancy can reflect pathologic placental conditions that could interfere with the normal passage of AFP to the maternal blood. Thus, the relatively low MSAFP levels during the mid-trimester of pregnancies with hypertensive disorders could be the result of transplacental passage impairment [11]. This observation could aid in the identification of women at risk for such disorders. The apparent paradox was further clarified in a study that found a relationship among MSAFP levels, PE and placental complications [19]. Low MSAFP levels in mid-trimester were found to correlate with a low risk of PE and placental abnormalities, whereas elevated MSAFP levels were associated with a much higher risk for these disorders [19]. However in cases of severe PE, elevated mid-trimester MSAFP levels were always significantly higher than in patients who had mild PE or gestational hypertension [20]. In our study none of the women, developed PE during the current pregnancy.

Placental abnormalities, such as villus lesions, coagulation-related lesions, acute and chronic inflammatory and unclassified lesions, are consistent characteristics of early onset severe PE [21]. The same placental lesions and mainly chronic vascular lesions, such as intervillus thrombosis and chronic villitis, have been described in patients with unexplained mid-trimester high MSAFP levels [21, 22]. This may suggest that early placental pathology permits a more rapid diffusion of AFP from the fetoplacental compartment to the maternal compartment [22].

Elevated MSAFP in mid-trimester has been shown to be associated with a 2.3- to 3.8-fold increased risk of developing PE [23, 24]. In our study none of the women with mid-trimester elevated MSAFP levels developed PE during the current pregnancy.

Recent studies have shown that MSAFP levels at the 22nd-24th week were not significantly different in cases that developed PE later, compared with those who stayed normotensive, questioning the value of this test for screening purposes [25].

In our study the main limitation was the small number of cases with gestational complications. According to the results shown in Table 2, elevated mid-trimester MSAFP levels alone can not detect all pregnant women with increased risk of developing pregnancy complications. However, uterine artery Doppler screening alone is superior to MSAFP screening for the identification of significant placental pathology leading to PE and IUGR [15, 26].

Conclusion

Multiparameter testing of placental function in the mid-trimester (uterine artery Doppler, placental morphology and MSAFP screening) may allow us to identify women with increased risk of developing severe placental insufficiency and pregnancy complications.

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