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RESEARCH ARTICLE

Elevated maternal serum alpha fetoprotein (MSAFP) level in second trimester as a screening test for predicting adverse pregnancy outcome

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ABSTRACT

Objectives: To determine the sensitivity, specificity, positive predictive value and negative predictive value when elevated MSAFP level in the second trimester is used as a screening test to predict subsequent adverse pregnancy outcome. **Methods**: MSAFP level was determined by using an immunometric immunoassay technique. Women with MSAFP level ≥ 2.5MoM were defined as elevated MSAFP. **Results**: The Sensitivity for elevated MSAFP level as screening test for predicting adverse pregnancy outcome was 39.62% (95%CI 26.45% to 54.00%), and the Specificity was 93.96% (95% CI 88.84% to 97.20%).The Positive Predictive Value was 70.00% (95% CI 50.60% to 85.27%) and the Negative Predictive Value was 81.40% (95% CI 74.76% to 86.91%). **Conclusion**: As a screening test for predicting adverse pregnancy outcome, elevated MSAFP level in the second trimester has a low sensitivity (40%) but high specificity (94%).

Keywords: MSAFP, Preterm birth, Preeclampsia, Eclampsia, Small for gestational age, Stillbirth, Neonatal death.

Alpha fetoprotein (AFP) is a glycoprotein which is synthesized early in gestation by the foetal yolk sac and later by the fetal gastrointestinal tract and liver. It is the major serum protein in the embryo – foetus and is analogous to albumin. Its concentration increases steadily in both foetal serum and amniotic fluid until 13 weeks, after which, levels rapidly decrease. Conversely, AFP is found in steadily increasing quantities in maternal serum after 12 weeks and reaches a peak between 28 and 32 weeks. The normal concentration gradient between foetal plasma and maternal serum is on the order of 50,000:1 [1, 2]. Foetal body wall defects uncovered by integument, such as neural tube defects (NTDs) and ventral wall defects, permit AFP to leak into the amniotic fluid, resulting in maternal serum AFP levels that may be dramatically increased. Thus, it has been used as a marker of open neural tube defects [3,4]. In addition to NTDs, many other types of birth defects and placental abnormalities are associated with AFP elevation. When no foetal or placental abnormality is detected after a specialized sonographic evaluation, with or without

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amniocentesis, the AFP elevation is considered unexplained. These pregnancies are at increased risk for a variety of subsequent adverse pregnancy outcomes. Some include a foetal anomaly not detectable prenatally, foetal-growth restriction, oligohydramnios, placental abruption, preterm membrane rupture, preterm birth, and even foetal death.[5,6,7]. Considering the number of abnormal conditions associated with an elevated MSAFP, screening for elevated MSAFP at 16 weeks to 20 weeks of gestation seems to be a useful test in order to predict adverse pregnancy outcome and to take measures to prevent them by frequent monitoring of the patients and timely intervention.

Aims and objectives

To determine the sensitivity, specificity, positive predictive value and negative predictive value when elevated MSAFP in the second trimester is used as a screening test to predict subsequent adverse pregnancy outcome.

Material and Methods

The type of study was prospective observational study conducted in Gauhati Medical College Hospital (GMCH) over a period of 1 year from 2014-2015. A proforma for the study was prepared and details of each case were recorded for proper evaluation and analysis. Pregnant women attending Antenatal OPD in GMCH who were between 16 weeks to 20weeks were counseled about MSAFP test and were enrolled in the study after obtaining written and informed consent. The study protocol was approved by the ethical committee of the institution and was sponsored by Department of Biotechnology (DBT), New Delhi. Gestational age in pregnant women was determined from her last menstrual period and confirmed by ultrasonography. Fresh blood sample (3-5ml) was collected from the participants between 16 to 20 weeks of gestation and the serum was then separated by centrifugation. Serum AFP levels were then measured. The VITROS AFP test was performed using the VITROS AFP Reagent Pack and the VITROS AFP Calibrators on the VITROS ECi/ECiQ Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System using Intellicheck Technology. An immunometric immunoassay technique was used. The value of MSAFP was expressed in terms of Multiples of Median (MOM). As the sample in this study, within the limited period of time, was small for the purpose of calculating the median value for unaffected pregnancies according to gestational age, the reference median value for gestation wise MSAFP was taken from a study that was conducted in North west India from 5420 pregnant women by Gurjit Kaur and associates, Genetic Centre, Government Medical College & Hospital, Chandigarh, India [8]. The MOM were calculated for rounded weeks (16th rounded week includes gestation from 15+4 to 16+3).

MSAFP level ≥ 2.5 MoM were considered abnormal. As the association between low MSAFP level and Down Syndrome is well established, pregnancies with MSAFP level below 0.5 MoM were excluded from the study. All the pregnancies were followed up until delivery for maternal and fetal outcome by contacting over the telephone number provided by the participant in the proforma. Data were analyzed using Microsoft Excel 2010 (Microsoft Corporation, USA).

Results and Observations

The Sensitivity for the elevated MSAFP level as screening test for adverse pregnancy outcome was 39.62% (95%CI 26.45% to 54.00%), and the Specificity was 93.96% (95% CI 88.84% to 97.20%). The Positive Predictive Value was 70.00% (95% CI

Table 1. MSAFP and Adverse Pregnancy Outcome

MSAFP	Abnormal Outcome	Normal Outcome	Total
≥2.5MOM	21 (10%)	9 (4%)	30 (15%)
<2.5MOM	32 (16%)	140 (69%)	172(85%)
Total	53 (26%)	149 (74%)	**202**

Table 2. MSAFP and Preeclampsia/ Eclampsia			
	Pre eclampsia/ Eclampsia		
MSAFP LEVEL	**Present**	**Absent**	**Total**
≥2.5MOM	7 (3%)	23 (11%)	30 (15%)
<2.5MOM	6 (3%)	166 (82%)	172 (85%)
Total	13 (6%)	189 (94%)	202

50.60% to 85.27%) and the Negative Predictive Value was 81.40% (95% CI 74.76% to 86.91%) (table 1). The table 2 shows the relationship between MSAFP level and the number of cases with Pre eclampsia / Eclampsia. When MSAFP level is used as screening test for predicting Pre eclampsia / Eclampsia, Sensitivity = 53.85% (95%CI 25.13% to 80.78%) and Specificity = 87.83% (95%CI 82.30% to 92.13%), Positive predictive value = 23.33% (95%CI 9.93% to 42.28%), Negative predictive value = 96.51% (95%CI 92.56% to 98.71%).

Table 3: MSAFP and SGA			
	SGA		
MSAFP level	**Yes**	**No**	**Total**
≥ 2.5 MOM	7(3%)	23(11%)	30(15%)
< 2.5 MOM	12(6%)	160(79%)	172(85%)
Total	19(9%)	183(91%)	202

The table 3 shows the relationship between MSAFP level and the number of cases with Small for gestational age. The Sensitivity when elevated MSAFP is used as Screening test for SGA = 36.84% (95 % CI 0.1628 to 0.6164), Specificity = 87.43% (95% CI 0.8175 to 0.9187), Positive Predictive Value = 23.33% (95% CI 0.09933 to 0.4227), Negative Predictive Value = 93.02% (95% CI 0.8811 to 0.9635).

The table 4 shows the number of preterm deliveries according to MSAFP level. The Sensitivity when elevated MSAFP is used as screening test for preterm delivery = 0.4000 (95% CI 0.1633 to 0.6774), Specificity = 0.8717 (95% CI 0.8150 to 0.9161), Positive Predictive Value = 0.2000 (95% CI 0.07714 to 0.3857), Negative Predictive Value 0.9477 (95% CI 0.9029 to 0.9758).

Table 4: MSAFP and Preterm Delivery			
	Preterm Delivery		
MSAFP Level	**Yes**	**No**	**Total**
≥ 2.5 MOM	6(3%)	24(12%)	30(15%)
< 2.5 MOM	9(4%)	163(81%)	172(85%)
Total	15(7%)	187(93%)	202

Table 5: MSAFP and Stillbirth/ Neonatal Death			
	Stillbirth/ Neonatal Death		
MSAFP Level	**Yes**	**No**	**Total**
≥ 2.5 MOM	6(3%)	24(12%)	30(15%)
< 2.5 MOM	2(1%)	170(84%)	172(85%)
Total	8(4%)	194(96%)	202

The table 5 shows the relationship between MSAFP level in the second trimester and the number of Stillbirth / Neonatal death. The Sensitivity when MSAFP level is used as a screening test for Stillbirth /

Table 6: Summary of sensitivities, specificities, false positive rate, positive and negative predictive value

Outcome	**Sensitivity**	**Specificity**	**False positive rate**	**PPV**	**NPV**
Preterm delivery	40	87	12.8	20	90
Pre eclampsia/ Ecclampsia	54	88	12	23	97
SGA	37	87	12.5	23	93
Still birth/ Neonatal death	75	87	14	20	98
All complications	40	94	6	70	81

Neonatal death = 0.7500 (95% CI 0.3490 to 0.9682), Specificity = 0.8763 (95% CI 0.8212 to 0.9192), Positive Predictive Value = 0.2000 (95% CI 0.07714 to 0.385), Negative Predictive Value = 0.9884 (95% CI 0.9586 to 0.9986).

Discussion

In the present study, it was observed that elevated MSAFP when used as a screening test for predicting adverse pregnancy outcome had a sensitivity of 39.62 % (95% CI 26.45 to 54.00%) and a specificity of 93.96 % (95% CI 88.84 to 97.20 %). The positive predictive value was 70% and the negative predictive value was 81.4 %. Thus only about 40 % of the susceptible pregnancies screened by the test would give a true positive result while 60% would give a false negative result. Whereas the specificity of this test is high and it means 94 % of pregnancies which would not be affected would give true negative result while 7 % of the unaffected pregnancies would be wrongly classified as susceptible for adverse pregnancy outcome. Similar findings were observed in a retrospective study by Rebecca and associates [9] where the sensitivity for the test was 24 %, specificity was 96 %, PPV was 52% and NPV was 88%, False positive rate was 4 %.

Conclusion

As a screening test for predicting subsequent adverse pregnancy outcome (preterm birth, preeclampsia, eclampsia, SGA, Stillbirth or neonatal death), elevated MSAFP level in the second trimester for adverse pregnancy outcome has a low sensitivity (40%) but high specificity (94%). Thus as a screening, though its detection rate is low, but because of its high specificity, it can effectively rule out those who will not have adverse pregnancy outcome.

Conflict of interest: None. **Disclaimer:** Nil.

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