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RESEARCH ARTICLE

Evaluation of first trimester serum double marker test in prediction of fetal growth restriction

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ABSTRACT

Objectives: To evaluate the clinical utility of the first trimester serum double marker test in their ability to predict subsequent delivery of a fetal growth restriction (FGR) infant. **Methods:** The association between first trimester double marker test and the incidence of FGR were assessed by comparing the relative incidence at their MoM cut-offs and their sensitivity, specificity were calculated. **Results:** The FGR group constituted 35 FGR pregnancy and non FGR case constituted 50 normal pregnancy. The mean level of β-hCG was reduced in FGR group (i.e.0.94 ±0.70 MoM Vs 1.49 ±0. 75 MoM; P value < 0.05) but its sensitivity for prediction of future FGR was found to be 48 % only. The mean level for serum PAPP-A was significantly reduced in FGR group of patients (i.e.0.76 ± 0.45 Vs 1.16 ± 0.53; p value = 0.0005) with the sensitivity for prediction of FGR of 54.3 %. With serum PAPP-A level, a weak positive relationship was found with birth weight the association of which was statistically significant. **Conclusions:** Low levels of maternal serum PAPP-A and serum free β-hCG are associated, in the absence of an abnormal karyotype, with an increased risk for subsequent delivery of an FGR infant.

Keywords: FGR, PAPP-A, β-hCG, MoM.

Fetal growth restriction (FGR) refers to a fetus that has been unable to achieve its growth potential remains <10th percentile for that gestational age and can affect up to 5-10% of pregnancies [1-3]. It is associated with an increase in perinatal morbidity and mortality that is due to a high incidence of intrauterine fetal demise, operative deliveries and intrapartum fetal morbidities. Long term complications include cerebral palsy, developmental delay, behavioural dysfunction, obesity and other metabolic syndrome (Barker's hypothesis). Fetal growth is an important predictor of pregnancy outcome and reflects the interaction between physiological and pathological factors affecting the fetus. Majority of SGA fetus are physiologically normal i.e constitutionally small whereas pathological FGR occurs only in about 9% of the fetus but the ability to differentiate both these condition is limited. Hence FGR is a condition that is easy to define but difficult to diagnose [3,4].

Maternal serum analytes were first studied with the aim of screening for aneuploidies during the first or second trimester of pregnancy and their use was then further extended in many studies to evaluate their utility as markers for impaired placentation. The trophoblastic invasion failure is thought to be responsible of the changes in the concentration of serum placental products. Double marker test measures the levels of hCG and pregnancy associated plasma protein (PAPP-A) in blood. This test is done from 9 to 13 weeks of pregnancy and was initially recommended to screen for fetal aneuploidies but now it's role has also been found in prediction of fetal growth restriction even if the fetus is genotypically normal [4].

Aim: To determine the significance of level of first trimester serum double marker test as predictor of fetal growth restriction.

Materials and methods

This observational study was carried out in the department of obstetrics and gynaecology, Moti Lal Nehru

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Medical College, Prayagraj from July 2019 to June 2020. 85 numbers of women were included after fulfilling of inclusion criteria.

Inclusion criteria:

All pregnant women in first trimester of pregnancy (9 -13 weeks 6 days).

Exclusion criteria:

1. Chronic hypertension
2. Overt diabetes
3. Renal disease
4. Autoimmune disease (SLE, APLA)
5. Other than singleton pregnancy

Study procedure: At first visit, pregnancy was confirmed by urine pregnancy test. After taking informed consent women were subjected to detailed history: past history, family history, personal history (especially regarding addiction to tobacco >5 packet/day, smoking >5 cigarettes/day, alcohol >60 ml/day and 5 days a week was defined addiction in our study), obstetric history, menstrual history. For double marker test 3 to 4ml of blood sample was collected in a plain redtop venipuncture tube without additive or anticoagulants taking all aseptic precautions. It was allowed to clot and then serum was separated by centrifuging it at 2, 500 rpm for 10 minutes. These markers were estimated by chemiluminencence immunoassay (enzyme linked immunosorbent assay). Interpretive unit was MoM (multiple of median) which took into account variables such as gestational age (USG), maternal weight, race, multiple gestation, IVF, smoking/tobacco addiction. β hCG< 0.5 MOM, PAPP-A< 0.5 MOM i.e., less than 10th percentile of reference range were considered as high risk cases and all these patients were followed for future development of FGR.

For statistical analysis, we applied chi square test, pearson correlation coefficient and linear regression equation between birth weight of babies and serum levels of β-hCG and PAPP-A were calculated. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for serum β-hCG and serum PAPP-A levels.

Results

The FGR group constituted 35 FGR pregnancy which resulted in live birth at term with no evidence of chromosomal abnormality and non FGR case constituted 50 normal pregnancy which resulted in live birth at term without any evidence of chromosomal abnormality. The maternal baseline characteristics are described in table 1. 17 (48%) cases in FGR group had β hCG level <0.5 MoM and 18 (52%) cases had β hCG levels ≥ 0.5 MoM. In non FGR group maximum 40(80%) cases had β hCG levels <0.5 MoM, least 10(20%) cases had levels ≥ 0.5 MoM. The mean value of serum β hCG in FGR group was found to be significantly low in relation to non FGR group (0.9±0.70 vs 1.49 ± 0.75; P value = 0.001) (table 2).

Table 1: The maternal characteristics of FGR and non FGR group

Characteristics	FGR group (n=35)	Non FGR group (n=50)	P Value
Maternal age (Mean±SD)	30.5 (5.5)	29 (4.1)	0.06
Maternal weight (Mean±SD)	56 (10.6)	58 (11)	0.08
Maternal tobacco addiction	5	0	
CRL (Mean±SD)	67.4(8.8)	66.4(8.6)	0.1
Gestational age at delivery (Mean±SD)	37(1.4)	38(1.6)	0.10
Birth weight (Mean±SD)	2.03(0.21)	2.7(0.16)	0.001

FGR – Fetal growth restriction; CRL – Crown rump length; SD – Standard deviation.

Table 2: Distribution of β hCG Levels in patients with and without FGR

Serum β hCG levels	FGR cases (n=35)	Non FGR cases (n=50)	P Value
<0.5 MoM	17(48%)	10(20%)	
≥0.5 MoM	18(52%)	40(80%)	0.001
Mean±SD	0.94±0.70	1.49±0.75	

FGR – Fetal growth restriction; MoM - Multiple of median.

19 (54.3%) cases in FGR group had serum PAPP-A level <0.5 MoM and 16(45.7%) cases had PAPP-A levels ≥ 0.5 MoM. In non FGR group 42(84%) cases had serum PAPP-A levels ≥ 0.5 MoM and only 8 (16%) cases had levels <0.5 MoM. Mean value of serum PAPP-A in FGR group i.e. 0.76 ± 0.45 was found to be significantly decreased in relation to non FGR group i.e.1.16 ± 0.5 (p value= 0.0005) (table 3).

Table 3: Distribution of serum PAPP-A levels in patients with and without FGR

Serum PAPP-A levels	FGR group (n=35)	Non FGR group (n=50)	P Value
< 0.5 MoM	19(54.3%)	8(16%)	0.0005
≥ 0.5 MoM	16(45.7%)	42(84%)	
Total	35	50	
Mean ± SD	0.76 ± 0.45	1.16 ± 0.53	

Table 4: The calculated sensitivity, specificity, PPV, NPV for double marker test

Parameters	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
Double marker	54.3%	66.04%	52.08%	66.97%	1.56	0.71
Serum beta hCG	48.57%	80%	62.79%	69.12%	2.43	0.64
Serum PAPP-A	54.2%	84%	70.22%	72.56%	3.39	0.54

According to Pearson correlation coefficient there is a negligibly positive correlation between first trimester serum beta hCG levels and birth weight of fetus which is not significant (figure 1). Linear regression equation between β hCG level and birth weight lead to the F value of 0.36 leading to p value of 0.548 which is statistically not significant at alpha value of 0.05. According to Pearson

correlation coefficient there is a positive correlation (weak positive as r value = 0.224) between first trimester serum PAPP-A levels and birth weight of fetus thus we can conclude that with decrease in first trimester serum level of PAPP-A the birth weight decrease (figure 2). Linear regression equation between birth weight and serum PAPP-A lead to the F value of 4.384 leading to p value of 0.0393 which is statistically significant at alpha value of 0.05.

Figure 1: Correlation of MoM of serum beta hCG level with birth weight

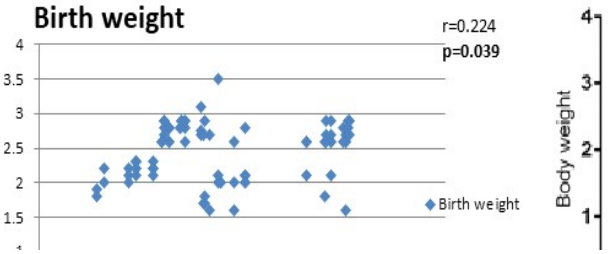

Figure 2: Correlation of MoM of serum PAPP-A level with birth weight.

Discussion

The study was done in 85 antenatal women attending our antenatal OPD. Majority of the patients in both groups i.e. 70% in FGR group and 76% in non FGR group were between the ages of 18 and 34 years. Though theoretically FGR is more being associated with increasing maternal age, but young women as well are at risk for FGR, thus screening for FGR should be implemented irrespective of the age. Majority of cases (55.2%) were found to be primigravida and 44.8 % were multigravida which only showed the trend of the patients attending our OPD. Pertaining to addiction we observed only tobacco chewing and no case of smoking or alcohol. Since maximum women were between age group 18-34 years and were of low to middle class family, the practice of smoking and alcohol consumption were not prevalent in this strata. Moreover even if they consume, women tend to stop them after conception knowing the harmful effects of substance addiction on the fetus. In the present study, though only 5 patients were found to have been addicted to tobacco chewing, during follow up we observed the development of FGR in all of them. This shows a strong co relation between tobacco addiction and FGR because long term tobacco addiction leads to some vasculopathy as well as nicotine exposure is known to induce vasoconstriction in placental vasculature, decrease placental blood flow and reduce trophoblast invasion leading to a delay in establishment of fetal maternal circulation [5]. 41% patients in our study developed FGR which is because of the fact that we did not distinguish SGA and FGR because of lack of clinical data and also in our setting we receive women mostly from lower socioeconomic strata who are malnourished and have risk factors thus low birth weight is much prevalent in our low resource settings. Low birth weight is a consequence of FGR and all LBW babies regardless of being SGA or FGR are liable to develop neonatal complications.

The mean level of β-hCG was reduced in significant number of the women who developed FGR in comparison to group of patients who did not developed FGR (i.e.1.29 ±0. 55 MoM vs1.51 ±0. 46 MoM; p value < 0.05) but its sensitivity for prediction of future FGR was found to be 48 % only. Thus we conclude that though serum beta hCG levels is significantly decreased in first trimester in patients destined to develop FGR fetuses, the sensitivity of the test is not that high. Our study was in accordance with study done by Stefan C Kane et al [6] and Kirkegaard I et al [7]. FGR rarely appear until second half of pregnancy but the process starts early in pregnancy. With maternal or fetal causes of FGR, there is decreased placental transfer of nutrient (including oxygen) resulting in reduced fetal body stores of lipid and glycogen. Human chorionic gonadotropin has been shown to regulate many processes that are related to fetal growth including trophoblast differentiation, various aspect of placentation as well as uterine angiogenesis and vasculogenesis. Beta hCG may also directly influence uterine and fetal growth by acting on gonadotropin receptors present in uterine tissue and fetal membrane [8].

PAPP-A is a protease for insulin like growth factor (IGF) binding protein 4 (IGFBP 4) which is known to influence fetal growth by controlling uptake of amino acids and glucose as well as having an autocrine and paracrine role in trophoblast invasion. Lowered levels of PAPP-A would have less of a protease effect on IGFBPs leading to higher levels of bound (biologically inactive) IGF-I and -II and thus reduced fetal growth [9]. We observed that mean value for serum PAPP-A level was significantly reduced in group of patient who developed FGR as compared to the group who did not develop FGR (i.e. 0.643 ± 0.02 vs 0.93 ± 0.42; p

value of 0.0004) with the sensitivity for prediction of FGR of 55 %. Thus likewise we can conclude that serum PAPP-A levels is also significantly decreased in first trimester in patients destined to deliver FGR fetuses with acceptable sensitivity rates. Similar to our study, Stephen C Kan et al [6], Kevin Spencer et al [10], Kirkegaard I [7] et al also found statistically significant relation between the low value of serum PAPP-A and the occurrence of FGR. Abnormalities in double marker test can also be used as an additional advantage in predicting FGR along with its usual utility as a screening test for aneuploidies [10].

With respect to birth weight, we observed that the mean birth weight of FGR infants were significantly decreased when compared to non FGR infants (2.02±0.2 kg vs 2.7±0.16 kg); p value <0.001). On applying Pearson correlation coefficient between birth weight and serum beta hCG level, negligible positive relationship was found. Similarly with serum PAPP-A level as a component of double marker test, a weak positive relationship was found with birth weight the association of which was statistically significant (p value <0.05). Since PAPP-A, free β-hCG as a component of double marker test are already assessed in pregnant women participating in prenatal screening programs, the use of these measures in early identification would be at no extra cost.

Conclusion

In this study, on applying Pearson correlation coefficient between birth weight and serum PAPP-A level as a component of double marker test, a weak positive relationship was found with birth weight. Patient should be individualized depending on other risk factors also and they should be offered the predictive test for FGR, so that early prediction can be done and treatment provided so as to prevent its complication.

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

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