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ASSESSMENT OF THE FIRST-TRIMESTER SERUM DOUBLE MARKER TEST CLINICAL EFFECTIVENESS

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ABSTRACT

Background: This test was first suggested for the screening of fetal aneuploidies and is performed between 9-13 weeks. **Aim**: The purpose of the current study was to evaluate the clinical effectiveness of the serum double marker test in the first trimester as a means of predicting fetal growth limitation.

Methods: The study analysed the incidence of fetal growth restriction in females in the first trimester who had a double marker test. The specificity and sensitivity of the test were assessed by comparing the relative incidence at respective MoM cut-offs.

Results: Pregnant women with fetal growth restriction had 70 pregnancies, while those without GFR had 100 pregnancies. With a difference of 0.92±0.68 MoM to 1.47±0.73 MoM ($p<0.05$), the FGR group's mean β-hCG levels were lower. Nevertheless, it has a 48% sensitivity for future FGR prediction. At a sensitivity of 54.3% for FGR prediction, the mean serum PAPP-A was considerably lower in the FGR group, measuring 0.74±0.43 as opposed to 1.14±0.51 with $p=0.0004$. Birth eight had a statistically significant correlation with the blood PAPP-A level, indicating a mild positive relationship.

Conclusion: In the absence of an aberrant karyotype, the current study finds that low levels of maternal blood PAPP-A and free β-hCG are linked to an increased chance of delivering a fetal growth-restricted child.

Keywords: β-hCG, FGR, MoM. PAPP-A, fetal growth restriction

INTRODUCTION

Nearly 5–10% of pregnant women may have fetal growth restriction (FGR), a disease in which the fetus is unable to reach its development potential as <10th percentile for a given gestational age. It is linked to higher mortality and perinatal death rates. Intrauterine fetal death, surgical deliveries, and intrapartum fetal morbidities are the causes of this. Barker's theory states that metabolic disorders, obesity, behavioral dysfunction, developmental delay, and cerebral palsy are examples of long-term FGR consequences.1

The interplay of physiological and pathological factors affecting the fetus is illustrated by fetal growth, which is a crucial predictor of pregnancy outcomes. Most SGA (small for gestational age) babies are tiny constitutionally and physiologically, but pathological FGR affects around 9% of the fetus.

However, there is limited capacity to distinguish between pathological and physiological FGR. As a result, FGR is an illness that is simple to describe yet challenging to diagnose. In order to screen for aneuploidies in the first or second trimester of pregnancy, maternal serum analytes were initially investigated. Their use was subsequently expanded to include studies to evaluate their potential as a marker for poor placentation. Changes in the concentration of placental products in serum are thought to be caused by trophoblastic invasion failure.3

The double marker test, which is performed between weeks 9 and 13, measures the levels of hCG and PAPP-A (pregnancy-associated plasma protein) in the blood of expectant mothers. It was first advised for screening of prenatal aneuploidies, but, nowadays, its role is also established for fetal growth limitation prediction even in genotypically normal pregnancies.[4]

MATERIALS AND METHOD

The current study sought to evaluate the clinical effectiveness of the serum double marker test in the first trimester as a means of predicting fetal growth limitation.

Assessing the clinical effectiveness of the first-trimester serum double marker test as a means of predicting fetal growth restriction was the goal of the current observational study. The participants in the study came from the Institute's Obstetrics and Gynaecology Department. All subjects gave their written and verbal informed permission prior to their involvement in the study.

All pregnant women in the first trimester, between weeks 9 and 13, who volunteered to participate in the research were enrolled. Participants who did not have a singleton pregnancy, autoimmune illnesses such APLA and/or SLE, renal disease, overt diabetes, or persistent hypertension were excluded from the research.

Following a urine pregnancy test to confirm pregnancy at the initial visit, a thorough medical history was obtained from each participant. This included information on menstruation, obstetrics, personal history of tobacco addiction (defined as consuming more than five packets of tobacco per day, smoking more than five cigarettes per day, and consuming more than 60 milliliters of alcohol per day and five days per week), family history, and the subjects' history.

Three to four millilitres of venous blood were drawn under stringent aseptic and sterile conditions in a simple tube devoid of additives or anticoagulants in order to perform the double marker test. The blood was then allowed to coagulate before the serum was separated by centrifugation at 2500 rpm for ten minutes. ELISA (enzyme-linked immunosorbent assay) chemiluminescence was used to assess three indicators using intraoperative units as MoM (multiple of median), taking into account factors like multiple gestation, IVF, maternal weight, race, smoking and nicotine addiction, and gestational age at ultrasound. All individuals were monitored for future FGR development, and a high-risk scale was taken into consideration for β hCG< 0.5 MOM and PAPP-A< 0.5 MOM, which is less than the 10th percentile of the reference range.

The chi-square test, linear regression equation, Pearson correlation coefficient, and SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk, NY, USA) were used to statistically analyse the collected data. In relation to PAPP-A and serum hCG levels, the double marker test's specificity, sensitivity, negative likelihood ratio, positive likelihood ratio, negative predictive value, and positive predictive value were also evaluated.

RESULTS

The goal of the current observational study was to evaluate the clinical effectiveness of the blood double marker test in the first trimester as a means of predicting fetal growth limitation.

In the research, 170 girls were evaluated, 70 of them were in the FGR group and the other 100 in the non-FGR group. With p=0.001, the non-FGR group's mean birth weight was substantially greater than that of the FGR group. The FGR and non-FGR groups showed statistically similar levels of maternal weight, age, CRL, and gestational age at delivery (p=0.12, 0.11, 0.07, and 0.06, respectively) (Table 1).

In terms of the distribution of β-hCG levels across study participants with and without FGR, the mean serum β-hCG levels were 0.92±0.68 in the FGR group and 1.47±0.73 in the non-FGR group. The non-FGR group had considerably higher values (p=0.001). Less than 0.5 MoM was seen in 20% (n=20) of the non-FGR group and 48.57% (n=34) of the FGR group.

Statistically significant levels of ≥0.5 MoM were seen in 52% (n=36) of FGR participants and 80% (n=80) of non-FGR subjects, with p=0.001 (Table 2). The distribution of serum PAPP-A levels in study participants with and without FGR was found to be 0.74±0.43 in the FGR group and 1.14±0.51 in the non-FGR group. The non-FGR group had a significantly higher mean value of PAPP-A (p=0.0004). In the non-FGR group, PAPP-A of ≥0.5 MoM was seen in 54.3% (n=38) and 16% (n=16) of the participants, whereas in the FGR group, it was observed in 45.7% (n=32) and 84% (n=84) of the subjects, demonstrating statistical significance with p=0.0003 (Table 3).

The results of the study indicated that serum PAPP-A had negative likelihood ratio, positive likelihood ratio, NPV, PPV, specificity, and sensitivity of 0.52, 3.37, 72.54, 70.20, 82%, and 54%, respectively, when evaluating the double marker test's negative likelihood ratio, positive likelihood ratio, negative predictive value, positive predictive value, specificity, and negative likelihood ratio. The corresponding NPV, PPV, specificity, sensitivity, negative likelihood ratio, and positive likelihood ratio of serum beta-hCG were 0.62, 2.41, 69.10, 62.77, 80%, and 48.55%. NPV, PPV, specificity, sensitivity,

and negative and positive probability ratios for the double marker test were 0.69, 1.54, 66.95, 52.06, 66.02%, and 54.1%, respectively (Table 4).

DISCUSSION

170 girls were evaluated in this study, 70 of them were in the FGR group and the remaining 100 in the non-FGR group. With p=0.001, the non-FGR group's mean birth weight was substantially greater than that of the FGR group. The FGR and non-FGR groups showed statistically similar levels of maternal weight, age, CRL, and gestational age at delivery (p=0.12, 0.11, 0.07, and 0.06, respectively). The findings were similar to those from earlier research by Spencer K et al. (2008) and Dugoff L et al. (2004), in which the authors evaluated participants with similar demographics to the current study.

The distribution of β-hCG levels in study participants with and without FGR was revealed by the findings. The mean serum β-hCG levels in the FGR group were 0.92±0.68, while the non-FGR group had 1.47±0.73 levels. The non-FGR group had considerably higher levels (p=0.001).

In the FGR group, 48.57% (n = 34) of the participants and 20% (n = 20) of the non-FGR group had <0.5 MoM. Five-two percent (n=36) of the FGR group and eighty percent (n=80) of the non-FGR group had levels of ≥0.5 MoM, which were statistically significant (p=0.001). These findings aligned with those of researchers Barjaktarovic M et al. (2014) and Kirkegaard I et al. (2011), who found that the distribution of β-hCG levels in study participants with and without FGR was similar to the findings of the current study.

The mean value of PAPP-A was 0.74±0.43 in the FGR group and 1.14±0.51 in the non-FGR group, which was substantially higher in the non-FGR group (p=0.0004). This contrast was seen in the distribution of serum PAPP-A levels in study individuals with and without FGR.

In the non-FGR group, PAPP-A of ≥0.5 MoM was observed in 54.3% (n=38) and 16% (n=16) of the subjects, while in the FGR group, it was observed in 45.7% (n=32) and 84% (n=84) of the subjects, demonstrating statistical significance with p=0.0003. These results were consistent with those of Kane S et al. (2014) and Harrington K et al. (1997), who previously reported similar serum PAPP-A level distributions in FGR and non-FGR subjects in their respective investigations.

On evaluating the double marker test's specificity, sensitivity, negative predictive value, positive predictive value, and negative probability ratio, the study's findings also demonstrated, the study results showed that serum PAPP-A had negative likelihood ratio, positive likelihood ratio, specificity, sensitivity, NPV, and PPV of 0.52, 3.37, 72.54, 70.20, 82%, and 54%, in that order. NPV, PPV, specificity, sensitivity, negative likelihood ratio, and positive likelihood ratio of serum beta-hCG were, respectively, 0.62, 2.41, 69.10, 62.77, 80%, and 48.55%. Specificity, sensitivity, NPV, PPV, negative likelihood ratio, and positive likelihood ratio for the double marker test were, in order, 0.69, 1.54, 66.95, 52.06, 66.02%, and 54.1%. These results were consistent with the findings of Kranrz D et al. (2004) and Goetzl L et al. (2010), who reported that the double marker test's specificity, sensitivity, negative likelihood ratio, positive likelihood ratio, negative predictive value, and positive predictive value were similar to those of the current study.

CONCLUSION

According to the current study's limitations, low levels of maternal serum PAPP-A and free β-hCG are linked to a higher chance of delivering a fetal growth-restricted kid even in the absence of an aberrant karyotype. However, in order to draw a firm conclusion, further longitudinal research is required in the future.

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Characteristics	FGR group n=70	Non-FGR group n=100	p-value
Mean birth weight	2.01±0.19	2.5±0.14	0.001
Gestational age at delivery	37±1.2	38±1.4	0.12
CRL	67.2±8.6	66.2±8.4	0.11
Maternal tobacco addiction	10	0	
Maternal weight	56±10.4	58±10.8	0.07
Maternal age	30.3±5.3	29±3.9	0.06

Table 1: Demographic data of mothers in FGR and non-FGR study subjects

Serum β-hCG levels	FGR group n=70 (%)	Non-FGR group n=100 (%)	p-value
Mean	0.92±0.68	1.47±0.73	0.001
<0.5MoM	34 (48)	20 (20)	
≥0.5 MoM	36 (52)	80 (80)	

Table 2: Distribution of β-hCG levels in study subjects with and without FGR

Serum PAPP-A levels	FGR group n=70 (%)	Non-FGR group n=100 (%)	p-value
Mean	0.74±0.43	1.14±0.51	0.0004
<0.5MoM	38 (54.3)	16 (16)	
≥0.5 MoM	32 (45.7)	84 (84)	

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

Parameters	Negative likelihood ratio	Positive likelihood ratio	Negative predictive value	Positive predictive value	Specificity	Sensitivity
Serum PAPP-A	0.52	3.37	72.54	70.20	82	54
Serum beta-hCG	0.62	2.41	69.10	62.77	80	48.55
Double marker	0.69	1.54	66.95	52.06	66.02	54.1

Table 4: Negative likelihood ratio, positive likelihood ratio, negative predictive value, positive predictive value, specificity, and sensitivity of double marker test in the study