

ORIGINAL RESEARCH

Association of maternal serum biochemical markers in fetal growth restriction in a tertiary care centre

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ABSTRACT

Intrauterine Growth Restriction is one of the major factors in perinatal morbidity and mortality. Routine antenatal care focuses on the detection of women at increased risk, aiming at careful monitoring and appropriate intervention. Although this problem manifests in the second half of pregnancy and most research has been employed accordingly, there is evidence that they are associated with events taking place in the first trimester of pregnancy. In the first trimester of pregnancy the placently derived biochemical markers (Pregnancy Associated Plasma Protein-A and free beta hCG) are increasingly being used in conjunction with the ultrasound measurement of nuchal translucency as part of screening programs for trisomy 21 and other aneuploidies. Approximately 90 percentage of such anomalies can be identified with a false positive rate of 5%. Preliminary studies have shown that reduced levels of these biochemical markers particularly PAPP-A may be of potential value in identifying those pregnancies that may result in adverse outcome including the delivery of small for gestational age.

Aims and Objectives: To determine the association of maternal serum biochemical markers with adverse pregnancy outcomes such as Fetal Growth Restriction.

Methods and Materials: A hospital based prospective study was done among 1084 pregnant women attending department of obstetrics and gynaecology, Sree Gokulam Medical College and Research Foundation during the study period from 1st May 2021 to 30th May 2022. All antenatal patients those who have fulfilled the inclusion and exclusion criteria were allocated in the study by random sampling method after obtaining informed consent. Maternal biochemical markers such as Pregnancy Associated Plasma Protein-A and beta HCG values were obtained from the double marker test done at 11-14 weeks. Data was entered into MS excel 2016 and was analyzed by ANNOVA, mean and standard deviation using SPSS software and data was represented using pie charts and bar charts.

Results: Majority of patients belong to age group of 21 to 30 years. The mean pre-pregnancy weight of the pregnant women was 62.19 ± 8.18 kg. The mean body mass index among the pregnant women was 23.77 ± 2.42 kg/m². 54.5% of pregnant women were primigravida. Incidence of FGR was 20.8%. There was statistical significant correlation between B-HCG and PAPP-A with FGR (P value <0.05).

Conclusion: It was concluded in present study that there was significant association of maternal serum biochemical markers such as PAPP-A and Beta HCG in FGR.

Key words: Fetal growth restriction, beta-HCG, PAPP-A, pregnancy, serum biochemical markers

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INTRODUCTION

The process of birth is the most dangerous journey an individual undertakes. A healthy newborn is the goal of every expectant mother and her obstetrician¹. A fetus with an estimated weight below the 10th percentile for a given gestational age is considered to have fetal growth restriction (FGR) also called as Intrauterine Growth Restriction (IUGR). It is estimated that the incidence of Fetal Growth Restriction is 3-10%^{2, 3}. Fetal Growth Restriction is

linked to an increased risk of perinatal morbidity and mortality. Growth restricted fetuses are more prone to intrauterine hypoxia/asphyxia.

In the first trimester of pregnancy the placently derived biochemical markers (Pregnancy Associated Plasma Protein-A and free beta hCG) are increasingly being used in conjunction with the ultrasound measurement of nuchal translucency as part of screening programs for trisomy 21 and other aneuploidies. Approximately 90 percentage of such

anomalies can be identified with a false positive rate of 5%. Preliminary studies have shown that reduced levels of these biochemical markers particularly PAPP-A may be of potential value in identifying those pregnancies that may result in adverse outcome including the delivery of small for gestational age infant¹⁰.

Hence, present study was done to correlate the maternal serum bio-markers such as free beta-HCG and PAPP-A and Fetal Growth Restriction.

MATERIALS AND METHODS

STUDY SITE: This study was conducted in the Department of obstetrics and gynecology, Sree Gokulam Medical College and Research Foundation, Trivandrum

STUDY POPULATION: All antenatal patients who were admitted in Sree Gokulam Medical College and Research Foundation

STUDY DESIGN: The current study was a hospital based observational study.

SAMPLE SIZE: Sample size was estimated using the formula:

$$n = \frac{z_{1-\alpha/2}^2 p(1-p)}{d^2}$$

Where, p= proportion of fetal growth restriction (primary outcome variable) in PAPP- A <10th percentile

(0.039 from Gomes *et al.*) d = relative precision

$\alpha=5\%$

Z $1-\alpha/2 = 1.96$ n = 2367 Applying finite population correction

Population size (anticipated number of deliveries during 1yr of data collection), n=2000. The sample size was fixed as 1084.

SAMPLING TECHNIQUE: All antenatal patients those who have fulfilled the inclusion and exclusion criteria were allocated in the study by random sampling method.

STUDY DURATION: The present study was conducted during the period from 1st May 2021 to 30th May 2022.

INCLUSION CRITERIA

1. Singleton pregnancy.
2. Gestational age of 11 - 13+6 weeks.

EXCLUSION CRITERIA

1. Unwilling patients.
2. Multiple gestation.
3. Chronic hypertension.
4. Chromosomal anomalies.
5. Known case of SLE, Anti-pholipid antibody syndrome and other autoimmune diseases.
6. Overt diabetes mellitus.

ETHICAL CONSIDERATION

Study was approved by institutional human ethics committee. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

METHODOLOGY

This study includes antenatal women in Sree Gokulam Medical College and Research Foundation. Maternal demographic characteristics such as age, parity, height, pre-pregnancy weight, weight gain during pregnancy, medical history are obtained from the antenatal records of the patients. Maternal biochemical markers such as Pregnancy Associated Plasma Protein-A and free beta hCG values were obtained from the double marker test done at 11-14 weeks. If double marker test was abnormal the patient was referred to the Department of Fetal Medicine for an amniocentesis to rule out chromosomal anomalies. On routine ANC symphysiofundal height was measured and 2 weekly scan was advised in patients with abnormal symphysiofundal height. Fetal growth restriction was assessed by plotting growth chart using abdominal circumference of fetus and estimated fetal weight from obstetrics scans done during antenatal period. Mediscan growth chart was used. Low dose aspirin was given to high-risk antenatal patients and those with abnormal serum biochemical markers (PAPP A <0.4).

STATISTICAL METHODS

Data was entered in to MS excel 2016 and analyzed. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram, pie diagram and box plots. Pearson chi square test and ANNOVA test were used to correlate variables. Statistical analysis was made with IBM SPSS 20.0 software and P value of <0.05 was considered significant.

RESULTS

Table 1: Distribution of pregnant women according to their age (n=1084)

Age (years)	Frequency	Percentage
≤ 20	107	9.9
21-30	857	79.1
31-40	110	10.1
>40	10	0.9
Total	1084	100.0
Mean ± SD	25.63 ± 4.06years	
Minimum age	18years	
Maximum age	43years	

In current study, majority of antenatal mothers (79.1%) belong to age group of 21 to 30years, 10.1% of pregnant women belong to age group of 31 to 40years, 9.9% of patients belong to age group of less than 20years and 0.9% of pregnant women belong to age group of more than 40 years.

Table 2: Distribution of pregnant women according to fetal growth restriction (n=1084)

FGR	Frequency	Percentage
No	859	79.2
Yes	225	20.8
Total	1084	100.0

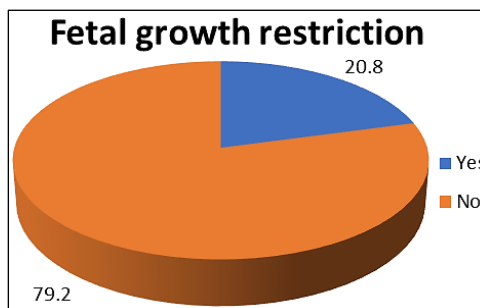


Chart 1: Pie chart showing distribution of pregnant women according to fetal growth restriction

Table 5: Comparison of mean maternal free beta hCG among normal pregnant women and pregnant women with fetal growth restriction (n=1084)

Group	Maternal β-hCG (MoM)		t value	p value
	Mean	SD		
FGR	1.66	1.08	6.02	<0.001*
Normal	1.17	0.79		

In current study, among normal pregnant women the mean maternal free β-hCG was 1.17 ± 0.79MoM whereas among pregnant women with fetal growth restriction, the mean maternal β-HCG was 1.66 ± 1.08MoM. There was statistical significantly increase in maternal free beta hCG among pregnant women with fetal growth restriction when compared with normal pregnant women (P value <0.001).

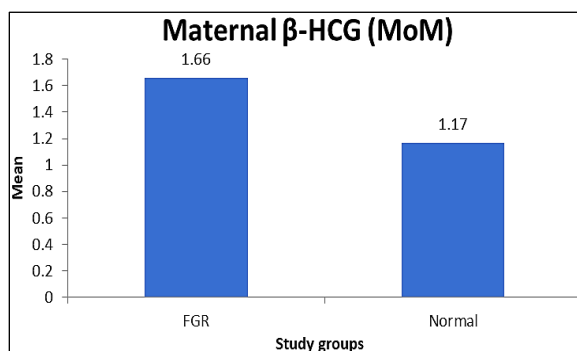


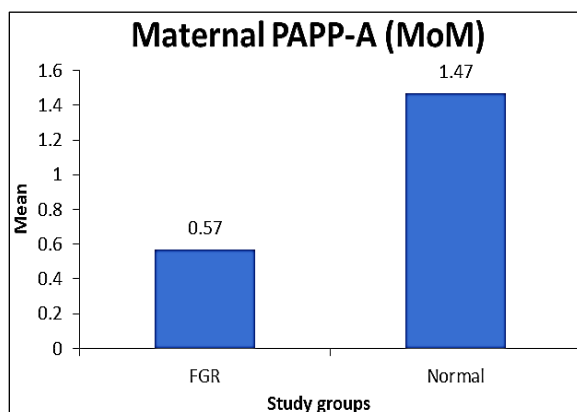
Chart 4: Bar chart showing comparison of mean maternal free beta hCG among normal pregnant women and pregnant women with fetal growth restriction

Table 6: Comparison of mean maternal PAPP-A among normal pregnant women and pregnant women with fetal growth restriction (n=1084)

Group	Maternal PAPP-A (MoM)		t value	p value
	Mean	SD		
FGR	0.57	0.38	-20.04	<0.001
Normal	1.47	1.05		

In current study, among normal pregnant women the mean maternal PAPP-A was 1.47 ± 1.05 MoM whereas among pregnant women with fetal growth restriction, the mean maternal PAPP-A was 0.57 ± 0.38 MoM.

There was statistical significantly decrease in maternal PAPP-A among pregnant women with fetal growth restriction when compared with normal pregnant women (P value <0.001).

**Chart 5: Bar chart showing comparison of mean maternal PAPP-A among normal pregnant women and pregnant women with fetal growth restriction**

DISCUSSION

A hospital-based study was done among 1084 pregnant women attending department of obstetrics and Gynaecology, Sree Gokulam Medical College and Research Foundation during the study period from 1st May 2021 to 30th May 2022. All antenatal patients those who have fulfilled the inclusion and exclusion criteria were allocated in the study by random sampling method after obtaining informed consent. Maternal biochemical markers such as Pregnancy Associated Plasma Protein-A and free beta HCG values were obtained from the double marker test done at 11-14 weeks.

AGE

In current study, majority of antenatal mothers (79.1%) belong to age group of 21 to 30 years, 10.1% of pregnant women belong to age group of 31 to 40 years, 9.9% of patients belong to age group of less than 20 years and 0.9% of pregnant women belong to age group of more than 40 years. The mean age of the pregnant women was 25.63 ± 4.06 years with minimum age of 18 years and maximum age of 43 years.

In a study done by **Yeshey Dorjey et al.** [21] showed that the mean age of the cases was 26.7 ± 4.79 years whereas the mean age of the controls was 27.1 ± 4.66 years where there was no statistical significance (P value 0.616).

CORRELATION BETWEEN FREE BETA HCG AMONG NORMAL PREGNANT WOMEN AND PREGNANT WOMEN WITH FETAL GROWTH RESTRICTION

In current study, among normal pregnant women the mean maternal free β -HCG was 1.17 ± 0.79 MoM whereas among pregnant women with fetal growth restriction, the mean maternal β -HCG was 1.66 ± 1.08 MoM. There was statistical significantly increase in maternal beta HCG among pregnant women with fetal growth restriction when compared with normal pregnant women (P value <0.001).

In a study done by **Kirkegaard I et al.** [15] showed that 6.5% of patients low beta HCG levels whereas 93.5% of patients had normal beta HCG levels where there was statistical significance (P value 0.001).

In a study done by **Sirikunalai P et al.** [19] showed that 4% of pregnant women with IUGR had normal HCG, among cases with low beta HCG 5.8% of pregnant women had IUGR and among cases with high beta HCG 3.8% of pregnant women had IUGR where there was no statistical significant (P value >0.05).

CORRELATION BETWEEN PAPP-A AMONG NORMAL PREGNANT WOMEN AND PREGNANT WOMEN WITH FETAL GROWTH RESTRICTION

In current study, among normal pregnant women the mean maternal PAPP-A was 1.47 ± 1.05 MoM whereas among pregnant women with fetal growth restriction, the mean maternal PAPP-A was 0.57 ± 0.38 MoM. There was statistical significantly

decrease in maternal PAPP-A among pregnant women with fetal growth restriction when compared with normal pregnant women (P value <0.001).

In a study done by Kirkegaard I *et al.* [15] showed that 9.3% of patients showed low PAPP-A levels whereas 90.7% of patients had normal PAPP-A levels where there was significant reduction in PAPP-A levels among patients with FGA when compared with normal pregnant women.

CONCLUSION

It was concluded in present study that the incidence of FGR was 20.8%. There was statistical significantly increase in maternal free beta HCG among pregnant women with fetal growth restriction when compared with normal pregnant women (P value <0.001). There was statistical significantly decrease in maternal PAPP-A among pregnant women with fetal growth restriction when compared with normal pregnant women (P value <0.001).

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