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Comparison of Placental Growth Factor Levels between Small for Gestational Age with Appropriate for Gestational Age Mothers

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ABSTRACT

Objective: To compare the levels of Placental Growth Factor among small for gestational age with appropriate for gestational age mothers.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Obstetrics and Gynecology, Ayub Medical complex, Abbottabad Pakistan, from Aug 2021 to Jan 2022.

Methodology: The studied population included a total 68 mothers in last trimester with 34 in each Group, i.e. appropriate for gestational age and small for gestational age. Fetal size was estimated either by clinical examination (symphysis fundal height) or estimated fetal weight by ultrasound examination. Sociodemographic factors, along with reproductive history were recorded and blood samples analyzed for Placental Growth Factor difference in both Groups.

Result: Participant's age ranged from 20-40 years (31.68±5.81 years) with no difference in their gestational periods (p=0.26). The Placental Growth Factor in small for gestational age was observed in below normal concentration (mean value =24.23 pg/mL ±14.03) while it was observed in normal ranges in appropriate for gestational age mothers (mean value =126.72 pg/mL ±19.89) with p-value <0.001.

Conclusion: Mothers with small for gestational age had significantly lower placental growth factor levels compared to mothers with appropriate for gestational age.

Keywords: Gestational Age, Intrauterine Growth Retardation, Placental Growth Factor, Small for Gestational Age.

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INTRODUCTION

Mortality in low-birth-weight babies is 20 times more common than normal.[1] The incidence of low birth weight in Pakistan is estimated to be around 10-25%.[2] The early detection of Intrauterine Growth Retardation (IUGR) can prevent most of these high-risk mothers. These high-risk mothers are detected by medical personal in hospitals by measuring symphysis-fundus height, which can miss affected fetuses in >70%.[3] Therefore, they are also offered ultrasound as an adjunct for fetal biometrics which include abdominal and head circumference & its ratio, biparietal diameter and femur length.[4]

New research suggests presence of abnormal levels of various maternal biochemical markers in IUGR which include Plasma Protein-A, Alpha fetoprotein and free β-human chorionic gonadotropin.[5,6] A unique maternal serum PlGF has also been noted to remain in low levels in second and third trimester of pregnancies in these patients.[7,8]

Literature search reveals scant local data on the association PlGF and IUGR, which forms the rationale for our study. Our objective was, in mothers of 20-41 weeks' gestation, to compare the levels of Placental Growth Factor among small for gestational age with appropriate for gestational age mothers and to identify the predictive value as a reliable biochemical marker in detecting / screening the small for gestational age.

METHODOLOGY

The cross-sectional study was conducted at the Obstetrics and Gynecology Department of Ayub Medical Complex, Abbottabad, Pakistan from August 2021 to January 2022. Permission was sought from Ethical Review Committee prior to commencement of the study.

Inclusion Criteria: Women aged 18 to 70 years, having gestation of 20-41 weeks with single live fetus were included.

Exclusion Criteria: Pregnant mothers with twin or multiple fetuses, diagnosed patients of preeclampsia

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and gestational diabetes, and known chromosomal and/or congenital abnormalities were excluded.

Sample size was calculated using WHO Sample Size calculator, 80% power with confidence level of 95% and Odds ratio of 10.73 for Low birth weight as per the research in local population by Badshah *et al.*,[1] which came to 68. Data collection started after obtaining written, informed consent use purposive, non-probability sampling. The studied population consist of all pregnant women who came for antenatal visits in their last trimester, they were categorized into two Groups, either having pregnancy which was appropriate for gestational age (Group-A, n=34) or small for gestational age (Group-B, n=34) which was confirmed by either clinical examination (symphysis fundal height) or estimated fetal weight by ultrasound examination.

The blood samples were taken within 14 days either after clinical or by ultrasound examination, in which venous blood was obtained by puncturing the vein. 10ml plasma tubes were used with EDTA and later the plasma was isolated by centrifugation at three thousand revolutions per minute for ten minutes. The samples were stored in pathology department of Ayub Medical Complex at -80°C. Samples were measured for PlGF in batch on automated Enzyme linked immunosorbent assay as per the manufacturer recommendation and guidelines. The blood samples were stored in 2-8°C, and those that need to be measured along with all kit items warmed naturally to room temperature for 30 minutes. Collected plasma using EDTA as anticoagulant. Then it was centrifuged at three thousand revolutions per minute for about twenty minutes and the supernatant was collected. The PlGF level greater than 100 pg/mL were considered normal, samples concentration in the range of 12 to 100 pg/mL PlGF level were considered low and less than 12 pg/mL PlGF concentration was considered very low in the study.[9]

The results were noted in the laboratory proforma in Microsoft Excel version 2016. All collected data was entered in the Statistical Package for Social Sciences (SPSS) version 26. Frequency and percentages were presented for all qualitative variables i.e., nulliparity. Mean and standard deviation were calculated for all numerical variables i.e., mother age (years), gestational age (weeks) and levels of PlGF in both Groups. The normality of the continuous data for PlGF was tested with Shapiro-Wilk test and revealed that it was not normally distributed. Mann-Whitney U test was used to test for the significance of the difference between both Groups. The *p*-value of ≤0.05 was taken as significant.

RESULTS

Among all 68 mothers' age range from 20-40 years (Mean±SD; 31.68±5.81 years). In Group-B and Group-A mothers, the mean age was 32.47±6.54 weeks and 30.88±4.95 weeks respectively, with no significant difference (p=0.26).

In the reproductive history of both groups, few mothers had history of previous low birth weight babies, but it did not show any statistical significance (p =0.493) as summarized in Table-I.

Table-I: Reporoductive History of Mothers across Groups (n=68)

Parameter	Total (n=68)	Group-B (n=34)	Group-A (n=34)
Previous history of low birth weight			
Present	10(14.7%)	04(11.7%)	06(17.6%)
Absent	58(85.3%)	30(88.3%)	28(82.4%)
Parity			
Primi (1)	40(58.8%)	20(58.8%)	54(79.5%)
Multi (>1)	28(41.2%)	14(41.2)	14(41.2%)
Baby delivery option			
Hospital	58(85.3%%)	29(85.3%)	29(85.3%)
Home	10(14.7)	05(14.7%)	05(14.7%)

Table-II: Comparison of PlGF between Groups (n=68)

Parameters	Study Groups		*p*-value
	Group-A (n=34)	Group-B (n=34)	
Placental Growth Factor	122.18 (100.41-168.89)	20.47 (3.05-55.69)	<0.001

The measured level of PlGF in the blood of Group-B participants was found to be below the normal range. The observed mean of the PlGF level was 24.23 pg/mL ±14.03 with minimum level of 3.06 pg/mL and maximum level of 55 pg/mL. Among these samples, 24(76.5%) samples were found in the range of low concentration, and 8(23.5%) samples were observed in the range of very low concentration. None of the sample was observed in the range of normal concentration for PlGF level.

In Group-A, PlGF remained in the normal range. The maximum level of PlGF was 168 pg/mL and minimum observed level was 100 pg/ml. The mean value was 127.23 pg/mL ±19.89. The PlGF levels of the 33(97%) samples were observed in normal range and 1(3%) sample level was below the normal range of PlGF. No sample was observed in the range of very low concentration.

This difference in the levels of PlGF between both Groups when compared, was found to be significantly lower in the GROUP-B as compared to Group-A, (*p*-value <0.001) (Table-II).

DISCUSSION

Pregnancies with Small for Gestational Age (SGA) fetuses cause significant childhood morbidity and mortality in South Asia, its incidence is the highest among the developing countries reaching up to 27% percent, while in Pakistan it was found to be round 19%.[10] Around 10% of live births are small for gestational age, and among those around 10% cannot achieve optimal growth, therefore detecting SGA fetuses earlier during pregnancy is important to reduce its chances and timely detection can help in the implementation of various treatments.

PlGF has proven to be an important key player in the diagnosis of pregnancy and has been researched previously in Pakistan.[11,12] But its role in the early detection of small-for-gestation pregnancies and as well intrauterine growth restriction is evolving.

The predictable outcome of the study in which PlGF was found to be in low concentrations in mothers having SGA fetuses will enlighten the clinicians to utilize this handy laboratory test for rapid detection of the vulnerable mothers. Benton et al. published a study to verify the sensitivity of the PlGF for early detection of SGA babies in mothers and claiming that low PlGF level in maternal serum can significantly identify placental pathology and is a promising tool for antenatal discrimination of FGR from fetuses who are constitutionally small.[13] Another study reported low PlGF levels in women having 36th week of gestation who delivered SGA infants. The PlGF at 36th weeks predicts with 69.2% sensitivity with 90% specificity which reveals its importance in antenatal surveillance.[14]

We reported a mean gestational age of 31.68±5.81 weeks in mothers which is similar to a study conducted at the neonatal intensive care unit (NICU) of Agha Khan University Hospital, Karachi. The study reported 32.9±2.4 mean gestational age which is close to our reported value.[15] Both studies have been conducted in Pakistan and this may be the cause of the similarities in the reports.

In our study, the frequency of low birth weight is 14.7% in the mothers while Ethiopian study reported 24% low birth weight cases which shows sufficient difference in the reported cases.[15] The difference may be due to certain factors such as economical and geographical differences. Another study performed in Kashmir, Pakistan, in 2017 reported 10% of low birth weight in a total of 1863 participants.[16]

A study carried out by Kamal *et al*.[17] in a large cohort of mothers researched for the incidence of low birth weight as per demography in Pakistan, the maximum number of mothers who had low birth weight babies were born in Baluchistan followed by Gilgit Baltistan. In KPK this percentage was 21%.

The current study reported parity of the study population as primigravid 59% and multigravida 41%. A study published in Ethiopia reported primigravid 44% and multigravida 56% in the total of 381 participants.[18] The findings show that more people are in the category of multigravida and mothers have the trend of more than one pregnancy in Ethiopia compared to Pakistan.

In our research, we found that PlGF values are lower in mothers with SGA fetuses, but when a study by Paules *et al*.[19] who researched on the cohorts came to the conclusion that despite use of special growth charts and normal doppler studies there were still chances of having SGA fetuses, and they concluded that there might be a subgroup of SGA fetuses that suffer from stunted fetal growth and which might be due to poor nutritional conditions and cannot be detected by standard biophysical tools. Anderson *et al.*[20] in their research also found association of gestational hypertension in the mothers who were found to have low placental growth factor. In our research few mothers were on antihypertensive medication, but due to the nature of our research we could not serially monitor their blood pressures and not able to develop the questionnaire for follow up in this regard.

One European study showed that various angiogenic biomarkers, including placental growth factor, are similar to serial doppler ultrasound examination in finding high-risk mothers especially with intrauterine growth restriction or small for gestational age.[21]

A study reported level of PlGF between SGA and non-SGA participants with gestational ages between 10th and 14th weeks, and found the trend of lower levels of PlGF in SGA participants.[21] Obliging to our hypothesis, one study reported a significantly lower levels of PlGF in SGA mothers, and found normal levels in AGA mothers.[16] We reported a mean PlGF concentration of 24.23 pg/mL maternal serum and 126.72 pg/mL mean PlGF concentration in AGA

maternal serum. One study reported 63.34 pg/mL of PlGF level in the SGA mothers and 116.75 pg/mL in the AGA mothers.[17]

We reported the existence of an association between maternal PlGF and SGA; this claim is also proved by many published reports.[22] These findings suggest a strong association of a low level of PlGF with SGA, and it also gives an indication of PlGF normal level with AGA pregnancy.

CONCLUSION

The current study concluded that mothers having low level gave indicator of SGA and mothers having high concentration of PlGF gave indicator for AGA.

Conflict of Interest: None.

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Authors Contribution:

Following authors have made substantial contributions to the manuscript as under:

MI & MS: Data acquisition, data analysis, critical review, approval of the final version to be published.

TS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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