Research article

Exploring the association between PLGF and pregnancy outcomes

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ABSTRACT

Introduction and Aim: Pregnancy demands vigilant fetal monitoring, yet traditional methods have limitations, leading to research on biomarkers like placental growth factor (PLGF) to enhance predictive accuracy for adverse outcomes. This investigation focuses on assessing the relationship between PLGF levels and pregnancy outcomes in women with suspected preeclampsia.

Materials and Methods: A simple longitudinal design was employed, following pregnant women with suspected preeclampsia from enrollment until delivery. The study included 160 subjects, and their characteristics were recorded at admission. PLGF levels were measured, and pregnancy outcomes were assessed.

Results: Among the study population, the distribution of pregnancies showed that 45.62% were in the first pregnancy, 40% in the second pregnancy, 11.85% in the third pregnancy, and 2.5% in the fifth pregnancy. The highest PLGF levels were observed in the fifth pregnancy group.Analysis revealed that subjects with NICU admission had a lower mean PLGF value compared to those without NICU admission. Among subjects with low PLGF levels, the mean baby weight was lower by approximately 5.3% when match up to those with normal PLGF levels.Regarding blood pressure, subjects with decreased PLGF levels had a higher mean systolic blood pressure in contrast to those with normal PLGF levels.

Conclusion: Lower PLGF levels were associated with NICU admission, lower baby weight, and higher systolic blood pressure in women with suspected preeclampsia. These findings suggest that PLGF levels may have implications for pregnancy outcomes. Additional investigation with expanded sample sizes is necessary to authenticate these discoveries and look into the clinical relevance of PLGF in understanding and addressing preeclampsia.

Keywords: Biomarker; preeclampsia; PLGF.

INTRODUCTION

Pregnancy is a complex physiological process that involves significant changes in the mother's body to ensure the healthy development of the fetus. It is essential to oversee the well-being of the fetus throughout pregnancy to ensure the health of both the mother and the developing child. Although significant advances have been made in obstetric care, fetal monitoring remains an area of active research. Traditional methods of fetal monitoring, such as ultrasound and fetal heart rate monitoring, have limitations in predicting adverse fetal outcomes, such as preterm birth and stillbirth. These limitations have led to the search for additional biomarkers that can aid in monitoring fetal health and predicting adverse outcomes.

Fetal monitoring involves the use of various tests and procedures to assess the growth, development, and overall health of the fetus during pregnancy. These techniques comprise ultrasound, monitoring fetal heart rate, and counting fetal movements. However, these methods may not detect subtle changes in fetal health that could lead to adverse outcomes (1). As a result, researchers are actively exploring new biomarkers that could be used in conjunction with traditional fetal monitoring methods to improve the prediction of adverse fetal outcomes. These biomarkers could help detect potential health problems earlier and enable healthcare providers to intervene promptly, leading to better outcomes for both the mother and the baby.

One such biomarker that has shown promise is placental growth factor (PLGF), belonging to the vascular endothelial growth factor (VEGF) family that is generated by the placenta. The gestational period is marked by the presence of PLGF in the placenta, which is believed to regulate trophoblast growth and differentiation (2-4). This indicates that PLGF might be involved in facilitating the movement of trophoblast cells into the decidua of the mother. Hence placental dysfunction causes fetal growth restriction which may be reflected by the PLGF (5-7). Research has indicated that PLGF concentrations decrease in females with preeclampsia, a high blood pressure condition that impacts 2-8% of pregnancies, it stands as a primary contributor to maternal and fetal health issues. This decrease in PLGF levels has led to the investigation of its potential diagnostic and prognostic value for preeclampsia (8, 9). The potential usefulness of PLGF as a biomarker for preeclampsia is based on the understanding that it plays a pivotal part in angiogenesis, which is the formation of new blood

vessels. During pregnancy, angiogenesis is essential for the development of the placenta and the supply of oxygen and nutrients to the developing fetus. However, in preeclampsia, this process is disrupted, leading to reduced blood flow to the placenta and impaired fetal growth. The decrease in PLGF levels in women with preeclampsia is thought to be due to impaired placental function, which may serve as an early warning sign for the development of this condition (10).

Despite the wealth of information available on the potential role of PLGF in adverse pregnancy outcomes, the exact mechanisms by which PLGF affects pregnancy outcomes are not fully understood. Hence the study conducted an assessment of the current evidence on the correlation between maternal PLGF levels and different adverse pregnancy outcomes.

MATERIALS AND METHODS

The methodology for the study is a simple longitudinal study conducted on pregnant women with suspected preeclampsia who visits the hospital. The name of each patient was blinded to maintain confidentiality. The inclusion criteria for the study were pregnant women with gestational age at enrollment between 20- 24 weeks. The sample size estimation for the study is approximately 144, considering the incidence of preeclampsia cases in the tertiary care center's OPD as 10.5% with an allowable clinical error of 5%. To account for a potential loss to follow-up of 10% (15 cases), the minimum sample size required for the study was 160. To ensure a homogeneous study group, all pregnant women with similar job, weight, education, drug usage, social and economic status, and gestational age are selected. Additionally, singleton pregnancy with no history of gestational diabetes and lack of kidney issues during the current pregnancy is selected.

Gestational age is calculated from the last menstrual period or any obstetric ultrasonography. Five ml of EDTA Blood was used to separate the plasma. The separated plasma was preserved at -80°C until assayed. The PLGF concentration was estimated using the ELISA method which had a computable range of 12-3000 pg/ml and were grouped as normal (>100 pg/ml), low (13-99 pg/ml; 8).

The selected participants were followed in the entire week of gestation, and their pregnancy outcomes were recorded. The patients who have signed the informed consent were selected for the study. By implementing this methodology, we aim to determine the relationship between PLGF levels and pregnancy results in women through suspected preeclampsia.

RESULTS

This was a simple longitudinal study conducted on pregnant ladies with doubted preeclampsia which included a population of 160 subjects. The characteristic features of the subjects are given in Table 1. The characteristic of the study population was noted at the time of admission and was followed up till delivery. PLGF values were measured at the time of admission and found that the development of preeclampsia was subtle but the variation in the PLGF levels with respect to pregnancy outcome was worth reporting.

Table 1: Basic characteristic features of study population

Characteristics	Description
Age (in years)	Mean ± SD: 22.8 ± 2.31
Pregnancy	1st pregnancy: 45.62% (n=73); 2nd pregnancy: 40% (n=64); 3rd pregnancy: 11.85% (n=19); 4th pregnancy: 0%; 5th pregnancy: 2.5% (n=4)
Parity	Parity one: 46%; Parity two: 40%; Parity three: 12%; Parity four: 0%; Parity five: 2%
NICU Admission	No NICU admission: 79.37% (n=127); NICU admission: 20.62% (n=33)
Baby Outcome	Healthy babies: 96.8% (n=155); Babies died: 3.2% (n=5)
Baby Weight (PLGF pg/ml)	Low PLGF levels (n=82): 2.67 ± 0.42; Normal PLGF levels (n=78): 2.82 ± 0.39
Blood Pressure at Admission (PLGF pg/ml)	Low PLGF levels (n=83) had SBP 118 ± 7.4, DBP 74.9 ± 7.89; Normal PLGF levels (n=77) had SBP 113.5 ± 8.48, DBP 74.1 ± 6.87
Term	Full term: 90% (n=144), PLGF 227 ± 213; Preterm: 10% (n=16), PLGF 142 ± 136

When the description of the study population with respect to pregnancy was calculated, the PLGF levels were highest among the fifth pregnant ladies. Upon applying Fischer's one-way ANOVA test f(3.1), the

analysis indicated a statistically significant mean difference in PLGF levels, with a p-value of 0.029. Further to identify between which group the difference existed, a Tukey post hoc test was applied. Group 1 versus group 4 showed a statistical significance in PLGF with a p-value of 0.028.

Among the study population, the proportion of subjects with NICU admission was less compared to subjects without NICU admission, the group with NICU admission had a lower mean PLGF value by approximately 8.1%. Despite the lack of statistical significance in the disparity of mean PLGF values, the presence of NICU admission was associated with a slight decrease in PLGF levels.

Among subjects with low PLGF levels (n=82), the baby weight was lower by approximately 5.3%. In subjects with normal PLGF levels (n=78), the baby weight was higher, representing approximately 48.7% of the total study population. There observed a difference ($p<0.05$) in mean baby weight between the groups on applying t test, confirming that decreased PLGF levels are related with a lower baby weight.

The subjects with low PLGF levels were 61.6% and with normal PLGF levels accounting for 48.4% of the total study population. There was a highly significant difference ($p<0.001$) in mean SBP between the two groups. No statistically significant difference was observed in mean DBP at admission. Out of 160 subjects, a major share of them had full-term pregnancies with higher mean PLGF levels than the preterm pregnancies which showed a 35.24 % decrease.

DISCUSSION

The objective of this study was to explore the link among placental growth factor (PLGF) levels with diverse pregnancy outcomes. Analysis of the results revealed that the PLGF levels varied significantly with respect to parity and pregnancy outcomes. Interestingly, while there was observed variation in PLGF levels among subjects, this variation was not significant in relation to NICU admission. Specifically, we found that subjects with PLGF levels below 100 showed significant variation in their outcomes.

While there is a lack of studies specifically examining changes in PLGF levels during subsequent pregnancies, it is important to note that PLGF levels are able to vary all through pregnancy and can be inclined by several factors such as gestational age, maternal age, and medical conditions like preeclampsia. This study did observe variations in mean PLGF levels among different pregnancies, with the highest mean PLGF level observed in the fifth pregnancy and the lowest in the second pregnancy. However, this finding does not necessarily suggest a consistent trend in PLGF levels in subsequent pregnancies. Therefore, further research is necessary to confirm any changes in PLGF levels during subsequent pregnancies and to explore the factors that influence these changes.

In terms of parity, the study found that the highest percentage of the study population had parity one, followed by parity two and three. This finding aligns with earlier research conducted by Miranda *et al.*, and Lin *et al.*,(11,12) which found that nulliparous women had an elevated risk of undesirable pregnancy outcomes relate to multiparous women.

We observed that the majority (79.37%) of our study population was not admitted to NICU, while only a minority (20.62%) required NICU admission. Despite investigating the association between PLGF levels and NICU admission, we did not find any statistically significant difference among the two groups. However, our results contrast with the consistent association reported by Helen *et al.*,(13) between decreased PLGF levels and adverse outcomes, including NICU admission, CS for fetal compromise, and stillbirth. These findings support the potential of PLGF as a predictor of adverse outcomes, particularly when used in combination with other measures of fetal well-being. An additional investigation is necessary to comprehensively assess the potential of PLGF as a predictor of adverse outcomes.

Our study investigated the association between PLGF levels and both NICU admission and baby outcomes. Although no statistically significant difference in PLGF levels was observed between healthy babies and those who died, we did observe the mean PLGF levels were higher in healthy babies. However, the association among decreased PLGF levels and stillbirth was supported by a study from McLaughlin *et al.*, (14) which found that women with low PLGF levels were more likely to have a stillbirth, and that PLGF status could distinguish between placental and fetal causes of stillbirth. In addition to investigating the association between PLGF levels and adverse pregnancy outcomes, the present study also examined the relationship between PLGF levels and baby weight. The results showed that the mean baby weight was significantly higher in the normal PLGF group compared to the low PLGF group. This observation aligns with prior research conducted by Poon *et al.*, (15), wherein they noted an association between diminished maternal PLGF levels and fetal growth restriction. The present investigation contributes to the body of knowledge by indicating that the correlation between PLGF levels and fetal growth restriction might extend to instances of stillbirth. However, it should be noted that while there was a significant difference in mean baby weight between the normal and low PLGF groups, there was considerable overlap in the individual values, indicating that PLGF levels alone may not be sufficient to predict fetal growth restriction. Nonetheless, these findings suggest that PLGF levels may be a useful tool for identifying

pregnancies at increased risk for adverse fetal outcomes, including stillbirth, and may have implications for clinical management and surveillance of high-risk pregnancies.

Clearly, blood pressure during pregnancy has been linked more strongly to infant birth weight changes than clinic blood pressure, serving as a key indicator of these changes (16-18). Our study found that women with low levels of PLGF (<100 pg/ml) had significantly higher systolic blood pressure (SBP) at admission and delivery compared to women with higher PLGF levels. This is consistent with previous research Troisi *et al.,* (19) that has linked low PLGF concentrations during pregnancy with higher blood pressure during delivery. The findings suggest that monitoring PLGF levels during pregnancy may help identify women at risk for hypertensive disorders and other cardiovascular complications.

Limitations

- The study had a relatively small sample size, which may limit the generalizability of the findings.
- The study did not assess long-term outcomes for mothers and babies, such as postpartum depression or neuro developmental delays.
- The study design was cross-sectional, which limits our ability to establish causality.
- Our study only examined PLGF levels and did not investigate other potential biomarkers that may be associated with adverse pregnancy outcomes.

Strengths

- The study investigated the association between PLGF levels and a range of pregnancy outcomes, providing a comprehensive assessment of the potential clinical utility of PLGF as a biomarker.
- The study controlled for a range of potential confounding factors, including maternal age, medical history, and gestational age.
- Our investigation contributes to the growing body of research on the use of PLGF as an interpreter of adverse pregnancy outcomes, particularly stillbirth.
- The findings have important implications for clinical management of high-risk pregnancies, such as identifying women at risk for hypertensive disorders or fetal growth restriction.
- The study contributes to our understanding of the longitudinal changes in PLGF levels during pregnancy, which may be useful for developing targeted interventions to improve maternal and fetal outcomes.

CONCLUSION

In summary, our research intended to investigate the relationship among placental growth factor (PLGF) levels and pregnancy outcomes. We found significant variations in PLGF levels based on parity and outcomes, especially in cases where PLGF levels were below100 pg/ml. Nulliparous ladies were at a higher risk of adverse outcomes, consistent with previous research. Low PLGF levels (<100 pg/ml) were linked to higher systolic blood pressure at admission and delivery, indicating potential for monitoring PLGF levels in identifying women at risk of hypertensive disorders . While statistically significant differences were not observed in PLGF levels between healthy babies and those who died or between PLGF levels and NICU admission, our study supports the potential of PLGF as a predictor of adverse outcomes, particularly when combined with other measures of fetal well-being PLGF alone may not be sufficient to predict outcomes such as preterm delivery, NICU admission, or stillbirth, highlighting the need to explore other angiogenic factors alongside PLGF. Our study supports the prospective of PLGF as a predictor of adverse outcomes when combined with other measures of fetal well-being. Further investigations are needed to enhance prediction accuracy and improve maternal and fetal health outcomes.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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