Placental Growth Factor as A Predictor of Preeclampsia in Teenage Pregnancy Study Conducted in Tertiary care Hospital of Peshawar

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ABSTRACT

Background: Preeclampsia is a condition of pregnancy categorized by high blood pressure and raised quantity of proteinuria.
Objective: This study was designed with the objective that whether low Placental Growth factor in first trimester can predict preeclampsia in second or third trimester in teenage pregnancy.
Methods: This was a longitudinal study conducted in the antenatal clinic of Hayatabad Medical Complex (HMC), Peshawar, Khyber Pakhtunkhwa. Consent form was taken for the study from Ethics Committee of Khyber Medical University (KMU) and HMC. Each participant was given a predesigned questionnaire and 3 to 5 ml blood was collected. After taking blood sample hematological parameters like hemoglobin, platelet count and placental growth factor were determined. A follow-up visit for examination of blood pressure was done on 20-24 weeks of gestation of each patient.
Results: A total of 88 teenagers (age 16±2 years) primigravida women were taken by random selection from tertiary care hospitals of KPK. It was found that preeclampsia is inversely related with placental growth factor (PLGF) with significant p value < 0.000. PLGF can predict preeclampsia in 3rd trimester the value of PLGF with age decreases, there is inverse relation between the serums PLGF with age and most of the preeclampsia developed in patients who have low concentration of PLGF.
Conclusion: Introduction of PLGF test in 1st trimester could be appropriate for early diagnosis, resource allocation, and cost saving treatment and to ovoid later complication. It is recommended to treat suspected preeclampsia primigravida women with PLGF early in pregnancy.

Keywords: Placental Growth Factor, Pre-Eclampsia, Pregnancy in Adolescence, Biomarkers, Predictive Value of Tests, Risk Assessment

INTRODUCTION

Preeclampsia is a condition of pregnancy categorized by high blood pressure and raised quantity of proteinuria. The condition decreases blood flow to the uterus and can cause premature birth and low weight babies.[1] The disorder happen in pregnant women after their 20th week of pregnancy and even get worse overtime.[2] In which usual hemodynamic reaction to pregnancy is cooperated. It rests a prominent reason of poor outcomes of maternal morbidity and mortality.[3] If left untreated, it may result in eclampsia, a condition that causes seizures and can be fatal.[4] Women with chronic hypertension about 25% will progress to overlaid preeclampsia. Nearly one tenth of all maternal deaths occur because of preeclampsia in Africa and Asia and one quarter in Latin America.[8] Previously diagnosed preeclampsia patient are at high risk to experience in consequent pregnancies.[5]

Teenage pregnancy is the most important public health issue worldwide having varying frequencies of proportion.[6] Recently it is massively increasing due to teenage sexual activity, early onset of puberty, relatively improper and lack of education on contraceptive methods.[7] Teenagers face the severe problems of pre-term birth, anemia, urinary tract infection (UTI), proteinuria, preeclampsia pyelonephritis. Teenagers are liable to bring small for gestational age infants, reduced placental growth.[8] The fundamental reason of fetal growth restriction in growing adolescent is the impaired placental development. The frequency of pregnancy induced hypertension (PIH), Preeclampsia, Eclampsia, premature onset of labor (POL), were found to be significantly higher in teenage pregnancy.[9]

Preeclampsia women have lower plasma PLGF and higher sFLT1 concentrations in comparison to women with normal or uncomplicated pregnancies, but these variances are higher in women with teenage preeclampsia.[10] The level of Serum PLGF was found reduced in females during diagnosis with preeclampsia and prior to the onset of disorder. The decreased expression of PLGF after adhering to sFLT-1, which is greater in preeclamptic patients.[11] The level of PLGF is lesser in early pregnancy of women who consequently develop preeclampsia than in average pregnant women. Though, there is unintended relationship between sFLT-1 and PLGF.[12] The hypothesis that abnormal placentation indicated by PLGF supported the observation that

women without preeclampsia also have low PLGF who give birth to low weight babies early in pregnancy.[13] Expression of PLGF due to placental hypoxia, hypothesized to be lowered resulting from weak utero placental movement.[14]

According to WHO that the teenager's pregnancy (15-19 years of age) is the second most frequent reason of death in low- and middle-income countries.[15] The born babies are at high risk of dying than those born to women 20 to 24 years of age. Pakistan demographic and health survey (PDHS) reveal that 40% of women are married by the 18 years of age.[16] In this group known cases of maternal complications are like pregnancy-induced hypertension (PIH), preeclampsia, eclampsia, prolonged labor and cephalo-pelvic disproportion in pregnant teenagers are mostly attributable to low socio-economic status, inadequate prenatal care, inadequate weight gains during pregnancy.[17]

This was the first study to look into the predictive value of PLGF in teenage primigravida in Khyber-Pakhtunkhwa. As stated earlier, teenage pregnancy-related with a higher possibility of preeclampsia compared to pregnancy after the age of 20 years. Low PLGF in early pregnancy could possibly be used as a marker of preeclampsia that may develop in 2nd or 3rd trimester, prompting early intervention.

METHODOLOGY

This was a longitudinal study conducted in the antenatal clinic of Hayatabad Medical Complex Peshawar Khyber Pakhtunkhwa from January 2023 to June 2023. Purpose and components of the study were explained to each participant. Once agreed, each participant was screened for eligibility criteria. All eligible participants were asked to give written knowledgeable consent in the study. Ethical approval was taken for the study from ethical committee of the Khyber Medical University, Peshawar.

A total of 88 teenage primigravida women were taken by random selection from tertiary care hospital of KPK

Height of pregnant women was determined using upright calibrated scale, in the footing position. Participant was asked to remove her footwear preceding height measurement. Head was positioned keeping in view the Frankfurt line. Head to toe length was measured in centimeters. Weight of teenage pregnant women was determined with the help of a precise physical balance, in standing position and with least amount of clothing. At least 500 g of weight was subtracted from the obtained weight to exclude the weight of the clothes.

Serum Placental Growth Factor in study group was determined by using Human PLGF ELISA KIT # 200-900-PLGF, 96 tests.

Data was statistically analysed using Minitab Version 17. Normality of the data was assessed using Anderson Darling test of Normality. Mean and standard deviations were used to express numerical data while categorical data was expressed as frequency and percentages. Two sample t tests were used to assess difference between two groups. One sample t test was used to assess the difference in blood pressure, and other biochemical parameters from their standard reference values. Correlation of plasma placental growth factor with systolic and diastolic blood pressure and change in systolic and diastolic blood pressure were assessed by Pearson correlation. Association of PLGF with blood pressure and other variables was assessed by linear regression analysis. A probability values (p value) <0.05 were considered significant using Minitab® V. 16 USA.

RESULTS

Table 1: Demographic characteristics of the Study Group descriptive Statistics

Variable	Mean	St Dev.	P-value*
Age (years)	18.54	0.88	
Age at marriage (years)	16.93	1.02	
Gestational Age-first visit (week)	9.77	1.38	
Gestational age-second visit (week)	27.32	1.70	
History of Diabetes	0.00	0.00	
History of hypertension	0.91	0.29	
History of heart diseases	0.00	0.00	
History of kidney disease	0.00	0.00	
Prenatal visits (n)	1.52	0.55	
Family Hx of Hypertension	0.57	0.95	
Family Hx of PIH	0.57	0.97	
1st trimester Systolic BP (mmHg)	107.27	14.80	<0.001
1st trimester Diastolic BP (mmHg)	71.82	12.25	0.000
Third trimester Systolic BP (mmHg)	125.16	13.21	0.013
Third trimester Diastolic BP (mmHg)	83.41	11.14	0.049
Weight (kg)	59.41	11.82	NC
Height (m^2)	6.23	6.92	NC
BMI (kg/m^2)	23.56	4.47	0.054
Serum placental growth factor (pg. /mL)	1.542	0.87	<0.001
Hb %	12.52	1.475	0.025
Platelets(µl)	216816	77437	0.000
Urinary protein(mg/dl)	0.30	0.51	0.000
Pus cell (HPF)	0.64	0.90	0.000

Dispersed variables which were collected in the filled trial was arranged in the excel sheets then statistics test was run on the data. After that the Count and Percentage were calculated and recorded in the table 2. Most of the patients included in this study were uneducated n%; 19(47.73) (table 2). Similarly, very few women were working outside home n%=8(18.18), most of them being house wives n%; (81.82) table 2.

Table2: Maternal characteristics of the study participants

Categorical variables	PE (n)	Percent's %
Patient education		
Higher Secondary	8	9.09
Metric	14	15.91
Middle	14	15.91
Primary	8	9.09
Uneducated	44	50.00
Patient occupation		
House Wife	72	81.82
Working	16	18.18
Husband Education		
Uneducated	22	25.00
Higher secondary	10	11.36
Bachelors	6	6.82
Masters	8	9.09
Post Graduate	2	2.27
Primary	22	25.00
Secondary	18	20.46
Family History of Hypertension		
No	58	65.91
Mother	18	20.45
Sister	4	4.55
Close Relatives	8	9.09
Family History of PIH		
No	62	70.45

Mother	8	9.09
Sister	12	13.64
Other close relatives	6	6.82

Most of the patients included in our study were uneducated [n=44 (50%)] and so were their husbands, who had either no education [n=22 (25%)] or were educated until primary level [n=22 (25%)] (table 1). Similarly, very few women were working outside home [n=16 (18.18)], most of them being house wives [n=72 (81.82).
Family history of hypertension in mothers [n=18 (20%)] was reported by the patients, while most of them had no any family history of hypertension. Most of the patients reported to have no previous history of pregnancy induced hypertension in the family [n=62 (70.45)] (table 1).
Blood pressure, BMI, Hb level, and platelets count and pus cells were significantly higher than the lower normal range. Significantly higher number of urinary pus cells and proteins were detected on urine examination.

Table3: Correlation of placental growth factor levels with systolic and diastolic blood pressure in 1st and 3rd trimester

Parameter	R	p-value
1st trimester (mean (SD); 9.77(1.38) weeks of gestation)		
Systolic blood pressure (mmHg)	0.318	0.035
Diastolic Blood pressure (mmHg)	0.365	0.015
3rd Trimester (mean (SD); 27.23(1.70) weeks of gestation)		
Systolic blood pressure (mmHg)	0.332	0.028
Diastolic Blood pressure (mmHg)	0.304	0.045
Change in Blood pressure		
Δ SBP (mmHg)	-0.044	0.775
Δ DBP (mmHg)	-0.109	0.480

R; correlation coefficient, SBP; systolic blood pressure, DBP; diastolic blood pressure, Significant correlation was found between PLGF and systolic and diastolic BP in first trimester [Systolic; r =0.318, p = 0.035 and diastolic; r= 0.365, p =0.015) as well as in third trimester (systolic BP; r= 0.332, p = 0.028, diastolic; r= 0.304, p = 0.045) (table 3)
Linear regression analysis revealed a significant association of PLGF with systolic [(r=10.12, P=0.035)] and diastolic [(r= 13.33%, P= 0.015)] blood pressure in first trimester. Moreover, there was a significant association of PLGF with systolic [(r= 11.04%, P= 0.028)] and diastolic [(r= 9.25, P= 0.045)] blood pressure, and weight of the patient [(r=14.24%, p=0.012)] in third trimester. However, no significant association was found between PIGF and the change in systolic and diastolic blood pressure (table 4).

Table 4: Risk factors for preeclampsia according to BMI

Age (years)	n=88	Gestational week	preeclampsia
(13-19) years		8-12 weeks	
underweight	9	-	-
Normal weight	48	-	1
Obese	31	-	16

In women with normal BMI, PLGF was reduced only in preterm preeclampsia, while in women with obesity it was reduced in term and preterm preeclampsia. Preterm delivery without preeclampsia was also associated with reduced PLGF in women with obesity but not in those with normal BMI, scatter plot also shows association between lower PLGF and term preeclampsia in women with obesity.

DISCUSSION

This study shows the association of preeclampsia in teenage primigravida women with many predisposing factors like placental growth factor (PLGF), urinary protein and other hematological parameters. The study was focused on primigravida women based on raising cases of preeclampsia in Khyber Pakhtunkhwa, Peshawar District. The cultural and social tradition emphases on early marriage of women (Average marriage age 16.93) (Table 2) predispose them to the risk of preeclampsia. Lack of awareness and education is the main cause of early marriage because 50% respondents of this study were illiterate and 25% of their husbands were illiterate and 25% having primary level education (Table-1). One of the studies shows that low education had a high risk of gestational hypertension about 30-52%.[18] Another study also shows that with improper antenatal care and insufficient management during pregnancy lead to increased risks of preeclampsia. In this study most of the participants were uneducated; witch lack of education there is lack of awareness in patient about diseases, good health maintenance as well as proper nutritional intake. So we can say that Low education achievement has no direct impact on patients but there is indirect representation of low socioeconomic status which may contribute to preeclampsia or other disease development.[19] Mother's educational status is the evaluated risk factors of preeclampsia, and its awareness can help to earlier diagnose and monitor the patients.[20] A positive family history of hypertension also develops severe preeclampsia. Women with a severe preeclampsia had a family history of hypertension in their close relatives.[21] Present study also justified the fact that 20.45% mothers, sisters 4.5%, and close relatives 9.09% having hypertensive history (Table 1). In these participants preeclampsia developed in 3rd trimester having a significant p value <0.001 (Table 2). Study of R.B. Cincota shows that primigravida participants with a family history of preeclampsia may lead to an increased risk of severe preeclampsia because out of 368 primigravida women, 34 (9.2%) developed preeclampsia. Eighteen (4.9%) women from the total sample size had preeclampsia in their mother (12), sister (five) or both (one). Among these 18 women preeclampsia developed in five (27.8%) patients.[22] The main emphasis of the present study was on placental growth factor (PLGF) as a predictor of preeclampsia in teenage pregnancy. Our Study provided a positive correlation of PLGF with diastolic and systolic blood pressure (P= <0.001 systolic P= <0.001 diastolic) at first trimester and (P= <0.001 systolic P= <0.001 diastolic) at 3rd trimester (Table 8). In previous studies many discrepancies have been observed and the use of PLGF as detector of preeclampsia in women became controversial, as some studies suggested that low level of PLGF in 1st trimester is the cause of preeclampsia, while other studies found no relationship between these two variables.[23] In the current study the association of PLGF with age shows that those teenage patients who have low level of PLGF from 15-19 years of age develop preeclampsia in later pregnancy. In previous studies gestational blood was collected at different gestational period and different ages ranged from 16 to 40 years. Among them teenagers included 20.6%, while most of the participants (56.4%), were aged 15 - 24 years in second and third trimester.[24] The advantage of present study was that sample was collected only in teenage on 1st trimester and correlation was determined in 1st and 3rd trimester. It has been determined that sever preeclampsia condition is observed with proteinuria during pregnancy.[25] The present study also provided that young women

having protein in urine were with moderate and sever preeclampsia and a significant correlation obtained at 1st (Mean 0.30± 0.51) trimester (Table 2). In this study majority of participants have no urinary protein, about 20% of the patients have minute quantity of proteinuria while few of them have severe proteinuria in 1st trimester that develop preeclampsia later in pregnancy. Excretion of protein in pregnant women is considered abnormal when it exceeds 300 mg/24 hours during gestation when the level of dipstick is 1+. The increased level of Proteinuria prediction before pregnancy or before 20 weeks of gestation suggests prior renal disease. The estimated level of proteinuria raised from a mean of 1.74 ± 1.33 grams/24 hour in the first trimester to a mean of 4.82 ± 4.7 grams/24 hour in the third trimester.[26]

WHO reported that pregnancy-related conditions are still a major cause of death among adolescent girls (15-19) years and young women in low and middle income countries, with an estimated 15 % of all deaths globally in women aged 10–25 years being a result of maternal causes.[27] Moreover teenage mothers are more probable to experience adverse outcomes such as perinatal or neonatal death, and their infants are more likely to be born prematurely or have low birth weight.[28] In middle income countries like Pakistan many child births occur at home in rural areas which may lead to proportion of maternal death, may be under-stated as many women never reach to a health facility they are unable to pursue a proper maternal care because of their poor economic status.[29] Studies conducted in Bangladesh which show that 22 %[30] in one study while 47 % (79) in other study of adolescent maternal deaths were attributable to preeclampsia or eclampsia. These estimations were significantly higher in teenagers than for older age groups in both studies.[31] The current study also justifies that maternal death proportion is high in adolescent mothers who attended the tertiary care hospital from rural areas with poor health condition which leads to development of PE in teenage pregnancy with a mean of 1.542 ± 0.87.

The current study was one of its kinds to look into the predictive value of PLGF in teenage primigravida. Among 88 pregnant women 64 participant have normal PLGF value with class interval of 0.5 during first trimester while in 24 pregnant women the value of mean serum PLGF recorded 32pg/ml below the standard value with class interval of 0.5 in first trimester in the gestational age of 8-12 of weeks of gestation. Out of 24 patients 17 pregnant women develop preeclampsia in later phase of 20-24 weeks of gestationas teenage pregnancy-related with a higher possibility of preeclampsia compared to pregnancy after the age of 20 years. This was the first evidence to give any possible association of low PLGF in early teenage pregnancy with preeclampsia in KPK. Low PLGF in early pregnancy could possibly be used as a marker of preeclampsia that may develop in 2nd or 3rd trimester prompting early intervention of preeclampsia.

CONCLUSION

The study provided that PLGF level in first trimester of young primigravida women is a potential indicator of preeclampsia condition later in gestational period. The findings of this study could potentially show the use of PLGF level in 1st trimester as biomarker in young women with suspected preeclampsia. This study also suggests that PLGF level in 1st trimester can be used as part of clinical management in women presenting with suspected preeclampsia. Introduction of PLGF test in 1st trimester could be appropriate for early diagnosis, resource allocation, and cost saving treatment and to avoid later complication. It is recommended to treat suspected preeclampsia primigravida women with determination of PLGF early in pregnancy. Further comprehensive study is needed taking large sample size and alone one factor is not enough for diagnosis imbalance with SFLT1 should also be taking in consideration The present study also has the same limitation of sample size due to many contributing factors like availability of patients, financial constraint and limited time for academic research. In spite of these limitations the present study provided useful correlation between these parameters and provided a conclusive point that low levels of PLGF in 1st trimester of teenage hypertensive, with family history of hypertension or urinary protein have a great chance to develop preeclampsia in third trimester.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Rabia Latif, Muhammad Shabbir Khan
Methodology: All authors
Data Collection and Analysis: All authors
Writing – Original Draft: Rabia Latif
Writing – Review & Editing: All authors

Informed Consent

Written informed consent was obtained from all participants before enrollment in the study.

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Conflict of Interest

The authors declare that they have no competing interests.

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Declaration of AI-Assisted Language Editing

Nil

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