International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2025; 9(1): 151-155
Received: 07-11-2024
Accepted: 12-12-2024

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Maternal serum placental growth factor at late second trimester as a predictor of fetal growth restriction

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DOI: https://doi.org/10.33545/gynae.2025.v9.i1c.1577

Abstract
Background: Fetal growth restriction (FGR) is a significant pregnancy complication where the fetus fails to reach growth potential. It increases the risk of adverse perinatal outcomes, including neonatal morbidity, mortality, and long-term health issues, such as chronic diseases in adulthood. This study aimed to assess the maternal serum placental growth factor at late second trimester as a predictor of fetal growth restriction.
Methods: This prospective study was conducted at the OPD of the Department of Fetomaternal Medicine and Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from September 2022 to August 2023. A total of 58 singleton pregnant women aged 18 to 40 years were enrolled purposively. Data were analyzed using SPSS version 23.0.
Results: In this study, 20.7% of participants developed fetal growth restriction (FGR). Serum placental growth factor (PlGF) levels were significantly lower in FGR cases. Low PlGF levels (<234 pg/mL) predicted a 12.1 times higher risk of FGR, with a sensitivity of 83.33% and specificity of 84.78%. The negative predictive value was particularly high at 95.12%.
Conclusion: This study suggests low placental growth factor can be considered a reliable predictor of fetal growth restriction.

Keywords: Fetal growth restriction, FGR, gravida, late second trimester, parity, placental growth factor

Introduction

Fetal growth restriction (FGR) refers to inadequate fetal growth due to pathological factors, most commonly placental dysfunction. It is defined by parameters such as EFW or AC below the 3rd percentile or UA with absent or reversed end-diastolic velocity or EFW or AC below the 10th percentile in association with UAPI exceeding 95 th percentile [1]. The incidence of FGR varies depending on the population and diagnostic criteria, with estimates ranging from 3% to 9% in developed countries and up to 25% in low- and middle-income countries [2]. Bangladesh ranks fourth globally for the highest-burden of fetal growth restriction (FGR), with a small gestational age (SGA) prevalence of 30.5% [3]. The occurrence of early-onset FGR is notably lower, ranging from 0.5% to 1%, in contrast to late-onset FGR, which has a higher prevalence of 5% to 10% (Crovetto *et al.*, 2016) [4]. Late-onset FGR is associated with lower mortality and morbidity rates but causes a large absolute number of adverse outcomes because of its higher incidence (Figueras and Gardosi, 2011) [5]. The etiology of fetal growth restriction (FGR) can be broadly divided into maternal, placental, and fetal factors. Maternal causes include conditions such as placental vascular insufficiency (e.g., preeclampsia), chronic hypertension, and chronic kidney disease, as well as lifestyle factors like malnutrition, smoking, and alcohol consumption. Fetal factors include chromosomal abnormalities, congenital infections, and congenital cardiovascular or renal anomalies [1,6]. FGR refers to a fetus not reaching its growth potential, increasing the risk of severe complications both short- and long-term [7]. Differentiating placental-mediated FGR from other causes involves integrating various diagnostic tools, such as sonographic assessments, infectious serologies, and, in some cases, invasive genetic tests to exclude non-placental etiologies. Additionally, incorporating serum biomarkers, when interpreted alongside clinical investigations, can improve the accuracy of diagnosing placental dysfunction as the cause of FGR [8]. The placental trophoblast produces PlGF, which is significantly elevated early in pregnancy following implantation [9]. In uncomplicated pregnancies, PlGF levels rise until the 32nd week and then decrease until delivery [10]. Early placental development is marked by relatively hypoxic conditions, promoting branching angiogenesis.

As pregnancy progresses into the third trimester under normoxic conditions, vascular development becomes predominantly non-branching. FGR usually manifests in the late second and third trimesters, but its underlying pathophysiology begins earlier during critical stages of placental formation and the establishment of feto-maternal circulation [11]. Disruption in PlGF production or release leads to insufficient blood vessel formation and impaired placental blood flow, reducing oxygen and nutrient supply to the fetus and contributing to fetal growth restriction [12]. A strong correlation between PlGF and maternal vascular malperfusion (MVM) has been observed, which is associated with adverse antenatal outcomes. Additionally, [8] suggested that PlGF is a useful tool in diagnosing placental FGR secondary to MVM.

Methodology: This prospective study was conducted at the OPD of the Department of Fetomaternal Medicine and Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from September 2022 to August 2023. A total of 58 women with singleton pregnancies, aged 18-40 years, attending the outpatient departments of Fetomaternal Medicine and Obstetrics and Gynecology at BSMMU, were included. Purposive sampling was used based on patient availability. This study included women aged 18-40 years with a singleton live pregnancy, gestational age between 20-24 weeks, and consent to participate, based on the inclusion criteria. Exclusion criteria comprised multifetal gestation, pre-existing diabetes mellitus, fetal structural anomalies, chronic hypertension, chronic renal disease, antiphospholipid syndrome, connective tissue diseases (e.g., SLE), as well as smoking, and alcoholism. The study was approved by the ethical committee of the hospital. Data analysis was performed using SPSS version 23.0.

Result: The majority of participants (58.6%) were aged 18-24 years, and. Over one-third (34.5%) had education up to the secondary school certificate level or equivalent. A significant portion (70.7%) were housewives. More than three-fifths (62.1%) of the participants were multigravida, while 37.9% were primigravida. The ROC curve, constructed using maternal serum placental growth factor levels, revealed a cut-off value of 234.0 pg/mL, showing 83.3% sensitivity and 84.8% specificity for predicting fetal growth restriction. Of the 58 study subjects, 12 (21%) experienced pregnancy with FGR, while 46 (79%) had normal pregnancies without FGR. Analysis of maternal characteristics based on PlGF levels showed no significant differences in maternal age, parity, or body mass index between the two groups ($p>0.05$). According to the distribution of respondents based on their estimated fetal weight, umbilical artery flow, and UA-PI, 8 (13.8%) participants had an estimated fetal weight below the 10th percentile, and 3 (5.2%) had an estimated fetal weight below the 3rd percentile. The absence of end-diastolic velocity in the umbilical artery was observed in 7 (12.1%) participants, while reversed end-diastolic velocity was found in 2 (3.4%). The average umbilical artery PI was 1.0±0.22, with a raised value above 1.3 observed in 10 (17.2%) study subjects. We observed that the mean (±SD) serum PlGF level was significantly lower in pregnant women with FGR (185.37±74.44 pg/mL) compared to those without FGR (384.25±135.98 pg/mL), with a highly significant statistical difference ($p<0.001$). Pregnant women with serum PlGF levels <234 pg/mL were found to have 12.1 times higher risk of developing fetal growth restriction compared to those with normal PlGF levels (≥234 pg/mL) ($p<0.001$; RR=12.059; 95% CI=2.947-49.342). In this study, the diagnostic accuracy of maternal serum PlGF for detecting fetal growth restriction showed that PlGF levels <234 pg/mL had 83.33% sensitivity and 84.78% specificity. The positive and negative predictive values for PlGF were 58.82% and 95.12%, respectively.

Table 1: Socio-demographic and obstetric characteristics.

ParametC5:E28ers	n	%
Age (Years)		
18 - 24 Yrs.	34	58.6%
25 - 32 Yrs.	22	37.9%
33 - 40 Yrs.	2	3.4%
Educational Qualification		
Illiterate	5	8.6%
Primary	17	29.3%
SSC or equivalent	20	34.5%
HSC & above	16	27.6%
Occupation		
Housewife	41	70.7%
Student	6	10.3%
Service holder	11	19%
Gravida		
Primigravida	22	37.9%
Multigravida	36	62.1%

Table 2: Sensitivity and specificity at different scores as per the maternal serum PlGF levels.

S. PlGF level (pg/mL)	Sensitivity	Specificity	Youden Index
200	0.667	0.913	0.58
204.5	0.75	0.913	0.66
209	0.75	0.891	0.64
214	0.75	0.87	0.62
218.5	0.75	0.848	0.6
234	0.833	0.848	0.68
250	0.833	0.826	0.66
257.5	0.833	0.804	0.64
265	0.833	0.783	0.62
274	0.833	0.761	0.59

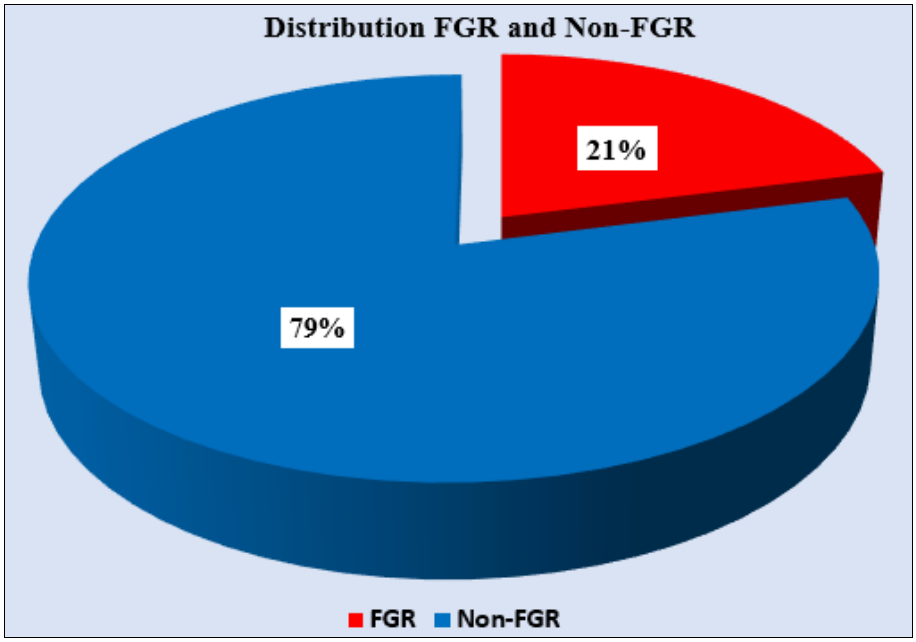

Fig 1: Pie chart showed Distribution of FGR and non-FGR

Table 3: Distribution of the maternal characteristics at the antenatal visit.

S. PlGF levels (pg/mL)	Characteristics	FGR (n=12)	Non-FGR (n=46)	p-value
Age (Years)				
Low (<234.0)	Mean±SD	27.0±4.74	25.4±4.43	0.500[a]
Normal (≥234.0)	Mean±SD	22.0±0.74	24.7±5.1	0.463[a]
Parity [n (%)]				
Low (<234.0)	Nulliparous	7 (70.0)	3 (42.9)	0.350[c]
	Parous	3 (30.0)	4 (57.1)	
Normal (≥234.0)	Nulliparous	1 (50.0)	14 (35.9)	0.686[c]
	Parous	1 (50.0)	25 (64.1)	
BMI (kg/m^2)				
Low (<234.0)	Mean±SD	24.5±3.63	25.9±2.69	0.388[a]
Normal (≥234.0)	Mean±SD	23.5±0.85	23.5±3.65	0.726[a]

[a]p-value reaches from unpaired t-test, [b]p-value reaches from the chi-square test

Table 4: Distribution of fetal weight, umbilical artery flow and UA-PI.

Parameters	n	%
Estimated fetal weight		
10-90th percentile	47	81
<10th percentile	8	13.8
<3rd percentile	3	5.2
Umbilical artery flow		
Normal	49	84.5
AEDV	7	12.1
REDV	2	3.4
Umbilical artery pulsatility index (UA-PI)		
Increased (>1.3)	10	17.2
Normal (≤1.3)	48	82.8
95th centile (Mean±SD)	1.3 (1.0±0.22)	

Table 5: Maternal placental growth factor at the antenatal visit within 20-24 weeks.

Serum PlGF level (pg/mL)	FGR group (n=12)	Non-FGR group (n=46)	p-value
Mean±SD	185.37±74.44	384.25±135.98	<0.001[a]

[a]p-value reaches from unpaired t-test

Table 6: Relative risk and 95% confidence intervals for FGR according to maternal serum PlGF levels.

PlGF level (pg/mL)	FGR (n=12)	Non-FGR (n=46)	p-value	RR (95% CI)
< 234.0	10 (83.3)	7 (15.2)	<0.001[c]	12.059
≥ 234.0	2 (16.7)	39 (84.8)		(2.947-49.342)

Table 7: Diagnostic effectiveness of maternal serum PlGF levels (<234 pg/mL) for prediction of FGR.

Diagnostic accuracy	S. PlGF level	95% CI (lower-upper)
Sensitivity (%)	83.33%	51.59% to 97.91%
Specificity (%)	84.78%	71.13% to 93.66%
PPV (%)	58.82%	40.83% to 74.73%
NPV (%)	95.12%	84.54% to 98.58%
Accuracy	84.48%	72.58% to 92.65%

Discussion

In this study, the majority (58.6%) of pregnant women were aged 18-24 years. The mean (±SD) maternal age of women with FGR was slightly higher (26.2±4.71 years) compared to those without FGR (24.8±4.95 years), but the difference was not statistically significant (p=0.395). Elkholi *et al.* [14] reported similar average ages for women with and without IUGR (26.3±1.85 vs. 26.78±3.78 years, p=0.584), while Wallner *et al.* [15] found that primigravida rates were lower in the control group (18.75%) compared to women with IUGR (46.67%), but this difference was not statistically significant. In this study, FGR was detected through fetal biometry and umbilical artery Doppler velocimetry at 28 and 32 weeks following FIGO guidelines. Among the 58 participants, 12 (20.7%) developed FGR, while 46 (79.3%) did not. Early FGR occurred in 5 (8.62%) and late FGR in 7 (12.07%). A similar study by Benton *et al.* [16] enrolled 211 patients and found that maternal serum PlGF levels could predict 35% of placental FGR cases. In this study, the mean BMI of women with FGR was 24.5±3.29 kg/m², compared to 23.8±3.60 kg/m² in women without FGR (p>0.05). Pre-pregnancy BMI also showed no significant difference between the two groups. These results suggest that BMI may not be a strong predictor of FGR in this study population. This aligns with Elkholi *et al.* [14], who found no significant difference in BMI between women with and without intrauterine growth restriction (IUGR) (p=0.087). The mean maternal serum PlGF level was significantly lower in women with FGR (185.37±74.44 pg/ml) compared to the non-FGR group (384.25±135.98 pg/ml), with a statistically significant difference (P<0.001). These findings align with previous studies [17]. The ROC curve analysis identified a PlGF cut-off value of 234.0 pg/mL. Among women with FGR, 83.3% had PlGF levels below this threshold, while 84.8% of women with normal pregnancies had PlGF levels at or above 234.0 pg/mL. This study found that pregnant women with serum PlGF levels below 234 pg/mL had a significantly higher risk of developing fetal growth restriction (FGR) compared to those with PlGF levels of 234.0 pg/mL or higher (p<0.001; RR=12.059; 95% CI=2.947-49.342). Using this 234.0 pg/mL threshold for predicting FGR, the sensitivity and specificity were 83.33% and 84.78%, respectively. The positive predictive value was 58.82%, and the negative predictive value was 95.12%. These results support the hypotheses of the current study, consistent with findings from previous research. Vrachnis *et al.* [18] reported that low levels of PlGF in maternal circulation are linked to impaired vasculogenesis, angiogenesis, trophoblast invasion failure, and inadequate placental development. Joó *et al.* [19] found that placental PlGF gene activity was significantly lower in fetuses with severe intrauterine growth restriction (IUGR) compared to less severe cases (Ln2α: 1.49; p<0.03). Molvarec *et al.* [20] demonstrated that all IUGR neonates had low or very low maternal PlGF levels, and a significant proportion exhibited abnormal fetal flow (p=0.0069). Sung *et al.* [21] also found that low PlGF levels were a predictor of small-for-gestational-age (SGA) infants, with an odds ratio of 0.143 (95% CI: 0.025 to 0.806). Benton *et al*, [16]. Identified low PlGF in FGR with an area under the receiver-operator characteristic curve of 0.96 [95% CI 0.93-0.98], 98.2% [95% CI 90.5-99.9] sensitivity and 75.1% [95% CI 67.6-81.7] specificity. Negative and positive predictive values were 99.2% [95% CI 95.4-99.9] and 58.5% [95% CI 47.9-68.6], respectively. Low PlGF outperformed gestational age, abdominal circumference and umbilical artery resistance index in predicting FGR. In the current study, the sensitivity of serum PlGF (83.33%) is found to be less than the specificity (84.78%), rendering it clinically unsuitable. Therefore, a reduced serum PlGF level during the 20-24 weeks of gestation may serve as a potential risk factor for the onset of fetal growth restriction. More research and external validation are needed to determine its therapeutic utility.

Limitation of the study

The study population was selected from one tertiary care hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the country, this study was conducted at a short period of time, a small sample size and a 95% confidence interval, which may affect the generalizability and precision of our findings and Doppler study of other fetal vessels not done.

Conclusion & Recommendation

In this study, cut-off value for PlGF was determined as 234.0 pg/ml (ROC curve), so <234.0 pg/ml was considered as low value. From this study, the patients with low PlGF were found 12.1 times more risk to develop FGR compared with normal PlGF. So, this study suggests low PlGF can be considered as a predictor of FGR. In the light of the findings of the present study and discussion, therefore, it is recommended: Maternal serum PlGF measurement can be used as an effective screening tool for the prediction of fetal growth restriction, pregnant women with maternal low serum placental growth factor level should be evaluated and managed more cautiously in order to prevent fetal growth restrictions and its related complications and in future further multicentric study with large sample should be conducted in our country.

Funding: No funding sources.

Conflict of interest: None declared.

References

1. FIGO. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet. 2021;152(Suppl 1):1-55.
2. Damhuis SE, Ganzevoort W, Gordijn SJ. Abnormal fetal growth: small for gestational age, fetal growth restriction, large for gestational age: definitions and epidemiology. Obstet Gynecol Clin North Am. 2021;48(2):267-279.
3. Lee AC, Kozuki N, Cousens S, Stevens GA, Blencowe H, Silveira MF, *et al.* Estimates of burden and consequences of infants born small for gestational age in low- and middle-income countries with INTERGROWTH-21st standard:

analysis of CHERG datasets. BMJ. 2017; 358:1-11.
4. Crovetto F, Triunfo S, Crispi F, Rodriguez-Sureda V, Roma E, Dominguez C, *et al.* First-trimester screening with specific algorithms for early- and late-onset fetal growth restriction. Ultrasound Obstet Gynecol. 2016;48(3):340-348.
5. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol. 2011;204(4):288-300.
6. Chew LC, Verma RP. Fetal growth restriction. StatPearls Publishing [Internet]. 2020 [cited 2023 Sep 17]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562268/
7. Sahana P, Jeevitha H, Prajwal M, Chandrashekar K. Risk factors of intrauterine growth restriction in term pregnancy. Eur J Mol Clin Med. 2022;9(2):1620-1624.
8. Kamphof HD, Posthuma S, Gordijn SJ, Ganzevoort W. Fetal growth restriction: mechanisms, epidemiology, and management. Matern Fetal Med. 2022;4(3):186-196.
9. Shinar S, Tigert M, Agrawal S, Parks WA, John C. Placental growth factor as a diagnostic tool for placental-mediated fetal growth restriction. Pregnancy Hypertens. 2021; 25:123-128.
10. Griffith OW, Chavan AR, Protopapas S, Maziarz J, Romero R, Wagner GP. Embryo implantation evolved from an ancestral inflammatory attachment reaction. Proc Natl Acad Sci U S A. 2017;114(32):E6566-E6575.
11. Knudsen UB, Kronborg CS, Von Dadelszen P, Kupfer K, Lee SW, Vittinghus E, *et al.* A single rapid point-of-care placental growth factor determination as an aid in the diagnosis of preeclampsia. Pregnancy Hypertens. 2012;2(1):8-15.
12. Sun C, Groom KM, Oyston C, Chamley LW, Clark AR, James JL. The placenta in fetal growth restriction: what is going wrong? Placenta. 2020; 96:10-18.
13. Fillion A, Guerby P, Menzies D, Bujold E. The association between maternal placental growth factor and placental maternal vascular malperfusion lesions. J Gynecol Obstet Hum Reprod. 2021;50(9):102179.
14. Elkholi D, Hefeda M, Nagy H. First trimester screening for preeclampsia and intrauterine growth restriction using uterine artery Doppler and maternal serum placental growth factor and pregnancy-associated plasma protein-A. Reprod Immunol Open Access. 2016;1(3):15.
15. Wallner W, Sengenberger R, Strick R, Strissel PL, Meurer B, Beckmann MW, *et al.* Angiogenic growth factors in maternal and fetal serum in pregnancies complicated by intrauterine growth restriction. Clin Sci (Lond). 2007;112(1):51-57.
16. Benton SJ, McCowan LM, Heazell AE, Grynspan D, Hutcheon JA, Senger C, *et al.* Placental growth factor as a marker of fetal growth restriction caused by placental dysfunction. Placenta. 2016;42:1-8.
17. Macdonald TM, Tran C, Kaitu'u-Lino TUJ, Brennecke SP, Hiscock RJ, Hui L, *et al.* Assessing the sensitivity of placental growth factor and soluble fms-like tyrosine kinase 1 at 36 weeks' gestation to predict small-for-gestational-age infants or late-onset preeclampsia: a prospective nested case-control study. BMC Pregnancy Childbirth. 2018;18(1):1-12.
18. Vrachnis N, Kalampokas E, Sifakis S, Vitoratos N, Kalampokas T, Botsis D, *et al.* Placental growth factor (PlGF): a key to optimizing fetal growth. J Matern Fetal Neonatal Med. 2013;26(10):995-1002.
19. Joó JG, Rigó J Jr, Börzsönyi B, Demendi C, Kornya L. Placental gene expression of the placental growth factor (PlGF) in intrauterine growth restriction. J Matern Fetal Neonatal Med. 2017;30(12):1471-1475.
20. Molvarec A, Gullai N, Stenczer B, Fügedi G, Nagy B, Rigó J Jr. Comparison of placental growth factor and fetal flow Doppler ultrasonography to identify fetal adverse outcomes in women with hypertensive disorders of pregnancy: an observational study. BMC Pregnancy Childbirth. 2013;13(1):1-7.
21. Sung KU, Roh JA, Eoh KJ, Kim EH. Maternal serum placental growth factor and pregnancy-associated plasma protein A measured in the first trimester as parameters of subsequent pre-eclampsia and small-for-gestational-age infants: A prospective observational study. Obstet Gynecol Sci. 2017;60(2):154-162.

How to Cite This Article
Mojumder J, Akhtar N, Yesmin F, Ripa IJ, Islam N, Haque F. Maternal serum placental growth factor at late second trimester as a predictor of fetal growth restriction. International Journal of Clinical Obstetrics and Gynaecology. 2025; 9(1): 151-155.