Placental Growth Factor (PlGF) associated with compromised Fetal Growth and Perinatal Outcomes in a High-Risk Pregnancy Population: A Retrospective Cohort

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Abstract

Introduction: Fetal Growth Restriction (FGR) is associated with placental dysfunction. Placental Growth Factor (PlGF) can help in the prediction and timely diagnosis of FGR. This study aimed to evaluate the association between FGR, PlGF, and perinatal outcomes. **Methods:** Retrospective cohort of 292 patients. The primary exposure was maternal PlGF levels. Primary outcomes were fetal growth, abnormal sonographic placental morphology, preeclampsia, fetal demise (IUFD), preterm birth (PTB) < 34weeks, low birth weight, neonatal admission to NICU and placental pathology findings. **Results:** Normal-grown fetuses had longer pregnancies when compared to FGR pregnancies. Low PlGF levels were statistically significant and almost 5-fold higher among pregnancies with compromised fetal growth. There were 12.5-fold chance of IUFD in fetuses with compromised growth. Low birthweight was over ten times higher in growth-restricted fetuses. PTB < 34w and neonatal admission to NICU were also increased among patients with compromised fetal growth. Abnormal sonographic placental morphology was associated with fetal growth restriction. Preeclampsia was not associated with compromised fetal growth in this cohort. Abnormal placental pathology was increased 7-fold in growth-restricted fetuses. **Conclusion:** PlGF for the management of high-risk cases with compromised fetal growth is useful. The results confirm that compromised fetal growth is representative of placental dysfunction, associated with or without preeclampsia. In this context, PlGF testing has the potential to improve healthcare outcome in obstetrical care, especially in remote or low-resource settings.

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Methods: Retrospective cohort of 292 patients. The primary exposure was maternal PlGF levels. Primary outcomes were fetal growth, abnormal sonographic placental morphology, preeclampsia, fetal demise (IUFD), preterm birth (PTB) < 34weeks, low birth weight, neonatal admission to NICU and placental pathology findings.

Results: Normal-grown fetuses had longer pregnancies when compared to FGR pregnancies. Low PlGF levels were statistically significant and almost 5-fold higher among pregnancies with compromised fetal growth. There were 12.5-fold chance of IUFD in fetuses with compromised growth. Low birthweight was over ten times higher in growth-restricted fetuses. PTB < 34w and neonatal admission to NICU were also increased among patients with compromised fetal growth. Abnormal sonographic placental morphology was associated with fetal growth restriction. Preeclampsia was not associated with compromised fetal growth in this cohort. Abnormal placental pathology was increased 7-fold in growth-restricted fetuses.

Conclusion: PlGF for the management of high-risk cases with compromised fetal growth is useful. The results confirm that compromised fetal growth is representative of placental dysfunction, associated with or without preeclampsia. In this context, PlGF testing has the potential to improve healthcare outcome in obstetrical care, especially in remote or low-resource settings.

Word Count: 234/250

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Bulleted Statements

What's already known about this topic?

- Fetal Growth Restriction (FGR) is associated with placental dysfunction.
- Growth-restricted fetuses have an increased risk of stillbirth, neonatal morbidity, and mortality.
- Identification of circulating Placental Growth Factor (PlGF) in maternal serum is important for the accurate prediction and timely diagnosis of FGR.

Word Count: 45/70

What does this study add?

- Real-time PlGF for the management of high-risk cases with compromised fetal growth is useful.
- The proposed clinical protocol for the use of PlGF in high-risk centres is effective in screening patients who need increased maternal-fetal surveillance.
- PlGF testing has the potential to overcome some of the challenges healthcare systems face in providing effective obstetrical care to patients in remote or low-income settings.

Word Count: 65/70

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Patient consent statement: This study was based on chart review of secondary data; thus patient consent was waived by Research Ethics Board (Approval #Bio3702).

Placental Growth Factor (PlGF) associated with compromised Fetal Growth and Perinatal Outcomes in a High-Risk Pregnancy Population: A Retrospective Cohort

Introduction:

Fetal Growth Restriction (FGR) is a failure of the fetus to reach its genetically determined growth potential(1), mostly associated with placental dysfunction(2). Growth-restricted fetuses have an increased risk of stillbirth, neonatal morbidity, and mortality(1, 3, 4). Identification of circulating Placental Growth Factor (PlGF) in maternal serum is important for the accurate prediction and timely diagnosis of FGR(1, 2, 5-7).

While FGR refers to a fetus that does not reach its growth potential (regardless of growth centile), Small for Gestational Age (SGA) includes constitutionally small but healthy fetuses at lower risk of adverse perinatal outcomes(5). SGA is typically defined by the deviation of fetal size from reference percentiles. The overlap between these definitions can cause some confusion, leading to the development of the Delphi Criteria(8) to better differentiate FGR from SGA. These criteria use a combination of abdominal circumference, Estimated Fetal Weight (EFW), and end-diastolic flow in the umbilical artery, rather than EFW alone, to define FGR(8). FGR is also further classified as either early-onset (< 32 weeks) or late-onset (> 32 weeks). The Canadian guidelines have adopted the Delphi criteria for FGR and SGA, defining SGA as an EFW or birth weight

below the 10^{th} percentile(5). The Delphi ultrasound-based criteria are used for diagnosis of FGR, requiring one of three criteria for early-onset FGR and two of three criteria for late-onset FGR(5).

Recent work has connected antenatal serum PlGF with the development of placental-mediated FGR(2, 9, 10), performing better than other markers of placental dysfunction for antenatal diagnosis(7). This suggests that measuring PlGF levels can not only help to identify higher-risk pregnancies in SGA fetuses but can also allow for early detection and monitoring(2, 6). The Canadian guidelines for screening, diagnosis, and management of FGR reflect the literature on PlGF and recommend measurement of PlGF to help identify growth-restricted fetuses affected by underlying placental disorders(8).

The objective of this study was to evaluate the association between Fetal Growth Restriction defined by Delphi Criteria(8), Placental Growth Factor and perinatal outcomes in a high-risk pregnancy population.

Methods:

2.1) Study design: Retrospective cohort study of 292 patients seen at the Fetal Assessment Unit, Regina General Hospital, from December 2021 until September 2024. The study received REB approval #Bio3702.

2.2) Inclusion criteria: High-risk pregnant patients who had an indication to test PlGF during the period of the study and followed the Clinical Protocol at the Fetal Assessment Unit, described below.

2.3) Exclusion criteria: low-risk pregnancies, non-singleton pregnancies, pregnancies with fetal malformations or fetal aneuploidies, patients who do not consent to participate in the study and minors (age < 18yo).

2.4) Clinical Protocol:

PlGF was ordered from 12w-36w at the initial visit at the Fetal Assessment Unit, following the indications below:

1) Previous obstetrical history of term or preterm severe preeclampsia/HELLP(1);

1. Fetal Growth Restriction currently or previously (defined by Delphi Criteria)(8);
2. Low PAPP-A (<0.4 MoM), High AFP (> 2.3 MoM), during $1^{st/2nd}$ trimester screening(9);
3. Previous history of pregnancy complications due to suspected placental insufficiency: previous FGR < 5^{th}, previous abruption, previous stillborn, significant placental pathology (maternal vascular malperfusion, fetal vascular malperfusion)(11);
4. Chronic Hypertension (PlGF can help to separate those patients that might develop superimposed preeclampsia)(11);
5. To differentiate other clinical conditions from preeclampsia(12).

PlGF classification:

Using the table from Mclaughlin et al. (2021)(13):

Low PlGF ([?] 5% for gestational age)

Normal PlGF ([?] 10% for gestational age)

2.5) Groups, Exposure and Outcomes:

The patients were divided into three groups depending on Fetal Growth. Patients presenting with compromised fetal growth were divided according to Delphi Criteria(8) (FGR < 3% and SGA 4-10%). Patients with compromised fetal growth were subdivided into < 32w (early onset) and > 32w (late onset), depending on the gestational age they were at their first visit to our Fetal Assessment Unit (time of diagnosis). Normal Fetal Growth was defined by Estimated Fetal Weight (EFW) assessed by ultrasound from 11%-90%ile (Normal Fetal Growth)(14).

A total of 292 participants were enrolled. The normal-grown fetuses' group (EFW11-90%) had 213/292 (73%) participants. The FGR < 3% and SGA 4-10% groups had in total 79/292 participants (27%). The

FGR < 3% had 46 participants (36 participants < 32w; 10 participants > 32w); the SGA 4-10% group had 33 participants (21 participants < 32w; 12 participants > 32w).

The primary exposure was maternal PlGF levels, which were divided into Normal ([?] 10%) and Low ([?] 5%), based on a previous study that classified PlGF values in percentiles for each gestational age from 12w to 36w(13).

The primary outcome assessed was fetal growth. The other outcomes assessed were abnormal placental morphology in the initial ultrasound (US) at the Fetal Assessment Unit (thin placenta, presence of echogenic cystic lesions, "bulky" placentas, small placentas or calcified placentas), the development of preeclampsia (PET) at any gestational age, fetal demise (IUFD), and preterm birth (PTB) < 34w. Secondary perinatal outcomes included birthweight < 3%(15), admission to the NICU, and findings in placental pathology consistent with placental insufficiency (fetal and maternal vascular malperfusion)(16).

2.6) Statistical analysis:

Assuming that 10% of the subjects in the reference population have FGR(5), the study would require a total sample size of at least 150 participants at a 1:2 rate (test: reference group) to achieve a power of 80% for detecting a difference in proportions of 0.22 between the two groups(17) at a two-sided p-value of 0.05(18). Exposure and outcomes were analyzed in contingency tables with a chi-square test ($\mathbf{X^2}$) or Fisher's Exact test to assess associations. Odds Ratio (OR) with a 95% Confidence Interval (CI 95%) was also calculated for the studied outcomes.

Parametric data (average of gestational age at first visit, gestational age at delivery and interval between gestational age at first visit and delivery) were analyzed with one-way ANOVA to compare variances and the differences between the means between the studied groups.

The software PRISM 10 for macOS version 10.4.1 was used for all analyses. Associations were significant if $p < 0.05$.

Results:

Table 1 summarizes the associations between exposure and outcomes. The association between maternal PlGF levels and compromised fetal growth was highly statistically significant with $p < 0.0001$ (OR 4.9 CI 95% 2.9-8.5). Patients with compromised fetal growth have almost 5-fold chances of having low maternal PlGF levels. Prenatally, abnormal sonographic placental morphology was also highly associated with fetal growth restriction (p< 0.0001; OR 5.3 CI 95% 3.1-9.1) (Figure 1).

Although patients with compromised fetal growth had an increased frequency of preeclampsia compared to patients with normal fetal growth (34% vs 26%), this association was not significant (p=0.18). On the other hand, there were 12.5-fold chances of fetal demise (IUFD) in fetuses with compromised growth compared to normal-grown fetuses (OR 12.5 CI 95% 2.08-75.42; p=0.001). The likelihood of low birthweight < 3% was also increased (OR 10.3 CI 95% 3.28-29.46) in growth-restricted fetuses, compared to normal-grown cases. The chances of preterm birth < 34w (OR 3.99 CI95% 2.12-7.22) and neonatal admission to NICU (OR 3.81 CI95% 2.15-6.52) were also augmented among patients with FGR/SGA fetuses.

Abnormal placental pathology findings, Maternal Vascular Malperfusion (MVM) and Fetal Vascular Malperfusion (FVM) were also increased 7-fold in patients with growth-restricted fetuses, compared to normal-grown cases (OR 7.06 CI95% 3.92-12.62).

Table 2 summarizes the average gestational age at the first visit, at delivery, and the difference between the gestational age at the initial visit and delivery. For normal-grown fetuses, the average gestational age at the first visit was 26.9±6.16 weeks; for FGR, 3% was 27.8±4.80 weeks, and for SGA, 4-10% was 30.2±4.16 weeks. The average gestational age at delivery for normal-grown fetuses, FGR 3% and SGA 4-10%, were respectively 36.5±3.0 weeks, 32.8±5.1 weeks, 35.9±2.9 weeks. The interval in days from initial visit until delivery for the studied groups was 66.5 days (9.5 weeks) for normal-grown fetuses, 35.5 days (5.07 weeks) for FGR 3% and 39.5 days (5.6 weeks) for SGA 4-10%. The differences between the averages of gestational

ages were statistically significant ($p < 0.05$) and are summarized and broken down (< 32 weeks and > 32 weeks) in Table 2.

Discussion:

This retrospective cohort studied perinatal outcomes associated with normal fetal growth and compromised fetal growth in patients from a high-risk pregnancy clinic.

In our studied population, the timelines of FGR/SGA pregnancies significantly differed from those of normal-grown fetuses, which had longer pregnancies. Pregnancies with normal-grown fetuses were on average initially seen at 27w and delivered at 36-37w (9.5w interval). While early onset (< 32 w) FGR/SGA had an average of initial diagnosis at 27-28w and delivery at 33-35w (5-7.5w interval), late-onset FGR/SGA was initially seen around 33-34w and delivered at 36-37w (2.5w interval). The significant differences between the initial visit and diagnoses of FGR and SGA and the delivery timing should be carefully analyzed, as timely delivery in infants with FGR/SGA should balance between preventing stillbirth and reducing risks associated with prematurity(19).

We demonstrated a statistically significant association between maternal low PlGF (< 5%) and compromised fetal growth, consistent with current literature(1, 2, 6, 7, 20). In a study evaluating 47 biomarkers and ultrasound parameters, PlGF had a sensitivity of 93% and a negative predictive value (NPV) of 90% for predicting delivery of an SGA/FGR infant in women presenting with suspected preeclampsia(21). Similarly, Kingdom *et al.* also showed an association between PlGF and placental FGR with a sensitivity of 70% and NPV of 60%(7). These results show a promising role of PlGF testing as a screening method for FGR in settings where access to ultrasound for diagnosis is limited(22). Of note, our Maternal Fetal Medicine Unit is the second centre in Canada utilizing real-time PlGF to manage high-risk pregnancies.

Our findings showed that abnormal sonographic placental morphology was seen in 62% of cases with FGR/SGA, which was a significant association. Thin or globular placentas and the presence of echogenic cystic lesions were among the most frequently documented placental abnormalities (Figure 1). Placental thickness is known to increase with gestational age, and a thin placenta is an early echographic sign of FGR(20).

Additionally, our results show a significant association between growth restriction and confirmed insufficiency in placental pathology. PlGF has been shown to mark placental insufficiency(3). Comparably, recent work by Shinar *et al.* has also demonstrated a significant association between low PlGF and MVM in SGA fetuses(7).

One interesting finding of our study was the non-statistically significant association between compromised fetal growth and preeclampsia, even though low PlGF levels were associated with compromised fetal growth in the analyzed sample. A recent literature review introduced the novel concept of normotensive Fetal Growth Restriction (n-FGR) versus Fetal Growth Restriction associated with hypertensive disorders (HDP-FGR)(21). Preeclampsia is the most frequent clinical presentation of placental dysfunction(1, 13, 16), but not the exclusive phenotype for placental insufficiency(23, 24). The results of this study confirm that compromised fetal growth is also strongly representative of placental dysfunction(24), associated or not with preeclampsia, reinforcing the concept of normotensive FGR(25).

Fetal demise (IUFD) remains a significant concern for pregnancies complicated by SGA and FGR(7). It is well documented that perinatal morbidity and mortality is increased for SGA infants born at any gestational age compared to healthy infants(26). In this study, we found the chance of IUFD was 12.5 times higher in fetuses with compromised growth. However, it should be noted that our study population was a high-risk one. With an overall rate of IUFD of 2.4%, our results are similar to other work examining high-risk pregnancies(27).

Preterm birth (PTB) before 34 weeks, low birth weight, and the need for NICU admission are critical complications frequently observed in pregnancies characterized by placental insufficiency(11). Reduced levels of PlGF have been strongly associated with these adverse outcomes, as low PlGF levels indicate impaired angiogenesis and suboptimal placental development(28). This disruption in placental function contributes

to FGR, which often necessitates preterm delivery to prevent further complications, resulting in low birth weight and increased NICU admissions due to prematurity-related morbidities (e.g. respiratory distress syndrome)(5).

Our results show rates of PTB under 34 weeks were 4 times higher in SGA/FGR infants, with early onset FGR being higher risk at 56%. We also observed increased NICU admissions (OR 3.81) for FGR/SGA infants. A randomized controlled trial looking at perinatal outcomes with the addition of enoxaparin to treat high-risk pregnancies with low PlGF showed a NICU admission rate of approximately 20%, which is similar to our overall rate of admission(27). However, it is worth noting that our data was limited, as ethics approval restricted our ability to follow infants after birth. It is likely that there are additional NICU admissions that are not accounted for in our data.

This study is a retrospective chart review, which inherently carries limitations such as missing or incomplete data and potential biases related to data collection and patient selection(29). While the cohort size is relatively small, our findings provide valuable insights into a high-risk pregnancy population, underscoring the potential relevance of these results for clinical practice. It is important to note that healthy, low-risk pregnancies were not assessed, limiting the generalizability of our findings to the broader population. As a cohort study, our work is also subject to confounding factors and cannot establish causality(29).

Nevertheless, these results lay the groundwork for future research, which aims to build on these findings. We are currently undertaking additional prospective work. A particularly intriguing avenue for further investigation is the potential role of enoxaparin in augmenting PlGF levels(13, 30, 31). In a small study by McLaughlin *et al.* , the daily administration of enoxaparin to patients with high-risk pregnancies and low PlGF showed promise for restoring deficient PlGF levels(13). However, a trial in New Zealand showed that the addition of enoxaparin did not reduce the risk of recurrence of preeclampsia or having an SGA fetus in patients with a known history(27). Hence, further studies are necessary to investigate the role of enoxaparin in augmenting PlGF levels and potentially preventing detrimental perinatal outcomes.

Conclusion:

The results show that real-time PlGF for the management of high-risk cases with compromised fetal growth is useful. The associated risks of imminent preterm birth, early-onset preeclampsia, and IUFD may warrant referral of high-risk women with low PlGF levels to maternal fetal medicine centers(11). The proposed clinical protocol for the use of PlGF in high-risk centres is effective in screening patients who need increased maternal-fetal surveillance. In this context, PlGF testing has the potential to overcome some of the real challenges healthcare systems in Canada and elsewhere face in providing effective obstetrical care to women(32), especially in remote or low-income settings, which is a reality in Saskatchewan(33).

Table 1 – Perinatal outcomes and Placental Growth Factor levels associated with Fetal Growth Restriction/Small for Gestational Age and Normal Grown Fetuses in a high-risk pregnant population in Canada

Total N = 292 Normal Growth = 213/292 (73%) FGR/SGA = 79/292 (27%)	**Fetal Growth Restriction (F**
	Early Onset FGR < 32w EF
Placental Growth Factor (PlGF)	
Low ([?]5%)	27 75%
Normal ([?]10%)	9 25%
US Findings	
Abnormal Placental Morphology	22 61%
Perinatal Outcomes	
Preeclampsia at any Gestational Age	14 39%
Fetal Demise (IUFD)	4 11%
Preterm birth < 34 weeks	20 56%
Birthweight < 3%	10 28%

Total N = 292 Normal Growth = 213/292 (73%) FGR/SGA = 79/292 (27%)	Fetal Growth Restriction (F
Admission to NICU	18 50%
Placental Pathology	
Confirmed Maternal/Fetal Vascular Malperfusion (MVM/FVM)	21 58%

* X^2 Test

**Fisher's Exact Test

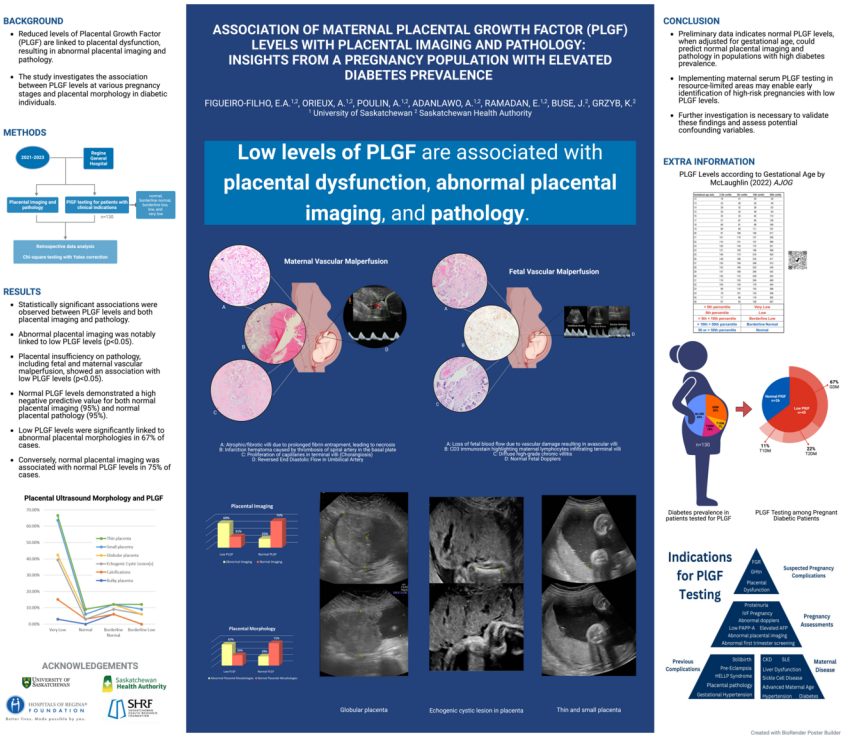
Table 2 – Average Gestational Age at First Visit, Gestational Age at Delivery and Interval between initial visit and Delivery in patients with Fetal Growth Restriction/Small for Gestational Age and Normal Grown Fetuses in a high-risk pregnant population in Canada

Total N = 292 Normal Growth = 213/292 (73%) FGR/SGA = 79/292 (27%)	Fetal Growth Restriction (F
	Early Onset FGR < 32w EF
Average Initial GA at First Visit	28w
Average GA at Delivery	33w
Average Interval First Visit-Delivery	5w

GA: Gestational Age

*One-way ANOVA

Figure 1 – Most common abnormal sonographic placental morphologies found in pregnant patients with compromised growth in a high-risk pregnant population in Canada



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