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Clinical markers for early diagnosis of small for gestational age births; a cross-sectional study

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Abstract

Introduction: Small for gestational age (SGA) births negatively impact neonatal outcomes.
Objectives: This study aimed to evaluate the prevalence of SGA, its associated risk factors, maternal complications, biochemical markers, and ultrasound/Doppler findings to identify predictors for the early detection of SGA.
Patients and Methods: A cross-sectional study was conducted involving 328 mother-newborn pairs (234 SGA; categorized as 90 mild, 96 moderate, and 48 severe fetal growth restriction [FGR]; 94 controls). Moreover, clinical, biochemical, histological, and immunomorphological variables were analyzed using SPSS version 26.
Results: The placental mass and area were lower in cases of FGR compared to controls. Among these, moderate FGR (subgroup II) exhibited the lowest mass (422.4 g) and area (244 cm^2). Poor maternal nutrition was observed in 75–83.3% of SGA infants, compared to only 5.1% of controls. Additionally, preeclampsia occurred more frequently in moderate (32.3%) and mild FGR (20.0%) than in controls (18.1%) ($\chi^2 = 9.164$, $P = 0.002$). Besides, logistic regression analysis indicated that acute respiratory infection (ARI) was independently associated with reduced odds of being SGA (adjusted OR = 0.07, $P = 0.016$), while tumor necrosis factor alpha (TNF-α) expression remained a significant independent predictor (adjusted OR = 1.03, $P<0.001$). Lower estimated fetal weight (EFW), smaller abdominal circumference, and higher umbilical artery pulsatility index (PI) were predictive of SGA status, whereas the uterine artery PI lost significance. Placental growth factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A) levels were lower in SGA infants (84.6 ± 29.2 pg/mL; 1.54 ± 0.42 ng/mL) compared to non-SGA infants (125.7 ± 31.6 pg/mL; 2.49 ± 0.95 ng/mL). Furthermore, SGA neonates exhibited higher rates of asphyxia (72.6%) and a greater need for resuscitation due to severe FGR (46.8%).
Conclusion: Abdominal circumference, EFW, TNF-α levels, elevated umbilical artery PI, and low-PlGF are significant predictors of SGA. This finding accentuates the importance of a comprehensive assessment that integrates clinical, biochemical, and sonographic evaluations for early diagnosis and management.

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Introduction

Small-for-gestational-age (SGA) deliveries represent a prevalent and significant obstetric complication that is associated with increased neonatal morbidity and long-term adverse health outcomes. This condition is defined as a newborn with a birth weight below the 10th percentile for gestational age, indicating a suboptimal attainment of genetically predetermined growth potential (1). When this impaired growth results from pathological processes, the condition is classified as fetal growth restriction (FGR), which may arise from maternal, placental, or fetal factors. Meanwhile, immunomorphological and biochemical markers serve as critical mediators of the multifactorial mechanisms underlying the development of SGA (2).

Routine Doppler ultrasonography conducted at three specific gestational time points provides essential insights into placental function and fetal growth dynamics. In accordance with antenatal screening protocols, pregnancy-associated plasma protein A (PAPP-A) testing is universally performed between 11 and 13 weeks of gestation, while placental growth factor (PlGF) testing is selectively employed in pregnancies identified as having an elevated risk of preeclampsia. These practices highlight the importance of early detection and ongoing monitoring of SGA infants.

SGA and FGR are widely recognized as multifactorial conditions influenced by maternal comorbidities such as hypertension and diabetes, placental insufficiency, and

Key point

This study aimed to evaluate the prevalence and risk factors associated with small for gestational age (SGA) births, as well as to assess biomarkers and ultrasound findings as predictors. The results demonstrated that placental mass and area were significantly lower in SGA cases, with inadequate maternal nutrition and preeclampsia which, frequently observed in these pregnancies. Furthermore, we identified low levels of placental growth factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A), along with elevated Doppler indices, as significant predictors of SGA status. These findings have the potential to facilitate early diagnosis and improve perinatal care.

environmental exposures (4). Maternal malnutrition and smoking during pregnancy are significant risk factors for FGR (5). Biomarkers associated with fetal distress or abnormal development enable timely interventions. Immunomorphological indicators, such as alterations in placental immune activity and morphology, provide additional insight into compromised fetal well-being (6).

Changes in immune cell populations and elevated inflammatory markers have been associated with adverse pregnancy outcomes, including SGA births (7). Proinflammatory cytokines are linked to placental dysfunction and FGR (8). These immunological alterations may serve as early indicators of pregnancies at risk for SGA, thereby providing opportunities for timely intervention.

Several biochemical indicators, including metabolites and hormones, reflect fetal well-being and growth status (9). Abnormal levels of placental hormones, such as human chorionic gonadotropin (hCG) and PlGF, have been reported in pregnancies complicated by FGR (10).

Maternal serum biomarkers, such as alpha-fetoprotein (AFP), are valuable in predicting adverse pregnancy outcomes, including SGA infants. A previous study found that second-trimester AFP levels were negatively correlated with fetal birth weight, suggesting their potential role in identifying at-risk pregnancies and guiding targeted screening protocols for high-risk cases (11). Incorporating immunomorphological and biochemical indices into standard care may enhance the early identification of pregnancies at increased risk for SGA (12,13).

International guidelines underscore the significance of regular surveillance through ultrasound and Doppler assessments, which are crucial for monitoring fetal growth and placental function (14).

Despite advancements in prenatal diagnostics, the clinical integration of advanced immunological and biochemical markers remains limited. This challenge can be addressed through targeted initiatives by healthcare providers. An expanding body of literature underscores the long-term health implications of SGA births. As an example, low-birth weight, often a consequence of FGR, is linked to neurodevelopmental disorders, metabolic syndrome, and cardiovascular diseases in adulthood (15).

A recent study revealed that, in patients with preeclampsia associated with metabolic syndrome, the standard treatment protocol, which utilized conventional antihypertensive therapy, resulted in significant histological alterations in the placenta. These alterations included metaplasia of the fetal surface epithelium and heightened proliferative activity. Conversely, a modified treatment protocol that combined antihypertensive therapy with antioxidant therapy resulted in fewer pathological changes, enhanced preservation of placental structure, including the amniotic epithelium, and reduced desquamation. This finding suggests that modified therapy may improve placental health in cases of preeclampsia (16).

Understanding the biological pathways underlying these outcomes is essential for developing effective prevention strategies. The early identification of at-risk fetuses enables enhanced monitoring and timely delivery, thereby reducing the risk of stillbirth associated with undiagnosed FGR (17). The effectiveness of interventions in SGA pregnancies is time-sensitive; initiating antenatal care early can mitigate complications related to FGR (18). These findings highlight the necessity for proactive approaches in managing high-risk pregnancies.

Consequently, current SGA risk assessments should extend beyond ultrasound to include immunomorphological and biochemical data. Therefore, a better understanding of these markers can improve early detection and facilitate timely interventions, ultimately leading to enhanced neonatal and long-term health outcomes.

Objectives

This study aims to determine the prevalence of SGA and its subtypes, assess maternal, biological, and social determinants of SGA risk, analyze maternal complications and biochemical markers, and investigate fetal growth measurements and Doppler results as predictors of SGA risk.

Patients and Methods

Study design and setting

A cross-sectional study was conducted at a tertiary care hospital, focusing on women who delivered in the postpartum ward. The objective of this study aimed to investigate factors associated with SGA infants, encompassing maternal, biochemical, immunomorphological, and fetal growth factors. Data were collected over a 12-month period, from January 1, 2022, to December 31, 2022. Participants were categorized into two groups: the SGA group, which comprised infants with birth weights below the 10th percentile for their gestational age, and the non-SGA group, consisting of infants with birth weights above the 10th percentile.

Study population

The study included 234 women who had given birth to SGA infants from singleton pregnancies. These women

were within a gestational age range of 38 to 40 weeks and had no known history of chronic diseases, such as hypertension, diabetes, or thyroid disorders. Additionally, there were no complications reported during the current pregnancy.

Sub-group classification of SGA/FGR

Infants classified as SGA were further categorized into three sub-groups based on the severity of FGR (12):

- I. Subgroup - Mild FGR: Birth weight between the 5th and 10th percentiles for gestational age.
- II. Subgroup - Moderate FGR: Birth weight between the 3rd and 5th percentiles for gestational age.
- III. Subgroup - Severe FGR: Birth weight below the 3rd percentile for gestational age.

Sample size

The sample size was determined based on the anticipated prevalence of SGA births, estimated at 17% within the general population. A final sample size of 328 participants was established to ensure sufficient statistical power (80%) for detecting significant differences between the SGA and non-SGA groups concerning the primary outcomes of interest.

$$n = \frac{Z^2.p.(1-p)}{E^2}$$

Sample size (n) = 328
Where:
Z-value for 95% confidence level; 1.96
Prevalence (p); 0.17 (17% for SGA) (17)
Margin of error (E): 0.05 (5% precision)

Data collection procedures

Demographic and clinical characteristics

A structured questionnaire was utilized to collect information on demographic and clinical variables. Participants' ages were calculated based on their self-reported dates of birth, with assessments made as of the enrollment date in the study. Women's previous childbirth experiences were evaluated to determine the number of pregnancies, categorized as follows: nulliparous (no history of pregnancy or first pregnancy) and multiparous (those with a history of more than one pregnancy). Socioeconomic status was assessed by gathering pertinent information and classifying participants into low, medium, and high socioeconomic classes.

Gestational age was established based on the last menstrual period and confirmed through early transabdominal scans, supported by clinical evaluations. In the maternity hospital, mothers of newborns classified as SGA were interviewed using a structured questionnaire specifically designed for this purpose, which included data on both the newborn and the mother. These procedures were conducted during antenatal visits.

Biochemical, immunomorphological, and fetal growth measurements

Blood samples from the mothers were collected during the 11-13 weeks of pregnancy. Detailed information is provided in Table 1.

Data analysis

The data collected in this study were analyzed using IBM SPSS Statistics version 26. Descriptive statistics were utilized to summarize the demographic and clinical characteristics of the participants. Frequencies and percentages were calculated for categorical variables, while means and standard deviations were computed for continuous variables. The chi-square test was employed to assess associations between categorical variables. For continuous variables, an independent samples T-test was conducted to compare groups, and Doppler ultrasound parameters were also evaluated using this test. Additionally,

Table 1. Biochemical, immunomorphological, and fetal growth measurements

Category	Marker/Measurement	Measurement method	Unit	Notes
Biochemical markers	PlGF	ELISA (duplicate)	pg/mL	Serum collected on EDTA, centrifuged, stored at −80 °C
	PAPP-A	ELISA	ng/mL	Collected in serum separator tubes
	Free β-HCG	CLIA	ng/mL	Processed as above
immunomorphological markers in the placenta	T-cell Infiltration	Immunohistochemistry using anti-CD3 antibodies	-	Formalin-fixed, paraffin-embedded, 5 µm sections evaluated microscopically
	Macrophage infiltration	Immunohistochemistry using anti-CD68 antibodies	-	Formalin-fixed, paraffin-embedded tissue sections
Fetal growth measurements	EFW	Formula-based (e.g., Hadlock) using head & abdominal circumference, femur length	-	Computed via ultrasound
	AC	Ultrasound measurement at the level of the liver in a transverse plane	-	Measured via ultrasound
	Umbilical artery doppler (PI)	Doppler ultrasound	-	Assesses placental blood flow resistance
	Uterine artery doppler (PI)	Doppler ultrasound	-	Specific to uteroplacental perfusion

Abbreviations: PlGF, Placental growth factor; PAPP-A, Pregnancy-associated plasma protein A; β-HCG, Beta-human chorionic gonadotropin; CLIA, Chemiluminescent immunoassay; ELISA, Enzyme-linked immunosorbent assay; IHC, Immunohistochemistry; EFW, Estimated fetal weight; AC, Abdominal circumference; PI, Pulsatility index.

univariate and multivariate logistic regression analyses were performed to identify predictors of SGA status across clinical, biochemical, immunological, and Doppler parameters. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of the associations between potential predictors and SGA. All variables that were significant in the univariate analysis or held clinical relevance were included in the multivariate models to determine independent predictors. All analyses were conducted with a significance threshold of $P < 0.05$.

Results

Table 2 presents data on a total of 328 individuals who participated in the study. Among them, 234 (71.3%) were classified as SGA, while 94 (28.7%) were classified as non-SGA. The SGA group was further categorized into three subgroups: 90 individuals (38.5%) were identified with mild FGR, 96 (41.0%) with moderate FGR, and 48 (20.5%) with severe FGR. The 94 non-SGA individuals served as the control group. These figures (SGA = 234; non-SGA = 94) illustrate the composition of the study sample.

Figure 1 presents the distribution of maternal age across various groups categorized by the severity of FGR and the non-SGA control group. In the mild FGR subgroup, 50% of mothers were aged 20-29 years, while 25% were over 35 years. The moderate FGR group exhibited the highest proportion (62.5%) within the 20–29 age range, with equal representation (12.5%) across the other age categories. Conversely, the severe FGR subgroup demonstrated an even distribution across all age categories, with each category constituting 16.7% of the group. Among the non-SGA participants, the majority (60.6%) were also in the 20–29 age bracket, followed by 24.5% aged 30–35 years, 10.6% under 19, and merely 4.3% over 35. These findings indicated that younger maternal age, particularly within the 20–29 year range, was predominant across all groups, whereas advanced maternal age (>35 years) was more frequently associated with mild FGR cases compared to non-SGA controls.

Table 2. Prevalence of SGA in study participants

SGA (n=234)			Non-SGA (n=94)
I Subgroup Mild form of FGR	II Subgroup Moderate form of FGR	III Subgroup Severe form of FGR	Control
90 (38.5%)	96 (41.0%)	48 (20.5%)	94

Abbreviations: SGA, Small for gestational age; FGR, Fetal growth restriction.

Figure 2 presents a comparison of mass (g) and area (cm^2) across three subgroups and a comparison group. Subgroup I exhibits a mass of 496.3 g and an area of 261.4 cm^2; subgroup II shows a mass of 422.4 g and an area of 244 cm^2; and subgroup III displays a mass of 467.5 g and an area of 252.4 cm^2. The comparison group reports the highest values, with 556.5 g and 308.24 cm^2. These findings underscore the variations in these characteristics.

Figure 3 illustrates the distribution of biological factors among SGA and non-SGA groups. Poor nutrition was significantly more prevalent in the SGA subgroups, observed in 83.3% of mild and severe FGR cases and 75% of moderate FGR cases, compared to just 5.1% in the control group. Low-maternal weight was noted in 41.7% of mild FGR, 25% of moderate FGR, and 33.3% of severe FGR cases, versus 9.2% in controls. Similarly, low

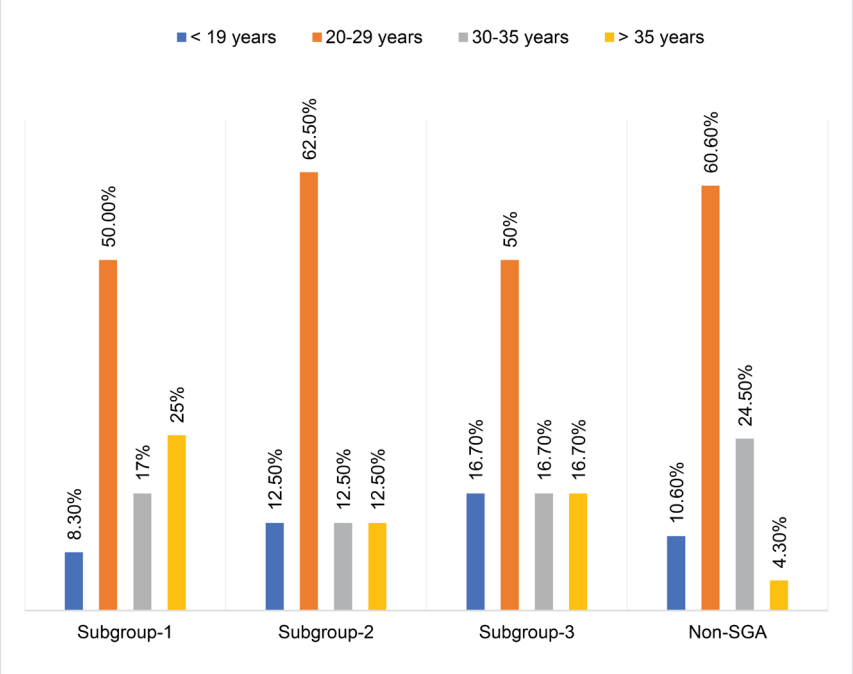

Figure 1. Maternal age distribution among study groups. Abbreviations: SGA, Small-for gestational age; FGR, Fetal growth restriction; Subgroup I, Mild form of fetal growth restriction; Subgroup II, Moderate form of fetal growth restriction; Subgroup III, Severe form of fetal growth restriction.

maternal height was reported in 41.7% to 50% of SGA cases compared to 30.6% of controls. These differences emphasize the importance of maternal health in SGA risk.

Figure 4 highlights the distribution of social factors among SGA (n = 234) and non-SGA (n = 94) groups. Accordingly, low socioeconomic status was observed in 50% to 66.7% of SGA subgroups versus 20.4% of controls, while high socioeconomic status was least prevalent (0% to 25% in SGA versus 28.6% in controls). Working status ranged from 50% to 75% in SGA subgroups compared to 71.4% in controls. Secondary education dominated in SGA (50% to 66.7%) and controls (61.2%), while higher education was less common, particularly in severe SGA cases (33.3%).

Table 3 represents the distribution of medical risk factors among SGA and non-SGA groups, emphasizing significant differences, especially regarding preeclampsia. Preeclampsia demonstrated a markedly higher prevalence in the moderate FGR subgroup (32.30%) and the mild FGR subgroup (20.00%) compared to the control group (18.09%), indicating a highly significant overall association ($\chi^2 = 9.164$, $P = 0.002$). Subgroup comparisons further revealed significant differences; mild FGR versus control ($\chi^2 = 3.03$, $P = 0.001$), moderate FGR versus control ($\chi^2 = 3.65$, $P = 0.046$), and severe FGR versus control ($\chi^2 = 2.99$, $P = 0.084$). Additional medical risk factors, such as anemia, acute respiratory infections (ARIs), and the risk of pregnancy termination, were also noted across all groups. The severe FGR subgroup exhibited the highest anemia rate (43.75%), while ARI was most prevalent in the mild FGR subgroup (41.11%); however, these associations were not statistically significant, as no significant chi-square values were reported. Consequently, preeclampsia exhibited the strongest statistically significant association with SGA, particularly in moderate FGR cases.

Table 4 presents the results of univariate and multivariate logistic regression analysis regarding medical risk factors associated with SGA. The univariate analysis revealed that anemia and ARI were significantly associated with lower odds of SGA, while preeclampsia and gestosis did not show significant associations, although they demonstrated borderline statistical trends. In the multivariate analysis,

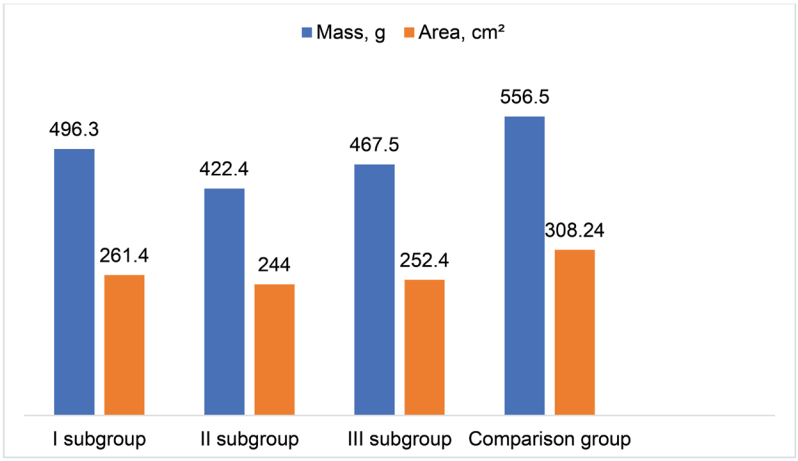

Figure 2. Placental weight (g) and area (cm) distribution in women giving birth in the compared group.

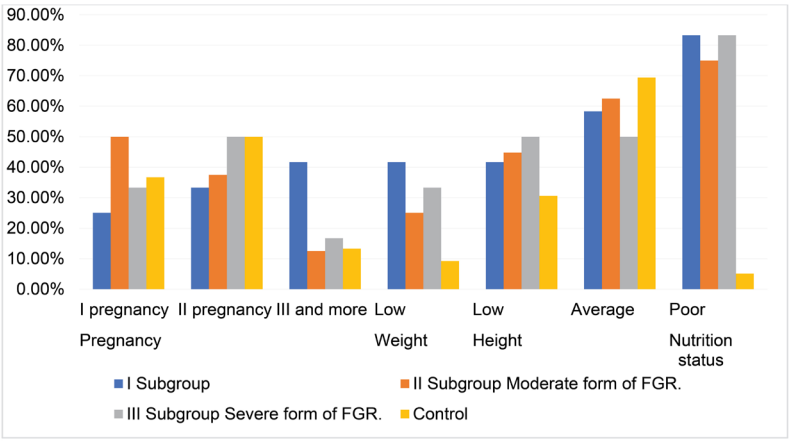

Figure 3. Distribution of biological factors.

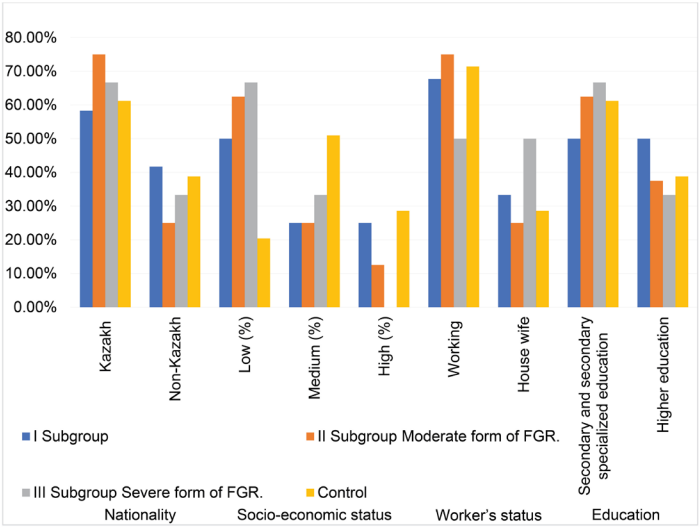

Figure 4. Distribution social factors

which was adjusted for preeclampsia, anemia, ARI, and the threat of termination of pregnancy, only ARI remained significantly associated with a decreased likelihood of SGA. Specifically, ARI was associated with a 93% reduction in the odds of having an SGA birth compared to individuals without ARI. Other factors, including preeclampsia, gestosis, anemia, and the threat of termination of pregnancy, were not found to be significant independent predictors after adjustment.

Table 5 presents findings on immunomorphological and biochemical indicators associated with the risk of SGA births, comparing SGA and non-SGA groups. Statistical significance was assessed using chi-square test for T-cell and macrophage infiltration, and T-test for cytokine expression (interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]). A highly significant difference was observed between the SGA and non-SGA groups ($P=0.002$). In addition, T-cell infiltration was more prevalent in the SGA group, with 57.7% of SGA cases exhibiting T-cell infiltration compared to 35.2% of non-SGA cases. This finding suggests a potential inflammatory response linked to SGA pregnancies. In contrast, no significant difference was found between the groups regarding macrophage infiltration ($P=0.369$), with prevalence rates of 50% in the SGA group and 55.6% in the non-SGA group, indicating that macrophage presence may not be a distinguishing factor for SGA births.

Meanwhile, cytokine expression levels of TNF-α were

Table 3. Distribution of medical risk factors among SGA and non-SGA groups

Variables	SGA (n=234)			Non-SGA (n=94)	Chi-square	*P* value
	I Subgroup Mild form of FGR (n=90)	II Subgroup Moderate form of FGR (n=96)	III Subgroup Severe form of FGR (n=48)	Control (n=94)		
Preeclampsia	18 (20.00%)	31 (32.30%)	13 (27.08%)	17 (18.09%)	3.03	<0.001
Anemia	25 (27.78%)	23 (23.96%)	21 (43.75%)	27 (28.72%)	3.65	0.046
ARI	37 (41.11%)	26 (27.08%)	9 (18.75%)	35 (37.23%)	2.99	0.084
Threat of termination of pregnancy	10 (11.11%)	16 (16.67%)	5 (10.42%)	15 (15.96%)	9.164	0.002

Abbreviations: SGA, Small for gestational age; FGR, Fetal growth restriction; ARI, Acute respiratory infection.

Table 4. Univariate and multivariate logistic regression analysis of medical risk factors associated with SGA and non-SGA groups

Predictor	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Preeclampsia	1.69 (0.98-2.91)	0.060	0.60 (0.11-3.16)	0.543
Gestosis	1.62 (0.99-2.67)	0.057	0.55 (0.11-2.86)	0.478
Anemia	0.55 (0.32-0.94)	0.029	0.26 (0.05-1.40)	0.117
ARI	0.16 (0.04-0.69)	0.014	0.07 (0.01-0.61)	0.016
Threat of termination	2.54 (0.50-12.81)	0.259	1.68 (0.32-8.89)	0.543

Abbreviation: SGA, Small for gestational age; OR, Odds ratio; CI, Confidence interval

Table 5. Immunomorphological markers in the placenta

Immunomorphological marker	SGA (n = 234)	Non-SGA (n = 94)	Total (N = 328)	Test of significance	*P* value
T-cell infiltration					
Yes	57.7% (15)	35.2% (69)	37.8% (84)	Chi-square test	0.026*
No	42.3% (11)	64.8% (127)	62.2% (138)		
Macrophage infiltration					
Yes	50.0% (13)	55.6% (109)	55.0% (122)	Chi-square test	0.369
No	50.0% (13)	44.4% (87)	45.0% (100)		
Cytokine expression (TNF-α)	108.75 ± 16.96	91.96 ± 19.42	93.92 ± 19.86	T-test	<0.001

Abbreviation: SGA, Small for gestational age.

Table 6. Univariate and multivariate logistic regression analysis of immunomorphological markers associated with SGA and non-SGA groups

Immunomorphological marker	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
T-cell infiltration	1.62 (0.99-2.63)	0.055	1.05 (0.45-2.43)	0.918
Macrophage infiltration	1.62 (1.00-2.63)	0.049	1.53 (0.67-3.50)	0.317
TNF-α expression (per unit)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	<0.001

Abbreviation: SGA, Small for gestational age; OR, Odds ratio; CI, Confidence interval

significantly higher in the SGA group than in the non-SGA group (SGA: 108.75 ± 16.96 pg/mL; non-SGA: 91.96 ± 19.42 pg/mL; $P < 0.001$). The elevated TNF-α levels may be involved in the pathophysiology of SGA pregnancies and could influence placentation and fetal development. In our study, PAPP-A levels were also assessed, as they are routinely measured during antenatal screening between 11 and 13 weeks of gestation, providing critical insights into placental function. Additionally, Doppler ultrasound results were analyzed to evaluate placental circulation, as this data was readily available in maternal histories.

In our study, IL-6 expression and PlGF markers were excluded from the analysis because they were either not routinely collected or limited to specific clinical indications (e.g., preeclampsia). The data on T-cell infiltration, TNF-α levels, and placental Doppler studies collectively suggest that immunological and inflammatory factors play a role in SGA pregnancies. The macroscopic and histological data of placentas were also analyzed based on protocols delivered to the pathology bureau. These results indicate that T-cell infiltration and cytokine markers (TNF-α) are strongly associated with SGA pregnancies, while macrophage infiltration is not significantly associated. Such markers may aid in identifying pregnancies at increased risk of SGA and contribute to a better understanding of the pathophysiology of FGR.

Table 6 presents the results of univariate and multivariate logistic regression analysis concerning immunomorphological markers in predicting SGA. In the univariate analysis, both T-cell infiltration (OR = 1.62, $P = 0.055$) and macrophage infiltration (OR = 1.62, $P = 0.049$) were associated with increased odds of SGA; however, the association for T-cell infiltration did not achieve statistical significance. Likewise, TNF-α expression was significantly associated with higher odds of SGA (OR = 1.03 per unit increase, $P < 0.001$). In the multivariate model, only TNF-α expression remained an independent predictor of SGA (adjusted OR = 1.03, $P < 0.001$), while the significance of T-cell and macrophage infiltration diminished after adjustment. To further evaluate the predictive utility of TNF-α, a receiver operating characteristic (ROC) curve analysis was performed, yielding an area under the curve (AUC) of 0.651 (95% CI: 0.584-0.718; $P < 0.001$). This indicates a fair discriminatory ability to differentiate between SGA and non-SGA cases. Although the AUC suggests moderate accuracy, TNF-α may serve as a valuable supplementary biomarker when utilized alongside other clinical parameters, as illustrated in Figure 5.

Table 7 presents a variation analysis between the SGA and non-SGA groups concerning key fetal growth dimensions and Doppler alterations, revealing significant differences. The SGA group demonstrated a substantially lower estimated fetal weight (EFW) of 1842.02 ± 327.41 g,

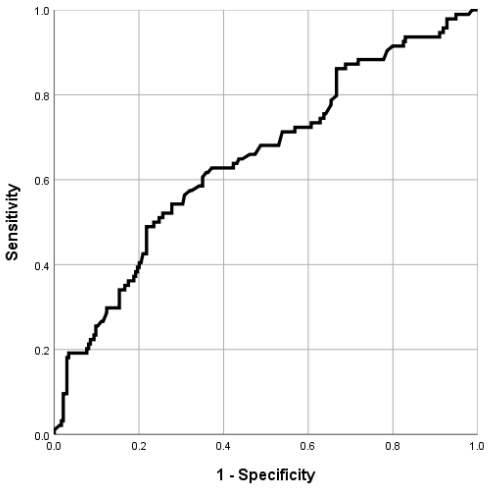

Figure 5. ROC curve for TNF-α expression in predicting small for gestational age (SGA) status.

Table 7. Fetal growth measurements, Doppler findings with SGA risk

Parameter	SGA (n = 234)	Non-SGA (n = 94)	Total (N = 328)	*P* value*
Estimated fetal weight (g)	1842.02 ± 327.41	2742.19 ± 438.24	2636.76 ± 515.51	<0.001
Abdominal circumference (cm)	25.94 ± 2.53	31.03 ± 2.09	30.44 ± 2.69	<0.001
Umbilical artery doppler (PI)	1.53 ± 0.3	1.12 ± 0.2	1.17 ± 0.25	<0.001
Uterine artery doppler (PI)	1.59 ± 0.39	1.4 ± 0.3	1.42 ± 0.32	<0.001

Abbreviation: SGA, Small for gestational age; PI, Pulsatility index.
*Independent samples T-test.

Table 8. Univariate and multivariate logistic regression analysis of fetal growth measurements and Doppler parameters associated with SGA and Non-SGA groups

Parameter	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Estimated fetal weight (g)	0.998 (0.998-0.999)	<0.001	0.999 (0.998-1.000)	<0.001
Abdominal circumference (cm)	0.713 (0.639-0.795)	<0.001	0.810 (0.713-0.920)	0.001
Umbilical artery doppler (PI)	36.49 (11.11-119.89)	<0.001	13.15 (3.45-50.04)	<0.001
Uterine artery doppler (PI)	2.40 (1.14-5.04)	0.021	0.59 (0.23-1.48)	0.257

Abbreviation: SGA, Small for gestational age; PI, Pulsatility index; OR, Odds ratio; CI, Confidence interval.

in contrast to the non-SGA group, which had an EFW of 2742.19 ± 438.24 g ($P<0.001$). This finding supports the previous observation that fetal growth is impaired in SGA pregnancies. Furthermore, the abdominal circumference in the SGA group (25.94 ± 2.53 cm) was significantly less than that of the non-SGA group (31.03 ± 2.09 cm) ($P<0.001$).

The umbilical artery pulsatility index (PI) was significantly higher in SGA cases (1.53 ± 0.3) compared to non-SGA cases (1.12 ± 0.2) ($P<0.001$), indicating compromised placental blood flow. Likewise, the uterine artery PI was elevated in SGA pregnancies (1.59 ± 0.39) relative to non-SGA pregnancies (1.4 ± 0.3) ($P<0.001$), suggesting compromised maternal blood circulation. These Doppler studies emphasize a significant correlation with SGA pregnancies and highlight the necessity for prompt diagnosis and intervention to mitigate associated risks.

Table 8 presents the results of univariate and multivariate logistic regression analysis that examine fetal growth measurements and Doppler parameters associated with SGA. In the univariate analysis, lower EFW, smaller abdominal circumference, and higher umbilical and uterine artery Doppler PI were significantly associated with an increased risk of SGA. In the multivariate model, lower EFW (adjusted OR = 0.999, $P<0.001$), smaller abdominal circumference (adjusted OR = 0.810, $P=0.001$), and higher umbilical artery Doppler PI remained significant independent predictors of SGA. However, the association between uterine artery Doppler PI and SGA was no longer significant after adjustment ($P=0.257$). The multivariate model accounted for maternal age, parity, gestational age at ultrasound, the presence of maternal comorbidities, as well as EFW, abdominal circumference, umbilical artery PI, and uterine artery PI. Complementary ROC curve analysis for uterine artery Doppler PI yielded an AUC of 0.563 (95% CI: 0.492–0.635, $P=0.072$), indicating limited discriminative performance and a lack of statistical significance in predicting SGA, as illustrated in Figure 6.

Discussion

The present study involved a total of 328 individuals, of whom 234 were identified as SGA and 94 as non-SGA. Among the SGA group, three subgroups were delineated based on the severity of FGR: 90 cases (38.5%) were categorized as mild FGR (subgroup I), 96 cases (41.0%) as moderate FGR (subgroup II), and 48 cases (20.5%) as severe FGR (subgroup III). These findings offer valuable insights into the prevalence of SGA and its clinical significance within this specific demographic.

In a related study, Applegate assessed mortality risk among preterm and SGA infants in rural Bangladesh,

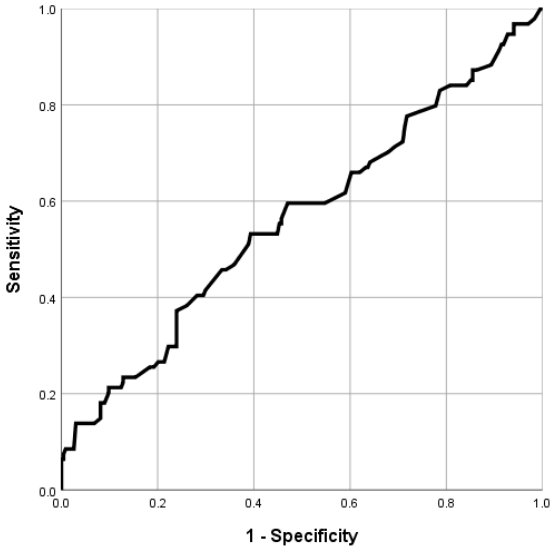

Figure 6. ROC curve for uterine artery Doppler pulsatility index in predicting small for gestational age status.

revealing that preterm-SGA infants exhibited the highest mortality risk during both the first and second months. This underscores the necessity for targeted interventions to enhance survival rates in these vulnerable groups (19). In contrast, a population-based study conducted by Xiang et al in China reported a 7.3% prevalence of SGA, which decreased to 5.3%, reflecting a 3.9% annual reduction attributable to maternal health interventions (20). Consequently, the prevalence figure from the current study is not consistent with global estimates and should not be interpreted as such.

Furthermore, the study by Lawn et al indicated that 23.4 million SGA births occurred in 2020, significantly contributing to neonatal mortality and stillbirths (21). Moreover, SGA-born cases are associated with an increased risk of stillbirth, neonatal mortality, and long-term health complications. These findings emphasize the critical need for targeted prenatal monitoring and improved neonatal care.

The current study revealed that the distribution of maternal age varied across SGA subgroups, with the majority of participants in the mild and moderate FGR subgroups aged 20-29 years. The non-SGA group exhibited the highest proportion of individuals within this 20-29age range. Another study by Palatnik et al examined the association between maternal age and the risk of SGA, comparing women aged 35 years and older with younger mothers. These findings indicated that the prevalence of SGA was significantly higher among women aged 20-29 years, lower in those aged 30-34 years, and lowest in women aged 35-39 years and older. These results suggest that younger mothers are more likely to experience mild to moderate forms of FGR, while older mothers may be susceptible to other factors that adversely affect fetal growth. Recently, Mangiza et al reported that, consistent with these findings, SGA infants particularly those born very preterm are at a higher risk of mortality and morbidity than non-SGA infants, with the association being most pronounced among the least mature infants (23). These findings are in alignment with our study and highlight the significance of addressing preterm delivery in at-risk pregnancies. Furthermore, existing literature emphasizes the distinction between SGA and intrauterine growth restriction (IUGR), underscoring that while IUGR can lead to SGA, they are not synonymous. This distinction is essential for understanding the influence of gestational age on SGA births and for developing effective interventions.

The current study demonstrates that placental weight and area were significantly lower in the SGA subgroups compared to the non-SGA group. Among the SGA subgroups, the mild FGR subgroup exhibited the lowest values, followed by the moderate FGR subgroup, while the non-SGA group displayed the largest measurements. Similarly, poor nutrition, low maternal weight, and low-maternal height were more prevalent in the SGA subgroups, particularly in cases of mild and severe FGR, compared to the non-SGA group. These findings emphasize the critical importance of maternal health in the risk of SGA.

A previous study by Ambreen et al assessed the influence of maternal nutritional status on SGA outcomes, revealing that underweight women and those with low mid-upper arm circumference had a heightened likelihood of delivering SGA infants. This finding emphasizes that maternal health encompasses factors beyond age, highlighting the pivotal role of nutritional elements in fetal growth outcomes (24).

More recently, Bligard et al identified FGR as a prevalent pregnancy complication that necessitates Doppler monitoring and often results in early delivery (25). Simultaneously, Bekmukhambetov et al, linked environmental pollution to increased morbidity and cancer risk, particularly among children, emphasizing the significant roles of environmental and prenatal factors in adverse health outcomes (26). Inadequate placentation and maternal health issues leading to premature births are common contributors to SGA, with complications related to SGA primarily stemming from placental insufficiency or maternal health problems (27).

Maternal age, parity, and socio-economic status did not appear to influence the outcomes in this study, contrasting with other research indicating that maternal factors can impact fetal growth under specific circumstances. For example, in rural Nepal, factors such as nulliparity, short interpregnancy intervals, and poor maternal appetite are associated with SGA, while greater wealth and appropriate weight gain serve as protective factors (28). Although not all cases achieve catch-up growth, many SGA infants do reach this milestone by age two. However, a specific subset of these SGA infants continues to experience growth difficulties later in childhood (29). In summary, these findings demonstrate a strong association between SGA births and gestational age, underscoring the complex interplay of maternal, placental, and socio-economic factors. To improve both neonatal and long-term health outcomes for SGA infants, effective interventions addressing these variables are essential.

The current study indicates that preeclampsia, anemia, and ARIs were more prevalent in the SGA subgroups, although preeclampsia did not show a statistically significant difference when compared to the non-SGA group. The risk of pregnancy termination was higher in the SGA subgroups, particularly among those with mild FGR. In univariate analyses, anemia and ARI were significantly associated with lower odds of SGA; however, only ARI remained significant in the multivariate model, indicating it as an independent predictor of SGA. Furthermore, studies by Arcangela et al and Franchuk et al noted that, the presence of preeclampsia in SGA subgroups, especially among those with mild FGR was not statistically significant. Preeclampsia is a recognized risk factor for SGA outcomes due to its association with placental insufficiency, which impairs blood flow and

nutrient delivery, thereby restricting fetal growth (30,31). Furthermore, anemia during pregnancy can adversely affect fetal outcomes by limiting oxygen transport to the fetus, exacerbating growth restrictions (32). The SGA fetuses are linked to an increased risk of stillbirth and poor neonatal outcomes. Distinguishing healthy small infants from those who are growth-restricted is crucial. FGR, often stemming from placental disease, necessitates early risk assessment, ultrasound monitoring, and timely delivery (33).

The current study also demonstrated that T-cell infiltration was more prevalent in the SGA group (57.7%) compared to the non-SGA group (35.2%), suggesting an inflammatory response associated with SGA pregnancies. In univariate analysis, both T-cell and macrophage infiltration were linked to increased odds of SGA; however, neither remained significant in the multivariate model. Conversely, TNF-α expression emerged as a significant independent predictor of SGA in both univariate and multivariate analyses. Cytokine levels, specifically IL-6 and TNF-α, were significantly elevated in the SGA group, indicating a correlation between inflammation and impaired fetal growth. Notably, macrophage infiltration did not differ significantly between the groups. These findings are consistent with existing literature. The study by Górczewski et al highlighted that low levels of PlGF and PAPP-A are critical for assessing the risk of SGA, rendering them useful for early SGA prediction (12). Similarly, the elevated malondialdehyde (MDA) levels observed in this study align with a 2024 systematic review by Ibrahim et al, which reported that exposure to oxidative stress markers is associated with adverse pregnancy outcomes, including SGA (34). These results reinforce the understanding that oxidative stress and placental dysfunction are significant contributors to FGR. The lack of substantial differences in free β-HCG levels raises questions regarding its utility as a marker for SGA, as increased free β-HCG does not enhance the diagnostic capability for SGA risk (35-37). Previous studies have demonstrated variability in the predictive value of certain biomarkers, underscoring the importance of a multifactorial approach to enhance predictive power. In conclusion, this study emphasizes the need for further investigation by monitoring biochemical markers such as PlGF, PAPP-A, MDA, and superoxide dismutase to gain insights into the pathophysiological aspects of SGA pregnancies. Free β-HCG exhibits limited predictive ability, and the variability in predictive accuracies among diverse biomarkers indicates a need to refine screening protocols. Future studies should integrate multiple biomarkers and clinical variables to improve the early prediction and management of adverse pregnancy outcomes.

The current study highlights key inflammatory mediators linked to the risk of SGA, indicating that systemic inflammation and immune dysregulation contribute to FGR. The increased T-cell infiltrate observed in SGA placentas may correlate with an enhanced immune response that negatively affects placental function and restricts fetal growth. In contrast, macrophage infiltration did not significantly differ between the SGA and non-SGA groups, suggesting that macrophages may not play a central role in SGA pathophysiology.

Higher levels of cytokines were significantly associated with SGA pregnancies, indicating a pro-inflammatory environment that is detrimental to placentation and the transfer of nutrients through the placenta. These findings align with previous studies showing that abnormal CD8+ T-cell infiltration in placentas contributes to FGR. Increased numbers of CD8+ T-cells were linked to poor pregnancy outcomes, suggesting that effector T-cells producing pro-inflammatory cytokines, such as TNF-α and IFN-γ, may be harmful (38,39).

Additionally, this study's findings of elevated IL-6 and TNF-α are consistent with Jiang et al, who reported that systemic inflammation in pregnancies complicated by systemic lupus erythematosus disrupts placental function, leading to adverse fetal outcomes (40). Similarly, Bezemer et al demonstrated that pregnancies with FGR exhibit altered decidual immune cell profiles, characterized by increased macrophages, a lower M2/total macrophage ratio, and elevated regulatory T-cells. This finding shows the role of immune dysregulation at the maternal-fetal interface in growth-restricted outcomes such as SGA (41).

However, in many instances, independent associations between heightened T-cell activity and SGA were not observed. Recently, Nüsken et al noted that while inflammatory markers are elevated in complicated pregnancies, the causal effects on SGA remain unclear and may involve interactions between inflammatory and other physiological factors (42).

In summary, the results underscore the critical roles that systemic inflammation and immune cell dynamics play in the pathophysiology of SGA conditions. The identification of T-cell infiltrates and elevated cytokine levels offers valuable insights into the mechanisms underlying FGR and highlights novel targets for early intervention in SGA pregnancies. Hence, further research is warranted to investigate the complex interactions between immune responses and placentation to develop more effective strategies for managing at-risk pregnancies.

Meanwhile, our study indicates that Doppler parameters, specifically umbilical artery PI and uterine artery PI, were significantly elevated in the SGA group, suggesting reduced placental blood flow and compromised maternal circulation. These measurements are strongly associated with an increased risk of SGA, emphasizing their clinical significance for early detection and management.

In this analysis, lower EFW, smaller abdominal circumference, and higher umbilical artery PI were identified as significant independent predictors of SGA in the multivariate model, whereas uterine artery PI lost significance after adjustment. Consistent with our findings,

other studies have reported significant decreases in EFW and abdominal circumference in SGA fetuses compared to their non-SGA counterparts, indicating that placental insufficiency is a key factor related to growth restriction. Moreover, Feucht et al demonstrated that umbilical artery Doppler screening in low-risk pregnancies led to a 43% reduction in stillbirths and identified infants with poorer postnatal growth (43).

Furthermore, elevated umbilical and uterine artery PI values above the median have been associated with adverse outcomes, including SGA status and perinatal mortality. The 51st Annual Scientific Meeting of the British Medical Ultrasound Society highlighted that Doppler assessments can facilitate risk stratification and inform clinical management, particularly in high-risk pregnancies (44). However, the inconsistent recommendations across guidelines concerning the use of Doppler-based assessments raise concerns about the standardization of care. While some guidelines endorse a multimodal approach to risk stratification that integrates both Doppler and other biophysical parameters, the variability in recommendations may result in differing clinical outcomes (45). The potential benefits of these assessments are evident if proven effective; however, further research is required to establish protocols for their implementation. Although Doppler monitoring is linked to improved outcomes, a prior review noted that the quality of evidence supporting reduced long-term effects on neonatal development and survival from Doppler monitoring is often moderate or low (46,47). Nevertheless, additional studies are crucial to formulate clinical recommendations and standardize care to optimize neonatal outcomes and the long-term health of SGA infants.

Conclusion

This research underscores critical findings that highlight the necessity for early detection and intervention in SGA pregnancies. The results reveal that SGA pregnancies are linked to significantly reduced levels of PlGF and PAPP-A, both of which are essential indicators of placental health. Besides, PAPP-A testing has been integrated into standard antenatal screening protocols and is conducted on all pregnant women at 11 to 13 weeks of gestation using venous blood, rendering it a highly accessible and reliable tool for identifying pregnancies at risk for SGA.

Conversely, PlGF, another biochemical marker, is primarily evaluated under specific clinical circumstances due to its limited application in routine practice, such as in cases of suspected preeclampsia. Consequently, its wider adoption for SGA prediction is constrained, indicating that PAPP-A may serve as a more effective screening marker than PlGF.

The findings from Doppler ultrasonography are significant, with the SGA group demonstrating elevated pulsatility indices in both the umbilical and uterine arteries. Increased PI values are indicative of compromised placental perfusion and reduced blood flow between the mother and fetus, which is a recognized factor contributing to FGR. Doppler studies are routinely incorporated into prenatal screening and play a crucial role in fetal-maternal medicine, aiding in the planning and timing of medical interventions for pregnancies at risk for SGA. Furthermore, macroscopic and histological evaluations of the placenta, conducted according to established pathology protocols, reveal structural changes associated with intrauterine growth restriction. These results highlight the connection between maternal health, placental modifications, and the incidence of SGA.

Consequently, the integration of PAPP-A levels, Doppler ultrasound parameters, biometric assessments such as EFW and abdominal circumference, along with placental histology, offers a comprehensive approach to the early diagnosis and management of SGA pregnancies. This multimodal strategy enables timely preventive interventions that can improve perinatal outcomes for both mother and child.

Recommendations

The utilization of PAPP-A, which is already incorporated into standard antenatal screening protocols, should be emphasized, and routine screening should be upheld due to its significant correlation with SGA pregnancies, its ease of implementation, and its early predictive value. Conversely, PlGF testing should be reserved for pregnant women at elevated risk of developing pre-eclampsia or those who have already exhibited measurable signs of the disease, allowing for selective application in instances where SGA is associated with pre-eclampsia. Findings from Doppler ultrasound, particularly elevated PI values in the umbilical and uterine arteries, are critical components of prenatal care and should inform decisions regarding the optimal timing and method of medical intervention. Additionally, expanding the routine use of placental histological and macroscopic examinations in clinical practice could yield deeper insights into the maternal and fetal pathologies contributing to SGA, thereby facilitating targeted prevention and management strategies.

Limitations of the study

One limitation of this study is its cross-sectional design, which precludes long-term follow-up to assess the outcomes of early diagnosis and treatment of SGA pregnancies. Furthermore, the focus on a single tertiary care hospital may limit the generalizability of the findings to other populations or healthcare settings. Although the reliance on biochemical markers and ultrasound findings is beneficial, it may not capture all the complex factors influencing SGA pregnancies. Lastly, the selective application of PlGF testing restricts its broader use in routine prenatal care, thereby diminishing its utility as a population-level screening tool, despite its significance in high-risk cases.

Authors' contribution

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Writing–review & editing: Aida Mussabekova, Nailya Khairullina.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

The data presented in this study are available upon request from the corresponding author. Due to privacy and ethical restrictions concerning participant confidentiality, the data are not publicly accessible.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity (https://www.perplexity.ai/) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

This study was conducted in accordance with the ethical standards of human experimentation as outlined in the 1975 Declaration of Helsinki and its subsequent amendments. Ethical approval was obtained from the Institutional Review Board (Ethics Committee) of Kazakh-Russian Medical University (protocol code 17/87; approval date: 8 November 2022; Almaty, Kazakhstan). Informed consent was secured from all participants, who were informed of the study's aims, procedures, potential risks, and benefits. Participation was entirely voluntary, and participants were assured that all data would remain confidential and anonymous. All ethical considerations, including plagiarism, misconduct, data fabrication, falsification, and redundant or double publication, were meticulously addressed and avoided throughout the study. The authors reaffirm their commitment to the highest standards of scientific integrity and transparency, adhering to the guidelines set forth by the Committee on Publication Ethics (COPE), the International Committee of Medical Journal Editors (ICMJE), and the EQUATOR Network.

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