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Original Research Article

Circulating serine peptidase inhibitor, Kunitz type 1(SPINT1) –A biomarker of pregnancies with poor placental function and fetal growth restriction

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Abstract

Introduction: Placental insufficiency and fetal growth restriction significantly contributed to stillbirth risk, particularly in India, where reliable maternal and newborn health statistics were scarce. The aim of this study was to investigate serum SPINT1 levels as a biomarker for detecting placental insufficiency potentially easing the global burden of preventable stillbirths. Therefore, the study's objective is to assess circulating SPINT1 levels at 28-36 weeks gestation to determine its effectiveness as a biomarker for placental insufficiency.

Materials and Methods: This prospective cohort study recruited 77 pregnant participants through convenience sampling, following ethical approvals and informed consent. Clinical data were collected, and serum SPINT1 levels were measured using enzyme-linked immunosorbent assay (ELISA) during 28-36 weeks of gestation. Postnatal follow-up evaluated neonatal outcomes through APGAR scores, focusing on cases with fetal complications. Statistical analyses were conducted using GraphPad Prism v9.

Results: The highest serum SPINT1 levels were observed at 28 weeks, with a significant correlation found with gestational age ($r = 0.54$, $p = 0.004$) and systolic blood pressure ($r = 0.45$, $p < 0.0001$). Multiple linear regression identified age, hemoglobin, and blood pressure as significant predictors of SPINT1 levels ($p = 0.0022$). Low APGAR scores were noted in five cases, indicating a link between impaired neonatal outcomes and placental insufficiency.

Conclusion: Serum SPINT1 had the potential to enhance early detection of placental insufficiency, improving management strategies for high-risk pregnancies. Further research was necessary to confirm these findings and explore broader clinical applications.

Keywords: Placental insufficiency, Fetal growth restriction, SPINT1, Biomarkers, Neonatal outcomes.

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1. Introduction

Placental insufficiency and fetal growth restriction are major complications resulting from poor placental function, significantly contributing to the risk of stillbirth.[1] In India, existing health statistics registries have been unable to produce reliable, region-specific estimates of maternal and newborn mortality and morbidity, which are essential for the effective planning and monitoring of health interventions.[2] Insufficient placental function initiates a series of pathological events as the fetus attempts to adapt, leading to restricted growth, low birth and placental weights, and increased blood flow resistance in the maternal uterine and placental umbilical arteries.[3] Current antenatal diagnostic methods, such as ultrasound Doppler assessments of the umbilical and middle cerebral arteries, lack sufficient reliability for near-term sensitivity.[4-6] Stillbirth rates are particularly elevated between 28 and 36 weeks, with an incidence of 52.63%,[7] highlighting an urgent need for improved diagnostic tests to reduce stillbirths by accurately identifying placental insufficiency earlier in pregnancy. Circulating maternal biomarkers have shown potential in addressing these limitations, with plasma serine peptidase

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inhibitor Kunitz type-1 (SPINT1) emerging as a promising candidate for detecting true placental insufficiency.

Placental insufficiency is a leading cause of fetal growth restriction (FGR) and adverse perinatal outcomes. Traditional biomarkers such as sFlt-1 and PlGF, while useful, lack sufficient specificity in identifying true placental dysfunction. Recent research has identified circulating maternal SPINT1 (serine peptidase inhibitor Kunitz type-1) as a promising biomarker with greater diagnostic potential. SPINT1 plays a critical role in placental development, particularly in regulating trophoblast invasion and maintaining placental barrier integrity. Reduced maternal plasma SPINT1 levels have been consistently associated with placental insufficiency, small-for-gestational-age infants, and heightened perinatal risk.[8,9]

Unlike angiogenic markers, SPINT1 offers specificity for placental pathology rather than general maternal endothelial dysfunction, potentially allowing for earlier and more accurate detection of at-risk pregnancies. Furthermore, longitudinal studies demonstrate that SPINT1 levels remain altered well before clinical signs of FGR become evident, highlighting its predictive value.[10] Integrating SPINT1 into prenatal screening may enhance risk stratification, guide surveillance intensity, and inform decisions around timing of delivery. However, large-scale studies are required to establish population-specific reference ranges and assess its additive value when combined with other biomarkers.

By combining SPINT1 levels with ultrasound findings across gestational stages, this study aims to validate a highly accurate diagnostic tool for fetal growth restriction, potentially easing the global burden of preventable stillbirths. Therefore, the study's objective is to assess circulating SPINT1 levels at 28-36 weeks gestation to determine its effectiveness as a biomarker for placental insufficiency.

2. Materials and Methods

This cross-sectional observational study with prospective follow-up study was conducted in the Department of Obstetrics & Gynecology, recruiting 77 pregnant participants through convenience sampling (CTRI/2023/08/057138 Registered on: 31/08/2023). Approvals from the Medical Superintendent and Institutional Ethical Committee were obtained, along with written informed consent from each participant and/or their families. Study sites were chosen based on participant availability to capture a range of demographic and clinical profiles.

The sample size was estimated by consulting a statistician and using the statistical software G* Power 3.0.10. Using a confidence level of 99%, a sample size of 77 participants was calculated based on a 2.97% prevalence of stillbirths reported in 2021 for the Belagavi region.[7] Participants were required to be at least 18 years old and were eligible if they had a history of certain obstetric complications, including anemia, hypertensive disorders (e.g., preeclampsia, eclampsia), infections (e.g., rubella, tuberculosis, malaria), or needed ovulation induction treatments or in-vitro fertilization. Maternal conditions such as gestational diabetes and fetal complications, including oligohydramnios, fetal distress, growth retardation, and placental abruption, were included to ensure a diverse clinical background. Exclusion criteria included pregnancies with significant genetic conditions, major congenital malformations, or aneuploidy which was screened by anomaly scan is typically performed between 18 and 22 weeks of pregnancy.

Clinical data for each participant were collected using a standardized data collection proforma, covering gestational age (calculated via Naegele's rule and confirmed by first trimester ultrasound) and maternal details such as age, gravidity, and socioeconomic status, based on the 2016 Kuppuswamy scale for urban populations and the 2016 BG Prasad scale for rural populations.[11] Data on antenatal checkups, past and current medical illnesses, and obstetric history were recorded to provide a comprehensive view of each participant's health. Full physical, systemic, and obstetric examinations were conducted to document baseline health.

2.1. Operational definitions

1. Registered gravida: a woman who had 4 or more antenatal visits
2. (Preterm stillbirth: stillbirth occurring before 37 completed weeks of gestation
3. Postterm stillbirth: stillbirth occurring after 42 weeks of gestation
4. Antepartum stillbirth: the intrauterine fetal demise occurred before the onset of labor
5. Intrapartum stillbirth: the intrauterine fetal demise occurred during labor
6. Early stillbirth: stillbirths which occurred between 20 and 27 weeks and 6 days
7. Late stillbirth: stillbirths which occurred after 28 weeks
8. Stillbirth: it was defined as birth of a baby, with no signs of life occurring after 20 weeks of pregnancy or with >500 grams of fetal weight.[12]
9. Extreme prematurity: birth before 28 weeks of gestation.

2.2. SPINT1 determination

SPINT1 levels were measured from blood samples collected at 28-36 weeks gestation. Each 5 ml blood sample was collected in ethylenediamine tetraacetic acid (EDTA) vials and then centrifuged at 2500 RPM at 4°C for 10 minutes. The supernatant plasma was separated and analyzed for SPINT1 levels using enzyme-linked immunosorbent assay (ELISA) following the manufacturer's protocol. This biomarker analysis aimed to determine SPINT1's reliability in identifying cases of placental insufficiency. Additional biochemical data (blood pressure, glucose tolerance,

hemoglobin levels, and infection markers) were retrieved from the MRD files of participants, without further biochemical or endocrine testing. Postnatal follow-up was conducted, particularly for cases with fetal complications such as distress or growth retardation, using APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores[13] to perform correlation analysis and assess neonatal outcomes related to placental function.

Standardized definitions were employed to categorize complications and outcomes, such as preterm and postterm stillbirth, antepartum and intrapartum stillbirth, and extreme prematurity, ensuring consistency in data collection and analysis. Through these detailed procedures, this study aimed to validate SPINT1 as a reliable biomarker for placental insufficiency, with potential to enhance early detection and reduce adverse outcomes in high-risk pregnancies. Statistical analysis of the present study was performed using the GraphPad Prism v9. $P<0.05$ was considered statistically significant.

3. Results

The results of this study indicated that the highest mean serum SPINT1 level (µg/L) was observed at 28 weeks of gestation, suggesting a peak in this biomarker during mid-pregnancy. A significant positive correlation was found between serum SPINT1 levels and gestational age, with a Pearson's correlation coefficient of ($r = 0.54$, $p = 0.004$), indicating that as gestational age increased, SPINT1 levels also rose substantially. Additionally, a strong association was noted between SPINT1 levels and systolic blood pressure ($r = 0.45$, $p < 0.0001$), while a moderate correlation was observed with diastolic blood pressure ($r = 0.24$, $p = 0.0013$). [**Figure 1-3, Table 1**)].This suggests that as blood pressure increased, serum SPINT1 levels tended to elevate, highlighting the potential role of this biomarker in the context of maternal hemodynamics during pregnancy.

In examining the relationship between serum SPINT1 levels and hemoglobin levels, a weaker correlation was identified ($r = 0.084$, $p = 0.06$) (**Table 1**), suggesting that while there is some association; it may not be clinically significant. To further assess the impact of various factors on serum SPINT1 levels, a multiple linear regression analysis was performed, which included age of the patient, hemoglobin levels, weeks of gestation, systolic blood pressure, and diastolic blood pressure. The regression model was statistically significant ($p = 0.0022$), indicating that these variables collectively explain a portion of the variance in serum SPINT1 levels. Within this framework, age and hemoglobin levels were found to be significant contributors, as were systolic and diastolic blood pressure, underscoring the multifaceted influences on SPINT1 levels during pregnancy.

This finding emphasizes the potential utility of serum SPINT1 as a biomarker for monitoring placental function and maternal health throughout pregnancy, particularly during the critical mid-gestational period when placental development and function are pivotal for fetal growth and well-being. Further research is warranted to elucidate the biological mechanisms underlying these associations and to explore the potential clinical implications of measuring serum SPINT1 levels in assessing risks related to placental insufficiency and adverse pregnancy outcomes.

Postnatal follow-up focused on cases with fetal complications, such as distress or growth retardation, using APGAR scores to assess neonatal outcomes. In five instances, moderate to low scores (4-6 is moderately abnormal, and 0-3 is low) which potentially indicated the need for medical intervention were recorded. This indicated suboptimal health conditions for the newborns. These findings suggest a potential link between low neonatal vitality and placental insufficiency, highlighting the impact of poor placental function on fetal development. The correlation between APGAR scores and maternal serum SPINT1 levels may provide further insights into the predictive value of SPINT1 for adverse outcomes. Overall, the low APGAR scores underscore the necessity for effective antenatal monitoring and timely interventions to improve neonatal health. A broader analysis of APGAR distribution could strengthen this link and is recommended for future studies with larger sample sizes.

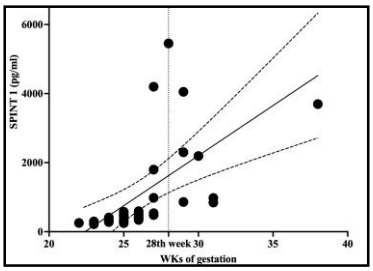

Figure 1: Association between SPINT1 Concentrations and Gestational Age
Abbreviations: X-axis-gestational age, Y-axis-Plasma serine peptidase inhibitor Kunitz type-1 (SPINT1)

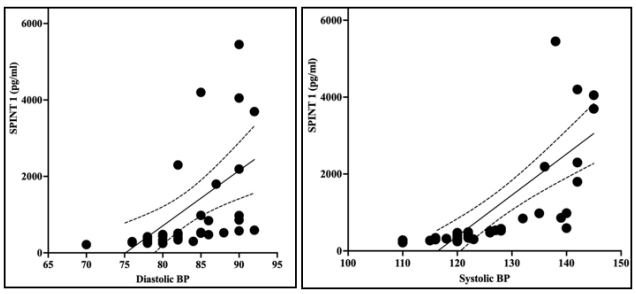

Figure 2: A & B: Relationship of SPINT1 concentrations with maternal blood pressure parameters
Abbreviations: X-axis- Diastolic and Systolic BP, Y-axis-Plasma serine peptidase inhibitor Kunitz type-1 (SPINT1)

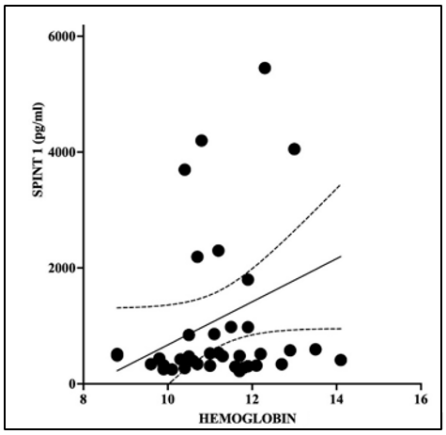

Figure 3: SPINT1 expression in relation to serum hemoglobin
Abbreviations: X-axis-Hemoglobin, Y-axis-Plasma serine peptidase inhibitor Kunitz type-1 (SPINT1)

Table 1: Correlation between ELISA results and maternal parameters in study samples (n = 77)

Groups	Correlation analysis r and p-value	Absolute values
Gestational age	**r:** 0.54	26.3
	p:0.004***	
Blood pressure Systolic	**r:**0.45	124
	p:<0.0001****	
Blood pressure Diastolic	**r:**0.24	82
	p:0.0013***	
Hemoglobin	**r:**0.084	11.23
	p:0.06	
SPINT 1		1130± 0.62

The results based on SPINT 1 Elisa Kit reports expressed in (ug/L).

Statistical test used: Pearson correlation test. $p<0.01^{****}$indicates highly significant difference, $p<0.05^{***}$indicates significant difference, $p>0.05$ indicates non-significant difference between Elisa and Maternal Parameters **Abbreviations:** Plasma serine peptidase inhibitor Kunitz type-1 (SPINT1).

4. Discussion

Our study offers new insights into the role of SPINT1 as a potential biomarker for placental insufficiency, specifically for pregnancies at risk of fetal growth restriction (FGR). We observed the highest mean SPINT1 levels at 28 weeks of gestation and found significant correlations between SPINT1 and both gestational age and blood pressure, supporting prior research that advocates for more effective markers of placental insufficiency. This condition remains a leading risk factor for stillbirth, and early detection could enable closer monitoring, timely interventions, and potentially reduce stillbirth rates.[1,14]

Our findings align with the existing literature on the detrimental impact of poor placental function. Placental insufficiency disrupts nutrient and oxygen supply, leading to FGR as the fetus copes by slowing growth and redirecting blood flow to vital organs like the brain.[3] In our study, SPINT1 levels were positively associated with gestational age, mirroring the progression of placental development. This association suggests that SPINT1 may reflect the functional state of the placenta as it matures. The observed peak in SPINT1 at 28 weeks also supports prior studies indicating that decreased SPINT1 levels might signal placental dysfunction, possibly even before clinical symptoms of FGR appear.[15]

The strong correlation observed between SPINT1 levels and blood pressure, particularly systolic blood pressure, highlights the biomarker's relevance to hypertensive disorders in pregnancy. Maternal hypertension increases vascular resistance, impacting placental blood flow and fetal oxygen supply, factors central to placental insufficiency.[16] Our findings align with studies that connect reduced SPINT1 with preeclampsia, suggesting that SPINT1 could serve as a diagnostic tool to identify pregnancies at risk of complications related to blood pressure. The relationship between SPINT1 and blood pressure indicates its sensitivity to vascular changes and adds weight to SPINT1's potential as a clinical marker for placental health.[17]

Although the correlation between SPINT1 and hemoglobin levels was weak, this may reflect hemoglobin's indirect role in assessing placental function. While both anemia and placental insufficiency can impact pregnancy outcomes, they do so through different mechanisms; for instance, anemia is less directly related to placental vascular dynamics compared to blood pressure.[1] This underscores the importance of considering SPINT1 alongside more direct indicators of placental function, such as blood pressure, in comprehensive assessments of maternal-fetal health.

Our multiple regression analysis revealed that age, hemoglobin, gestational age, and blood pressure are significant predictors of SPINT1 levels, with blood pressure and gestational age showing the strongest associations. Given that risk factors for placental insufficiency are often multifactorial, future studies could explore SPINT1 as part of a larger biomarker panel. Such a panel could enhance the diagnostic sensitivity and specificity for placental insufficiency, offering a more holistic approach to identifying pregnancies at risk for adverse outcomes.[14]

These findings have significant implications for clinical practice. Doppler ultrasound remains the standard tool for assessing placental and fetal health, yet its accuracy decreases in later gestation, especially around term, when compensatory fetal adaptations to placental insufficiency can obscure Doppler readings.[3,15] SPINT1, as a biochemical marker, could complement Doppler findings by providing a clearer indication of the placenta's functional status,

improving the accuracy of risk assessment for FGR and placental insufficiency near term. This is critical because stillbirth risk increases significantly around 38 weeks, making timely decision-making on delivery crucial.[1] A combined approach using SPINT1 and Doppler ultrasound may allow for better detection of high-risk pregnancies, helping clinicians determine the appropriate timing for interventions like labor induction, which remains a safe and effective option at term.[18,19]

Despite promising associations, our study is limited by a modest sample size, which may affect the generalizability of our results. Further large-scale studies are necessary to establish SPINT1 reference values and validate its use across different populations. Additionally, while this study confirmed that SPINT1 correlates with key indicators like gestational age and blood pressure, the underlying mechanisms remain unclear. Experimental studies on SPINT1's function in placental biology are limited, yet animal models suggest it plays a significant role in placental development, as evidenced by its impact on placental architecture in SPINT1-deficient mouse models.[20] Future research could examine regulatory pathways involving SPINT1, potentially identifying therapeutic targets for placental disorders.

In the broader context of maternal health, SPINT1 could play a vital role in regions where maternal and perinatal morbidity remain high, such as rural India, where hypertensive disorders and limited healthcare access challenge pregnancy outcomes. Despite recent advances, such as improved access to institutional births, maternal mortality and morbidity rates vary significantly across India, particularly in rural areas.[21-24] Health inequities continue to contribute to higher maternal mortality in underserved areas, where timely, quality healthcare is often out of reach. Given the role of hypertensive disorders in placental insufficiency and adverse outcomes, SPINT1's integration into routine diagnostics could potentially improve care quality by identifying high-risk pregnancies sooner, thus aiding in the prevention of severe complications and reducing maternal and fetal mortality.[25,26]

5. Conclusion

Our findings contribute to the emerging evidence that SPINT1 is associated with gestational age, blood pressure, and placental health, underlining its potential as a biomarker for placental insufficiency. The correlation between SPINT1 and placental indicators points to its clinical value, especially in identifying pregnancies at risk of FGR. Although further research is essential to confirm its utility, SPINT1 could serve as a valuable addition to diagnostic protocols for placental insufficiency, offering a novel approach to improving maternal and fetal health outcomes.

6. Limitations

The study's limitations include a relatively small sample size, which may limit the statistical power and generalizability of the findings, and the observational nature of the study, which restricts the ability to establish causality. SPINT1 levels were measured at specific points during gestation, yet fluctuations in SPINT1 over time could influence our results. Additionally, potential confounding variables, such as maternal lifestyle factors and socioeconomic status, were not thoroughly controlled, which could influence the association between SPINT1 levels and placental insufficiency. Future studies with larger cohorts and adjusted analyses are needed to account for their possible influence on biomarker expression.

7. Ethical Approval

All ethical principles for human research were followed and ethical approval was obtained from the Institutional ethics committee of the hospital from where the data was collected [FMMC/FMIEC/412/2023]. We have obtained informed consents from sample population involved in this study.

8. Authors' Contributions

All authors have equal contribution towards the study.

9. Availability of Data and Materials

Datasets used can be accessed on request mail to the corresponding author.

10. Source of Funding

None.

11. Conflict of Interest

None.

12. Acknowledgements

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