Biomarker profiling of Annexin A2 and IL-15 in Preeclamptic pregnancies with periodontitis and its impact on placental and neonatal outcomes

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ABSTRACT

Background: Preeclampsia represents a significant contributor to both maternal and neonatal morbidity and mortality on a global scale. Periodontitis has been identified as a potential risk factor for negative pregnancy outcomes, attributed to the systemic spread of inflammatory mediators and periodontal pathogens. Altered placental morphology, inflammatory biomarkers, and impaired fetal growth are often linked to preeclampsia. Annexin A2 and Interleukin-15 (IL-15) play significant roles in angiogenesis, inflammation, trophoblastic invasion, and immune regulation.

AimTo evaluate serum and salivary levels of Annexin A2 and IL-15 in preeclamptic and normotensive pregnant women with and without periodontitis and to assess their association with placental morphology, umbilical cord characteristics, and neonatal anthropometric outcomes.

Materials and Methods This cross-sectional analytical study involved 210 pregnant women divided into four groups: preeclamptic women with periodontitis (A1, n=35), preeclamptic women without periodontitis (A2, n=70), normotensive women with periodontitis (B1, n=35), and normotensive women without periodontitis (B2, n=70). Assessment was conducted on periodontal parameters such as PPD, CAL, GI, GBI, OHI-S, PI, and PDI. Levels of serum and salivary Annexin A2 and IL-15 were analysed utilising ELISA methodology. The evaluation included placental morphology, umbilical cord parameters, and neonatal anthropometric measurements.

Results Preeclamptic women with periodontitis exhibited notably worse periodontal health and increased serum and salivary IL-15 levels, whereas serum Annexin A2 levels were diminished. The parameters of placental weight, diameter, surface area, circumference, volume, and cotyledon number exhibited significant reductions in pregnancies affected by preeclampsia. Neonates delivered by mothers with preeclampsia demonstrated reduced measurements in birth weight, head circumference, chest circumference, mid-upper arm circumference, and ponderal index. The most unfavourable placental and neonatal outcomes were noted in preeclamptic women diagnosed with periodontitis.

ConclusionPreeclampsia related to periodontitis is connected to changes in inflammatory biomarkers, placental insufficiency, and compromised neonatal growth. Increased levels of IL-15 and decreased levels of Annexin A2 may play a role in abnormal placentation and negative fetal outcomes.

Keywords: Annexin A2; IL-15; Periodontitis; Preeclampsia; Placental morphology; Neonatal anthropometry; Umbilical cord; Pregnancy outcomes.

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INTRODUCTION

Periodontal disease encompasses inflammatory conditions affecting the supporting structures of the teeth, including the gingiva, periodontal ligament, cementum, and alveolar bone. This condition ranks among the most common chronic inflammatory diseases globally and is linked to various systemic issues, such as cardiovascular disease, diabetes mellitus, and negative pregnancy outcomes. [1]

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Pregnancy leads to physiological changes in hormonal and immune responses, making women more susceptible to gingival inflammation and periodontal disease.[2] Recent findings indicate that periodontal inflammation may increase the systemic inflammatory burden by allowing inflammatory cytokines and periodontal pathogens to enter the bloodstream.[3] Preeclampsia is a complex hypertensive disorder that affects multiple systems during pregnancy, defined by the presence of hypertension and proteinuria occurring after 20 weeks of gestation. Abnormal trophoblastic invasion, endothelial dysfunction, oxidative stress, an exaggerated maternal inflammatory response, and placental insufficiency play a significant role in the pathogenesis of preeclampsia. [4]

The placenta serves as a crucial organ that facilitates nutrient exchange, oxygen transfer, endocrine regulation, and supports fetal growth. Placental abnormalities, such as reduced placental size, infarctions, calcifications, vascular lesions, and impaired villous development, are frequently noted in cases of preeclampsia. These changes negatively impact uteroplacental circulation and lead to fetal growth restriction as well as unfavourable neonatal outcomes. Interleukin-15 (IL-15) serves as a pro-inflammatory cytokine that plays a crucial role in immune activation and the signalling pathways associated with inflammation. Elevated IL-15 levels have been associated with inflammatory disorders and may play a role in endothelial dysfunction and placental inflammation in preeclampsia. [5]

Annexin A2 is a phospholipid-binding protein that plays a significant role in angiogenesis, fibrinolysis, vascular integrity, and trophoblastic invasion. The diminished expression of Annexin A2 may hinder placental vascular remodelling and lead to compromised placentation. [6]

While research has separately assessed the impact of periodontal disease, placental pathology, and inflammatory biomarkers on pregnancy complications, evidence is scarce concerning the collective relationship between Annexin A2, IL-15, placental morphology, and neonatal anthropometric outcomes in preeclamptic pregnancies affected by periodontitis.

This study sought to assess the biomarker profiling of annexin A2 and IL-15 in pregnancies affected by preeclampsia and periodontitis, while also examining their relationship with placental morphology, umbilical cord characteristics, and neonatal outcomes.

Objectives

Primary Objectives

1. To evaluate serum and salivary levels of Annexin A2 and IL-15 in preeclamptic and normotensive pregnant women with and without periodontitis.
2. To assess placental morphology and umbilical cord characteristics in the study groups.
3. To evaluate neonatal anthropometric outcomes among the study groups.

Secondary Objectives

1. To determine the association between periodontal disease severity and preeclampsia.
2. To correlate inflammatory biomarkers with placental and neonatal outcomes.
3. To determine the influence of periodontitis on placental insufficiency and fetal growth restriction.

MATERIALS AND METHODS

Study Design

A cross-sectional analytical study was conducted at a tertiary care centre.

Study Population

A total of 210 pregnant women aged 18–45 years with gestational age ≥20 weeks were enrolled after obtaining informed consent.

Grouping

Participants were categorized into four groups:

- Group A1: Preeclamptic pregnant women with periodontitis (n=35)
- Group A2: Preeclamptic pregnant women without periodontitis (n=70)
- Group B1: Normotensive pregnant women with periodontitis (n=35)
- Group B2: Normotensive pregnant women without periodontitis (n=70)

Inclusion Criteria

- Pregnant women aged 18–45 years
- Gestational age ≥20 weeks
- Primigravida or multigravida women
- Diagnosed cases of preeclampsia or healthy normotensive pregnancies

Exclusion Criteria

- Gestational diabetes mellitus
- Chronic hypertension
- Gestational hypertension
- Thrombophilia
- History of recurrent abortions
- Smoking or alcohol consumption
- Recent periodontal treatment
- In vitro fertilisation pregnancies
- Congenital fetal anomalies

Periodontal Evaluation

The following clinical periodontal parameters were assessed: [7,8]

- Plaque Index (PI)
- Gingival Index (GI)
- Gingival Bleeding Index (GBI)
- Oral Hygiene Index-Simplified (OHI-S)
- Probing Pocket Depth (PPD)
- Clinical Attachment Level (CAL)
- Periodontal Disease Index (PDI)
- Tooth mobility

Biochemical Evaluation

Sample Collection

Five milliliters of venous blood were collected before delivery. Serum was separated by centrifugation and stored at -80°C.

Unstimulated whole saliva samples were collected and stored at -80°C.

Biomarker Analysis

Serum and salivary levels of IL-15 and Annexin A2 were estimated using ELISA kits.[9]

Placental Examination

Placentae were collected immediately after delivery, cleaned, weighed, and preserved in 10% formal saline.[10]

The following parameters were assessed:

- Placental weight
- Placental diameter
- Placental radius
- Placental thickness
- Placental circumference
- Placental surface area
- Placental volume
- Number of cotyledons
- Placental shape
- Maternal surface lesions

Umbilical Cord Evaluation

The following parameters were recorded:[11]

- Umbilical cord length
- Umbilical cord circumference
- Umbilical cord diameter
- Number of vessels
- Type of placental insertion
- Coiling pattern
- Presence of knots

Neonatal Anthropometric Measurements

The following measurements were assessed:[12]

- Birth weight
- Head circumference
- Chest circumference
- Mid-upper arm circumference
- Foot length
- Abdominal circumference
- Ponderal index
- APGAR scores

Statistical Analysis

Data were entered into Microsoft Excel and analysed using SPSS version 25.0. Descriptive statistics were expressed as mean ± standard deviation. Student t-test, Chi-square test, correlation analysis, and ANOVA were used. A p-value <0.05 was considered statistically significant.

Results

Periodontal Findings

Preeclamptic women with periodontitis demonstrated significantly higher periodontal disease severity compared to normotensive pregnant women.

There more prevalent among preeclamptic women, as represented below in Figure 1.

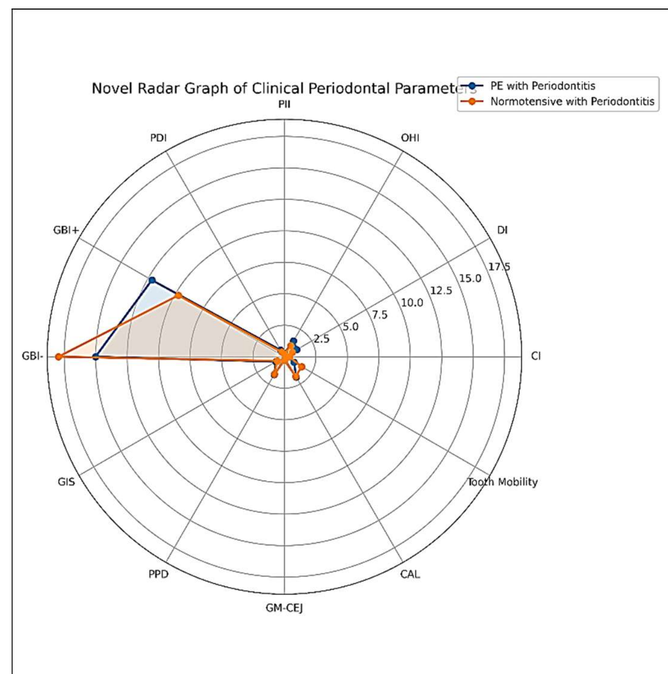

Figure 1: The Radar graph for multiple periodontal clinical parameters

- The radar graph compares multiple periodontal clinical parameters between preeclamptic pregnant women with periodontitis and normotensive pregnant women with periodontitis.
- Each axis of the graph represents one periodontal parameter, and greater outward extension indicates higher mean values.

- Preeclamptic women showed a larger overall radar area, indicating increased periodontal inflammatory burden.
- Significant increases were observed in:
  - Debris Index (DI)
  - Oral Hygiene Index (OHI)
  - Plaque Index (PII)
  - Periodontal Disease Index (PDI)
  - Gingival Bleeding Index positive scores (GBI+)
  - Probing Pocket Depth (PPD)
- These findings suggest poorer oral hygiene, greater plaque accumulation, active gingival inflammation, and increased periodontal tissue destruction in preeclamptic women.
- Slightly elevated Gingival Index (GIS) and Clinical Attachment Level (CAL) further support enhanced periodontal inflammation in preeclampsia.
- The normotensive group showed relatively higher GBI negative scores and tooth mobility values.
- Overall, the radar graph visually demonstrates that periodontal disease severity and inflammatory burden are greater in preeclamptic pregnancies.
- The findings support a possible association between chronic periodontal inflammation and the pathophysiology of preeclampsia.

Biomarker Analysis

IL-15

Serum and salivary IL-15 levels were significantly elevated in preeclamptic women with periodontitis compared to normotensive groups.

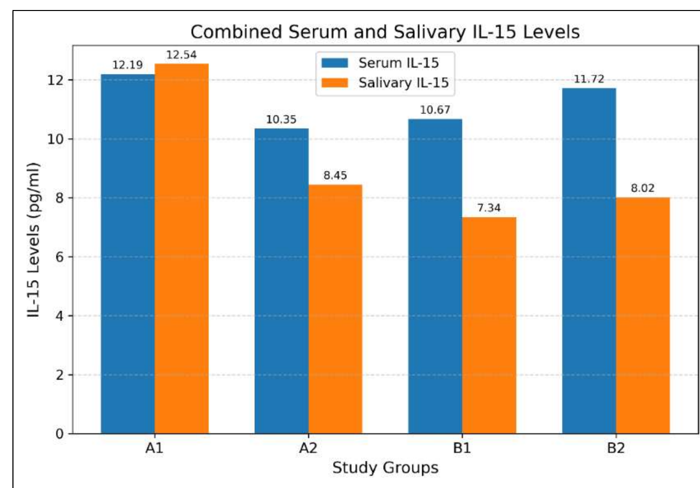

Figure 2: Serum and Salivary IL-15 levels

- The graph simultaneously compares serum and salivary IL-15 levels across all study groups.
- Preeclamptic women with periodontitis (A1) demonstrated the highest IL-15 levels in both serum and saliva.
- Salivary IL-15 levels showed a marked elevation in the A1 group compared to normotensive groups.
- The combined visualisation highlights the enhanced systemic and oral inflammatory burden associated with preeclampsia and periodontitis.
- Parallel elevation of serum and salivary IL-15 suggests a possible inflammatory link between periodontal disease and placental dysfunction.

Annexin A2

Serum Annexin A2 levels were reduced in preeclamptic pregnancies, whereas salivary Annexin A2 levels were higher among normotensive women without periodontitis. These findings indicate a possible imbalance between inflammatory cytokines and angiogenic proteins in preeclamptic pregnancies complicated by periodontal disease.

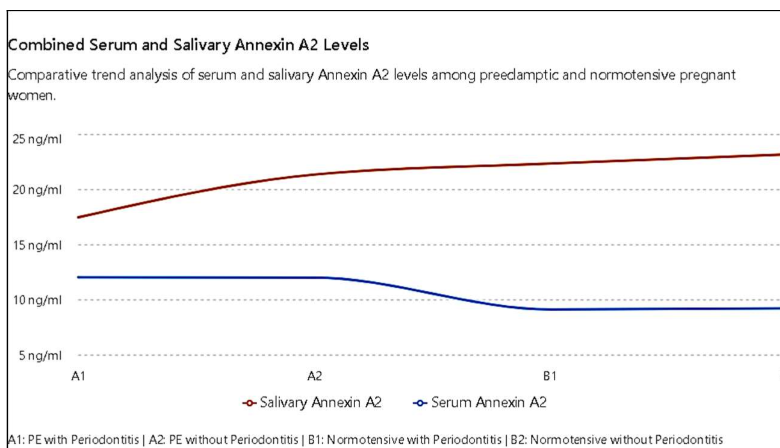

Figure 3: Serum and Salivary Annexin A2 levels

Placental Morphology

Placental morphometric parameters, including weight, diameter, radius, surface area, circumference, volume, and number of cotyledons, were significantly reduced in preeclamptic groups.

Placental infarctions, calcifications, and haemorrhagic lesions were more frequently observed in preeclamptic pregnancies.

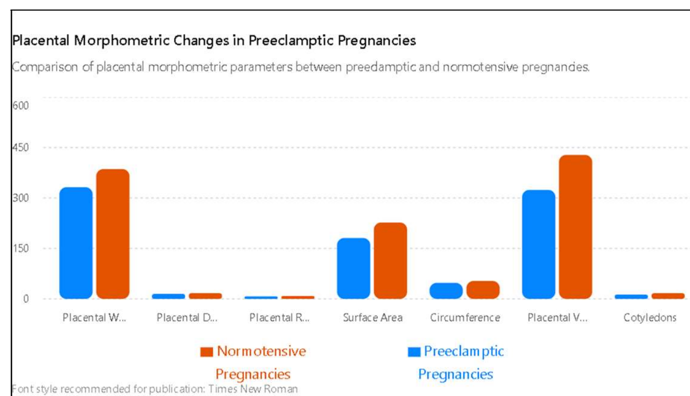

Figure 4: Placental morphometric changes in Preeclamptic pregnancies

- The graph demonstrates a consistent reduction in placental morphometric parameters in preeclamptic pregnancies.
- Placental weight, diameter, radius, surface area, circumference, and volume were lower in preeclamptic groups compared to normotensive pregnancies.
- Reduced placental dimensions indicate impaired placental growth and uteroplacental insufficiency.
- The number of cotyledons was also reduced, suggesting altered placental development and vascular compromise.
- Placental infarctions, calcifications, and haemorrhagic lesions were more frequently observed in preeclamptic pregnancies, supporting the presence of placental ischemia and endothelial dysfunction.
- These placental abnormalities may contribute to fetal growth restriction and adverse neonatal outcomes.

Umbilical Cord Morphology

No statistically significant differences were observed in umbilical cord circumference, diameter, or vessel number among groups.

Hypercoiling was observed more frequently among preeclamptic pregnancies.

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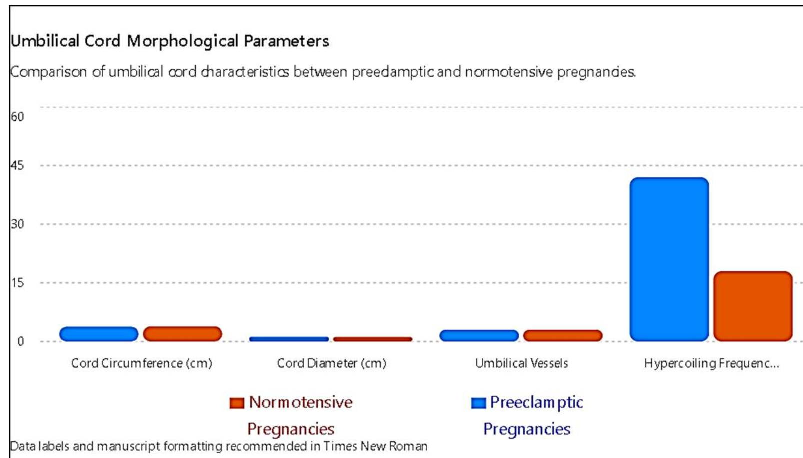

Figure 5: Umbilical cord morphological parameters

Neonatal Anthropometry

Neonates born to preeclamptic mothers demonstrated:

- Lower birth weight
- Reduced head circumference
- Reduced chest circumference
- Reduced mid-upper arm circumference
- Lower foot length
- Lower ponderal index

The poorest neonatal anthropometric outcomes were observed among neonates born to preeclamptic women with periodontitis.

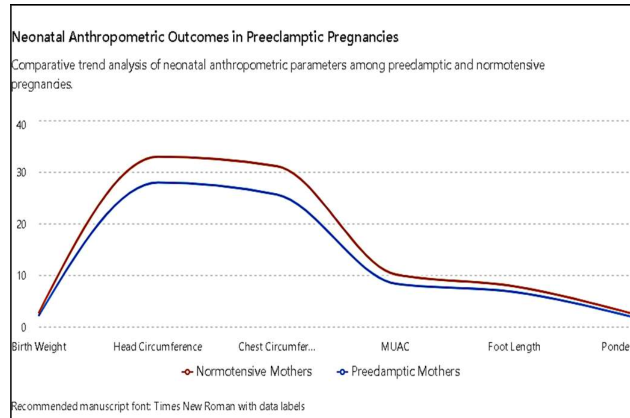

Figure 6: Neonatal anthropometric parameters

Correlation Analysis

Significant correlations were observed between:

- Maternal systolic blood pressure and intrauterine growth restriction
- Maternal blood pressure and APGAR scores
- Gestational age and ponderal index
- Preeclampsia severity and reduced placental dimensions

Table 1: Correlation analysis of all parameters

Correlation Parameters	Observation	Interpretation	Statistical Significance
Maternal Systolic Blood Pressure vs. Intrauterine Growth Restriction (IUGR)	Increased maternal systolic blood pressure was associated with higher incidence of IUGR	Elevated maternal blood pressure may impair uteroplacental perfusion leading to fetal growth restriction	Significant positive correlation ($p < 0.05$)
Maternal blood pressure vs APGAR scores	Higher maternal blood pressure was associated with lower APGAR scores	Severe maternal hypertension adversely affects immediate neonatal adaptation after birth	Significant negative correlation ($p < 0.05$)
Gestational age vs Ponderal index	Increased gestational age was associated with improved ponderal index	Longer gestational duration contributes to better fetal growth and nutritional status	Significant positive

			correlation ($p < 0.05$)
Preeclampsia severity vs Placental dimensions	Severe preeclampsia was associated with reduced placental weight, diameter, surface area, and volume	Increased disease severity contributes to placental insufficiency and impaired placental development	Significant negative correlation ($p < 0.05$)

DISCUSSION

This study illustrates that preeclampsia related to periodontitis is associated with notable changes in inflammatory biomarkers, placental structure, and neonatal growth measurements. [13,14] The notably high levels of IL-15 found in preeclamptic women with periodontitis reinforce the hypothesis that heightened systemic inflammatory responses play a role in endothelial dysfunction and placental insufficiency. IL-15 is recognised for its role in activating inflammatory pathways and immune cells, which subsequently exacerbate placental inflammation and vascular injury.

Lower serum Annexin A2 levels noted in preeclamptic pregnancies may suggest compromised fibrinolysis, angiogenesis, and trophoblastic invasion. Annexin A2 is essential for vascular remodelling and the maintenance of placental circulation. Decreased expression may consequently lead to impaired placentation and maternal vascular malperfusion.[15] The current findings also emphasise the significance of periodontitis as a possible contributing factor in preeclampsia. Chronic periodontal inflammation has the potential to elevate circulating inflammatory mediators and bacterial endotoxins, which may further aggravate maternal systemic inflammation and endothelial injury. [16-18]

The noted decrease in placental weight, diameter, surface area, and volume in preeclamptic pregnancies indicates compromised placental development and diminished exchange capacity. Placental lesions, such as infarctions and calcifications, provide additional evidence for the existence of uteroplacental insufficiency. [17-22]

Neonatal outcomes were significantly affected in pregnancies complicated by preeclampsia. Decreased birth weight, diminished head circumference, reduced chest circumference, and altered ponderal index suggest fetal growth restriction resulting from placental dysfunction. [23-25]

The interplay between preeclampsia and periodontitis resulted in the most significant placental and neonatal alterations, indicating a synergistic relationship between vascular dysfunction and chronic inflammation.[26] The results of this study align with existing literature that illustrates the connections among periodontal disease, systemic inflammation, placental insufficiency, and negative pregnancy outcomes.

LIMITATIONS

- The cross-sectional design limits causal inference.
- Microbiological assessment of periodontal pathogens was not included.
- Longitudinal follow-up was not conducted.
- The study population was restricted to a single tertiary care centre.

CONCLUSION

This study illustrates that preeclampsia linked to periodontitis is marked by increased IL-15 levels, modified Annexin A2 expression, negative placental morphology, and compromised neonatal growth. Periodontal disease seems to exacerbate systemic inflammation and placental dysfunction in preeclamptic pregnancies, leading to adverse maternal and fetal outcomes. The findings indicate that biomarker profiling utilising IL-15 and Annexin A2 could offer significant insights into the underlying pathophysiology of preeclampsia, abnormal placentation, and placental insufficiency. Additionally, the study emphasises the significance of early periodontal screening and prompt periodontal management during pregnancy, which may contribute to reducing the inflammatory burden and enhancing both maternal and neonatal health outcomes.

Conflicts of Interest

The authors declare no conflicts of interest.

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