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Original Article

Biochemistry Section

Association of Maternal Inflammatory Markers and Risk Factors with Adverse Pregnancy Outcomes: A Cross-sectional Study

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ABSTRACT

Introduction: Adverse pregnancy outcomes are a common health problem, particularly in resource-poor settings. However; their multifaceted causes are not fully understood. Investigating the association between inflammatory markers throughout pregnancy and adverse birth outcomes may provide insights into potential intervention pathways.

Aim: To determine the association between maternal inflammatory markers and risk factors with adverse pregnancy outcomes.

Materials and Methods: The present cross-sectional study was conducted at Dr Prabhakar Kore Hospital, Belagavi, Karnataka, India between August 2021 and August 2022. The present study included 714 pregnant women aged between 18-40 years, who presented for delivery at the institution. Maternal blood samples were collected before delivery to measure high-sensitivity-C Reactive Protein (hs-CRP), ferritin, albumin, and Erythrocyte Sedimentation Rate (ESR). Chi-square tests were performed to assess the association between these inflammatory markers and adverse pregnancy outcomes (Preterm Birth (PTB), Low Birth Weight (LBW), and stillbirth).

Results: The median age of participants was 24 years (Q_1, Q_3: 21, 26). Education level, gestational age, higher Body Mass Index (BMI), and history of hypertension were associated with adverse pregnancy outcomes. Serum ferritin levels were significantly higher in the adverse pregnancy outcomes group (48.0 ng/mL; Q_1, Q_3: 26.0, 86.0) compared to the group without adverse outcomes (35.0 ng/mL; Q_1, Q_3: 18.0, 62.0). Other inflammatory markers showed no statistically significant associations ($p<0.05$).

Conclusion: The present study found a significant association between serum ferritin levels and adverse pregnancy outcomes. Other inflammatory markers (hs-CRP, albumin, and ESR) showed no significant association at the time of labour presentation.

Keywords: Pregnant women, Biomarker, Serum ferritin, Preterm birth, Low birth weight

INTRODUCTION

Adverse pregnancy outcomes are a global health concern, particularly affecting families in resource-limited settings with weak health systems and poor access to healthcare services [1]. Annually, over 15 million babies are born prematurely worldwide, more than 9 million infants die within their first year, and approximately 20 million infants are born with Low Birth Weight (LBW; <2500g) [2]. These outcomes manifest as early pregnancy loss (miscarriage), late pregnancy loss (stillbirth), Preterm Birth (PTB), and LBW [3].

Infants born with LBW or PTB face higher risks of mortality, morbidity, and various short and long-term physical, developmental, and psychological problems [4]. The causes of adverse pregnancy outcomes are diverse and often not fully understood. Risk factors include obesity, anaemia, diabetes, inadequate antenatal care, smoking, history of abortion, hypertension, and inflammation [5]. Emerging evidence suggests that inflammation, a key biological response to infection and other pathological stimuli, plays a significant role in initiating adverse pregnancy outcomes [6]. Notably, approximately 30-50% of premature deliveries can be directly attributed to infection. Inflammatory pathways are crucial in fundamental reproductive processes such as ovulation, implantation, and parturition, impacting maternal and placental health as well as foetal development [7].

Previous studies have explored the association between maternal inflammatory markers such as hs-CRP, ferritin, albumin, and ESR with adverse pregnancy outcomes; however, findings have been inconsistent and context-specific [7-9]. Much of this research originates from high-income countries, often focusing on individual markers in isolation, which limits broader applicability [8,9]. Evidence from resource-limited settings like India, where maternal morbidity and adverse outcomes are disproportionately high, remains sparse. Furthermore, most existing studies assess inflammatory markers in early or mid-pregnancy, leaving limited data on their relevance at the time of delivery [10,11]. This gap makes it unclear whether inflammation serves as a causal factor or merely reflects underlying pathology. Comprehensive evaluation of multiple inflammatory markers, alongside maternal risk factors, is necessary to clarify these associations.

By addressing these gaps, Present study aimed to determine the association between maternal inflammatory markers and risk factors with adverse pregnancy outcomes and contributes novel insights from a large Indian cohort.

MATERIALS AND METHODS

The present cross-sectional study was conducted at Dr Prabhakar Kore Hospital, Belagavi, Karnataka, India between August 2021 and August 2022. The present study was part of the larger "Limiting Adverse Birth Outcomes in Resource-limited Settings" (LABOR) Study [12]. The study was approved by the Institutional Ethics Committee KAHER, (KAHER/EC/21-22/002), Belagavi, Karnataka, India. All procedures were conducted in accordance with the ethical standards of the Institutional Ethics Committee and adhered to the principles outlined in the Declaration of Helsinki (1975).

Inclusion criteria: Current study only enrolled women aged between 18-40 years with a single intrauterine pregnancy who presented for the delivery at the institution.

Exclusion criteria: Women with multiple pregnancies, those admitted for elective caesarean without co-morbid conditions, those unable to provide informed consent, and those with any social or medical condition deemed unsafe or unfeasible for participation by study staff were excluded.

Sample size calculation: Sample size was estimated based on prevalence of adverse birth/pregnancy outcomes take as 35% from a previous study, where employed 5% of significance and a relative precision of 10 % [13]. The sample size was calculated using the formula: $n=[z^2_{1-\alpha/2}(pq) / (10\% \text{ of } p)^2]$. The final calculated sample size for the study was 714 participants. A total of 714 women, who consented for the study, were recruited through a consecutive sampling approach.

Study Procedure

Adverse pregnancy outcomes were defined as the presence of one or more of the following: preterm birth, low birth weight, or stillbirth. Women experiencing a normal live birth without these outcomes were classified as having "no adverse pregnancy outcomes" [9]. Data collected included maternal age, height, gestational age, educational background, pregnancy smoking status, history of hypertension, thyroid disorders, diabetes mellitus, ANC visits, parity, and gravidity. BMI was calculated as weight (kg) divided by height squared (m^2), along with these variables, were considered risk factors based on prior epidemiological evidence, biological plausibility, and established associations with adverse pregnancy outcomes reported in previous studies [14-15].

Sample collection and biochemical analysis: Maternal blood samples were drawn from a large peripheral vein under aseptic conditions upon hospital admission, following approved standard operating procedures. Sample processing, testing, and result reporting were conducted in accordance with good clinical laboratory practice standards. A 5 mL maternal blood sample was collected before delivery, with 3 mL in a serum separator tube (SST) used for biochemical evaluation. Serum was separated by centrifugation (3500 RPM for 10 minutes) using a Remi C-852 laboratory centrifuge. Inflammatory markers were analysed using a Cobas6000 automated analyser. High-sensitivity C-reactive protein (hs-CRP) levels (<1 mg/L) were measured by immunoturbidometric method. Ferritin levels (15-150 ng/mL) were measured by Electro-chemiluminescence (ECL) immunoassay. Albumin levels (3.5-5.0 g/dL) were measured by Bromo-cresol Green (BCG) method. Erythrocyte Sedimentation Rate (ESR) (<10 mm/h) was measured by the Westergren method [16-19].

STATISTICAL ANALYSIS

Continuous variables, such as maternal age and inflammatory markers (Ferritin, ESR, etc.), were summarized using median with first and third quartiles due to non-normal distribution, as assessed by the Kolmogorov-Smirnov test. Comparisons of average inflammatory marker values between adverse and no adverse pregnancy outcomes groups were conducted using the Mann-Whitney U test. Categorical variables were summarized using frequency and percentage. Chi-square tests were performed to assess the association between maternal characteristics and adverse pregnancy outcomes. Univariate logistic regression was used to determine risk factors associated with adverse pregnancy outcomes. Factors found to be significant in the univariate analysis (p-value <0.10) or deemed clinically relevant were included in the multivariable logistic regression model. Both unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported. All statistical analyses were performed using SPSS version 29.0, with a p-value less than 5% considered statistically significant.

RESULTS

A total of 714 pregnant women were included in the study. Lower maternal education, abnormal BMI, preterm delivery and history of hypertension were significantly associated with adverse pregnancy outcomes (p<0.001). Other factors, including age, diabetes, thyroid disorders, and ANC visits, showed no significant association [Table/Fig-1].

Maternal characteristics		Adverse pregnancy outcomes: No N=571	Adverse pregnancy outcomes: Yes N=143	p-value
Education	Primary education	52 (9.1)	6 (4.2)	< 0.001*
	middle- high school	216 (37.8)	73 (51.0)	
	10th to college	303 (53.1)	64 (44.8)	
Maternal age (years)	18-25	400 (70.1)	98 (68.5)	0.94
	26-30	133 (23.3)	35 (24.5)	
	31-40	38 (6.7)	10 (7.0)	
BMI(Body mass index) (kg/m^2)	<18.5	11 (1.9)	5 (3.5)	< 0.001*
	18.5-24.9	287 (50.3)	87 (61.3)	
	>25.0	273 (47.8)	50 (35.2)	
ANC visit	1-2	107 (19.0)	31 (22.1)	0.68
	3-4	173 (30.7)	40 (28.6)	
	>=5	283 (50.3)	69 (49.3)	
Gestational age at delivery (week)	<34	0 (0.0)	6 (4.2)	<0.001*
	34- 36.6	0 (0.0)	43 (30.1)	
	>=37	568 (100)	94 (65.7)	
History of diabetes mellitus	Yes	7 (1.2)	3 (2.1)	0.43
	No	564 (98.8)	140 (97.9)	
History of thyroid	Yes	25 (4.4)	6 (4.2)	0.92
	No	546 (95.6)	137 (95.8)	
History of Hypertension	Yes	4 (0.7)	5 (3.5)	0.02*
	No	567 (99.3)	138 (96.5)	
Tobacco use	Yes	3 (0.5)	0 (0.0)	1.00
	No	568 (99.5)	142 (100.0)	
Gravidity	<3	476 (83.4)	122 (85.3)	0.57
	≥ 3	95 (16.6)	21 (14.7)	
Parity	No child	308 (53.9)	75 (52.4)	0.74
	≥ 1 child	263 (46.1)	68 (47.6)	

[Table/Fig-1]: Demographic and clinical characteristics of mothers and Adverse pregnancy outcomes.
*Statistically significant, #certain clinical parameters were unavailable for a small subset of participants due to logistical constraints during data collection.

The median age of participants was 24 years (Q_1, Q_3: 21, 26), and the median gestational age was 39 weeks (Q_1, Q_3: 38, 40). Within the composite adverse pregnancy outcome, low birth weight (LBW) had the highest proportion at 17.23% (95% CI: 17.15, 23.15), followed by preterm birth (PTB) at 6.89% (95% CI: 5.14, 9.01), and stillbirth at 0.84% (95% CI: 0.31, 1.82).

Serum ferritin levels were significantly higher in the adverse outcomes group [48.0 ng/mL (26.0, 86.0)] compared to the no adverse outcomes group [35.0 ng/mL (18.0, 62.0)]. This difference was statistically significant. Other inflammatory markers (HsCRP, ESR and albumin) showed no statistically significant differences between groups. Among the inflammatory markers assessed, only serum ferritin levels were statistically associated with adverse pregnancy outcomes [Table/Fig-2].

The results of the logistic regression are provided in [Table/Fig-3]. Several factors were independently associated with adverse pregnancy outcomes after adjustment for maternal age, BMI, serum ferritin, education, and hypertension history. Mothers with

only primary school education had 1.57 times higher odds of experiencing adverse pregnancy outcomes compared to those with higher education [adjusted OR (aOR): 1.57 (95% CI: 1.05, 2.34)]. Additionally, history of hypertension was associated with adverse pregnancy outcomes [aOR: 5.47(95% CI: 1.28, 23.24), p-value=0.02]. Furthermore, ferritin levels also showed a significant association with adverse pregnancy outcomes [aOR: 1.004(95% CI: 1.002,1.006), p-value <0.001].

Parameters	Adverse pregnancy outcomes				Mann-Whitney U statistic	p-value
	Yes		No			
	Median (Q_1,Q_3)	n	Median (Q_1,Q_3)	n		
Ferritin (ng/mL)	48.0 (26.0,86.0)	139	35.0 (18.0,62.0)	558	30353.00	<0.001*
hs CRP (mg/L)	6.0 (3.0,13.0)	141	7.0 (3.0,12.0)	560	39232.50	0.91
ESR (mm/h)	57.0 (39.0,80.0)	141	49.0 (33.0,75.0)	566	36003.00	0.60
Albumin (g/dL)	4.0 (3.0, 4.0)	140	4.0 (3.0,4.0)	562	36003.00	0.07

[Table/Fig-2]: Comparison of levels of inflammatory markers across normal and adverse pregnancy outcomes
*Statistically significant, # certain biochemical parameters were unavailable for a small subset of participants due to logistical constraints during data collection.

Variables		Unadjusted OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Maternal age (years)	18-25	ref		ref	
	26-30	1.07 (0.70,1.66)	0.75	0.92 (0.58,1.48)	0.75
	31-40	1.07 (0.52,2.23)	0.85	1.10 (0.50,2.39)	0.8
BMI(Body mass index) (kg/m2)	<18.5	1.50 (0.51,4.43)	0.46	1.49 (0.48,4.55)	0.48
	18.5-24.9	ref		ref	
	≥ 25.0	0.61 (0.41,0.89)	0.01*	0.57 (0.38,0.87)	0.009*
Education	primary	0.55 (0.23,1.33)	0.54	1.57 (1.05,2.34)	0.027*
	middle-school	1.60 (1.10,2.34)	0.01*	0.33 (0.11,0.98)	0.04*
	10th to college	ref		ref	
History of Hypertension	Yes	5.14 (1.36,19.38)	0.01*	5.47 (1.28,23.34)	0.02*
	No	ref		ref	
Ferritin at delivery		1.004 (1.002,1.006)	<0.001*	1.004 (1.002,1.006)	<0.001*

[Table/Fig-3]: Association of potential risk factors with Adverse pregnancy outcomes.
OR: Odds Ratio; *statistically significant; CI: Confidence interval

DISCUSSION

In this large, cross-sectional study, it was found that ferritin levels were associated with adverse pregnancy outcomes. However, no significant association between inflammatory markers (hsCRP, ESR, and albumin) and the composite measure of adverse pregnancy outcomes. The study also revealed significant associations between adverse pregnancy outcomes and gestational age, education, BMI, and history of hypertension.

A series of studies have reported the relationship between inflammatory markers and adverse pregnancy outcomes [20,21]. Inflammation appears to play a pivotal role in regulating normal infant growth and development during pregnancy. Inflammatory biomarkers are particularly significant in the context of labour initiation and associated pathways. These biomarkers are often associated with conditions like hypertension and preeclampsia, where inflammation, oxidative stress, and vascular dysfunction are critical factors in the evaluation of preterm birth, potentially leading to Small for Gestational Age (SGA) infants and other birth complications. A better understanding of proinflammatory markers and their regulatory anti-inflammatory counterparts could lead to a more comprehensive understanding of the biochemical pathways that give rise to adverse health outcomes both at birth and in later stages of life [22].

Hs-CRP is an acute-phase protein of inflammation and is frequently studied as a marker of adverse pregnancy outcomes [23]. However, current study found no significant difference in hs-CRP levels between groups with and without adverse pregnancy outcomes. This finding aligns with previous studies that showed no significant association between CRP and foetal birth weight in preeclamptic women [24]. A systematic review by Gomes j et al., found that inflammation-related biomarkers and growth factor/hormone-related biomarkers are associated with a higher risk of adverse birth outcomes. Proinflammatory markers such as CRP were associated with preterm birth (PTB) and low birth weight (LBW) [24]. Another study revealed a significant association between elevated serum CRP levels in early second trimester primigravida women and adverse pregnancy outcomes, including preterm delivery, Premature Rupture of Membranes (PROM), and low Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores [25]. These conflicting findings highlight the complex nature of the relationship between inflammatory markers and pregnancy outcomes, suggesting the need for further research in this area.

Serum ferritin concentration is considered one of the most sensitive indicators of body iron stores and has been extensively used as the criterion standard for the diagnosis of iron deficiency [26]. In the present study, significant difference was found in ferritin levels between groups with and without adverse pregnancy outcomes. This finding is consistent with a previous study conducted by Khambalia AZ et al., showed that elevated maternal serum ferritin concentrations in early pregnancy are associated with an increased risk of spontaneous preterm birth [27]. However, the relationship between ferritin levels and pregnancy outcomes is not universally consistent across studies [27]. For instance, a study conducted by Rahman SM et al., demonstrated no association between ferritin levels and birth weight [28]. These varied findings suggest that while ferritin may play a role in certain adverse pregnancy outcomes, its relationship with pregnancy complications may be complex and influenced by various factors. Further research is needed to elucidate the precise nature of this association and its implications for maternal and foetal health.

Present study found no significant difference in albumin levels between groups with and without adverse pregnancy outcomes. This aligns with a study by Ahmadu BU et al., which found no significant association between albumin and low birth weight [29]. However, several other studies have reported decreased levels of albumin associated with preeclampsia and birth weight [30,31]. These conflicting results suggest that the relationship between albumin levels and pregnancy outcomes may be complex and warrants further investigation.

In the present study, gestational age, education, BMI, ferritin and history of hypertension were significant factors associated with increased risks of adverse pregnancy outcomes, consistent with previous findings [32,33]. A systematic review revealed that the main risk factors for adverse pregnancy outcomes were pregnancy frequency, education level, gestational diabetes mellitus, and maternal age. In contrast, gestational weeks, smoking, and parity did not significantly impact adverse pregnancy outcomes in that review [34].

Regarding hypertension, Nzelu D et al., showed that pregnant women with a history of gestational hypertension face a 49% likelihood of developing complications associated with hypertensive disorders and adverse pregnancy outcomes [35]. These results are consistent with our findings. However, Zhang J et al., revealed

no association between hypertension and adverse pregnancy outcomes [36], highlighting the need for further research in this area. These varied findings underscore the complex nature of factors influencing pregnancy outcomes and emphasize the importance of comprehensive prenatal care and risk assessment.

Overweight and obesity represent increasing global health problems. Obesity is associated with many adverse reproductive outcomes, including subfertility, pregnancy loss, stillbirths, and birth defects [37]. Present study found a positive correlation between BMI and adverse pregnancy outcomes, which is consistent with previous research. One study resulted that maternal overweight and large for gestational age (LGA) [38]. Another study conducted in India showed that Obese (Indian guidelines, BMI ≥ 25 kg/m^2) mothers had a significantly higher risk of maternal complications compared to non-obese mothers [39]. And these results substantiate our findings, which reveal a positive correlation between BMI and adverse pregnancy outcomes. Strength of the current study is that it focusses on a resource-limited Indian setting and the comprehensive evaluation of multiple inflammatory markers in relation to maternal risk factors. The use of standardized protocols and robust statistical analyses ensures rigor, reliability and reproducibility, thereby addressing important gaps in evidence on adverse pregnancy outcomes.

Limitation(s)

The present study has certain limitations that should be considered while interpreting the findings. Being a single-centre study conducted in a Tertiary Care Hospital, the results may not be fully generalizable to other populations, particularly those in rural or primary care settings. The cross-sectional design, restricted to the time of delivery, limited the ability to assess longitudinal changes in inflammatory markers throughout pregnancy. Additionally, the modest sample size in certain subgroups may have reduced the statistical power to detect smaller associations. Finally, the possibility of residual confounding cannot be excluded, as factors such as pre-existing medical conditions, lifestyle behaviours, infections, and medication use were not fully accounted for.

CONCLUSION(S)

The present observational study underscores the complex relationship between inflammatory markers and adverse pregnancy outcomes, highlighting the potential role of proinflammatory biomarkers in influencing birth complications. The present study revealed that ferritin levels were associated with adverse pregnancy outcomes, while other inflammatory markers (hs-CRP, albumin, and ESR) were not statistically significant. Additionally, factors such as gestational age, education, BMI, and history of hypertension were found to be associated with adverse pregnancy outcomes. These findings emphasize the multifaceted nature of pregnancy risks and the importance of comprehensive prenatal care. Further research is essential to validate and expand upon these findings, potentially leading to improved risk assessment strategies and interventions in prenatal care. Such advancements could contribute significantly to enhancing maternal health outcomes and reducing the incidence of adverse pregnancy outcomes.

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