

Association between Maternal Serum Zinc Level and Preterm Birth

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Abstract

Background: Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation, remains a major cause of neonatal morbidity and mortality globally, with Bangladesh reporting one of the highest prevalence rates worldwide. Zinc, an essential trace element involved in immune regulation, oxidative stress modulation and hormonal balance, has been hypothesized to influence gestational duration. This study aimed to evaluate the association between maternal serum zinc level and preterm birth. **Methods:** This case-control study was conducted at the Department of Obstetrics and Gynaecology, Bangladesh Medical University (BMU), (former BSMMU), Dhaka, from September 2022 to August 2023. Sixty pregnant women aged 18–40 years, at 28 to <42 weeks of gestation, presenting in spontaneous labour with intact membranes and delivering a live singleton baby, were enrolled. Thirty women who delivered before 37 completed weeks constituted the cases, while 30 women with term deliveries served as controls. Serum zinc levels were measured using a colourimetric method on a Thermo Scientific™ Indiko™ Plus Clinical Chemistry Analyzer. **Results:** Maternal serum zinc was significantly lower in the case group (68.13 ± 32.73 mcg/dL) compared to controls (102.41 ± 60.97 mcg/dL) (p=0.009). Women with zinc levels below 68 mcg/dL had 4.7 times higher odds of preterm birth than those with levels ≥ 68 mcg/dL (OR=4.667; 95% CI=1.571–13.866; p=0.001). Socio-demographic, obstetric and anthropometric variables did not differ significantly between groups. **Conclusion:** Low maternal serum zinc level was significantly associated with preterm birth. Serum zinc estimation may serve as a potential predictor for preterm birth risk and supports consideration of routine zinc supplementation during antenatal care.

Keywords: Preterm birth, maternal serum zinc, zinc deficiency.

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INTRODUCTION

Preterm birth (PTB), defined as delivery between age of viability and 37 completed weeks of gestation, constitutes one of the foremost challenges in perinatal medicine [1]. Globally, an estimated 13.4 million babies were born prematurely in 2020, accounting for more than one in ten live births. Approximately 900,000 children died from complications of prematurity in 2019 alone [2]. Beyond immediate neonatal consequences, preterm birth carries long-term risks including cerebral palsy, impaired

neurodevelopment, learning disabilities and chronic disease burden in adulthood [3]. Women with a history of preterm delivery also face modestly elevated future risks of hypertension, diabetes and hyperlipidemia [4].

Preterm birth rates range from 4 to 16% across countries. The United States recorded a rate of 10.23% in 2019, while rates in India and Australia were reported at 7.4% and 8.7%, respectively [5,6]. Bangladesh, however, bears a disproportionate burden, with a reported prevalence of approximately 19% [7] and a

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substantial neonatal death toll attributable to prematurity each year.

Approximately two-thirds of all preterm deliveries are spontaneous, with identified risk factors including prior preterm birth, short cervical length, multiple gestation, uterine anomalies and genital tract infections [8]. Maternal nutritional deficiencies, particularly micronutrient inadequacies, have also been implicated in inflammatory pathways that precipitate spontaneous preterm labor [9].

Zinc is an essential trace element involved in catalytic enzyme activity, gene regulation, immune function and hormonal balance. It is indispensable for embryogenesis, fetal development and the maintenance of normal immune responses during pregnancy [10]. Despite its critical role, over 80% of pregnant women worldwide are estimated to have inadequate zinc intake, a problem particularly pronounced in low- and middle-income settings [11].

Zinc deficiency during pregnancy has been proposed to contribute to preterm labor through several mechanistic pathways. Zinc ions regulate T- and B-lymphocyte activity and their deficiency increase susceptibility to infections—a leading trigger of spontaneous preterm birth [12]. Low circulating zinc levels promote the production of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), which weaken fetal membranes and induce uterine contractions [13]. Elevated IL-6 in particular is a recognized risk factor for PTB [14]. Additionally, zinc deficiency results in excessive activation of matrix metalloproteinases (MMPs)—zinc-dependent endopeptidases implicated in cervical remodeling and membrane degradation—with higher concentrations of MMP-2, -3, -8 and -9 documented in women delivering preterm [15].

Several investigators have reported an inverse relationship between maternal zinc status and preterm birth risk [16, 17], while others have found no significant association and at least one study reported paradoxically elevated zinc concentrations among women delivering preterm [18, 19]. Given these conflicting findings and the limited data from Bangladesh, where preterm birth prevalence is particularly high, the present study was conducted to assess the association between maternal serum zinc level and preterm birth in a Bangladeshi hospital-based population.

MATERIALS & METHODS

This was a hospital-based case-control study conducted at the Department of Obstetrics and Gynaecology and the Department of Feto-maternal Medicine, Bangladesh Medical University (BMU), (former BSMMU), Shahbag, Dhaka, Bangladesh, from September 2022 to August 2023. A total of 60 pregnant women, 30 in the case group (preterm delivery) and 30 in the control group (term delivery), were enrolled.

Selection Criteria

Inclusion criteria (Cases – preterm birth):

- Mothers aged 18–40 years
- Gestational age at delivery between 28 to <37 completed weeks
- Delivered a single live baby
- Provided written informed consent

Inclusion criteria (Controls – term birth):

- Mothers aged 18–40 years
- Gestational age at delivery between 37 to <42 weeks
- Delivered a single live baby
- Provided written informed consent

Exclusion criteria:

- Multiple pregnancy
- Delivery before 28 weeks of gestation (miscarriage)
- Known anemia, molar pregnancy, polyhydramnios, preeclampsia, gestational diabetes mellitus, or pre-gestational diabetes
- Chronic medical conditions: hypertension, renal disease, liver disease, thyroid disorder, or cardiovascular disease
- Placental pathology (placenta previa, abruption, antepartum hemorrhage)
- Prior preterm birth or abortion due to cervical incompetence
- Zinc supplementation within the preceding four months

Study Procedure

Gestational age was established using the last menstrual period (LMP) and confirmed by ultrasonography. Following Institutional Review Board (IRB) approval and written informed consent, relevant socio-demographic, obstetric and clinical data were collected using a semi-structured questionnaire administered by the investigator. Body mass index (BMI) was calculated from height and weight measurements obtained at enrollment.

For serum zinc estimation, 5 mL of venous blood was drawn aseptically from the antecubital vein of each participant (from an arm without an active intravenous infusion). Blood samples were transferred into clean, dry test tubes and transported promptly to the Department of Biochemistry and Molecular Biology, BMU (former BSMMU), where serum zinc levels were measured using a fully automated Thermo Scientific™ Indiko™ Plus Clinical Chemistry Analyzer. The assay principle involved the formation of a stable-colored complex between zinc and the specific complexant 5-Br-PAPS, the intensity of which was proportional to the zinc concentration in the sample. Interfering oligoelements (iron and copper) were masked by specific masking agents incorporated into the reaction conditions. The reference range for serum zinc was 68–107 mcg/dL and

a cut-off of <68 mcg/dL was applied to define zinc deficiency for this study.

Ethical Considerations

The study was approved by the Institutional Review Board of BMU (former BSMMU). Written informed consent was obtained from all participants after explaining the purpose, procedures, risks and benefits of the study in their preferred language. Participation was entirely voluntary and withdrawal at any time was permitted without affecting the clinical care received. All data were coded and stored securely; personally identifiable information was not disclosed in any report or publication.

Statistical Analysis

Data were analyzed using SPSS for Windows (version 27.0; IBM Corp., USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD) and

categorical variables as frequency and percentage. Between-group comparisons of means were performed using the unpaired t-test, while associations between categorical variables were assessed using the Chi-square test or Fisher's exact test, as appropriate. The strength of association between maternal serum zinc level and preterm birth was estimated by calculating the odds ratio (OR) with 95% confidence intervals (CI). The cut-off for serum zinc deficiency (<68 mcg/dL) was applied based on the normal reference range for the assay. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 60 singleton pregnant women between 28 and <42 weeks of gestation were enrolled: 30 in the preterm birth group (cases) and 30 in the term birth group (controls). All findings are summarized in Tables 1 through 6.

Table 1: Distribution of respondents according to socio-demographic characteristics by group (Case=30, Control=30)

Socio-demographic Variables		Case (N=30) n (%)	Control (N=30) n (%)	p-value
Age (years)	≤ 20	4 (13.3)	1 (3.3)	0.273
	21–30	19 (63.3)	24 (80.0)	
	31–40	7 (23.3)	5 (16.7)	
	Mean $\pm$ SD	26.17 $\pm$ 4.42	26.47 $\pm$ 2.57	0.776
Educational qualification	Up to Primary	16 (53.3)	19 (63.3)	0.728
	Secondary/equivalent	8 (26.7)	6 (20.0)	
	HSC & above	6 (20.0)	5 (16.7)	
Occupation	Housewife	15 (50.0)	12 (40.0)	0.685
	Student	9 (30.0)	8 (26.7)	
	Service holder	5 (16.7)	7 (23.3)	
	Day laborer/Garments worker	1 (3.3)	3 (10.0)	
Monthly family income (BDT)	Lower class ($\leq 7,378$ Tk.)	2 (6.7)	3 (10.0)	0.858
	Lower middle class (7,379–28,810 Tk.)	19 (63.3)	17 (56.7)	
	Upper middle class (28,811–89,280 Tk.)	9 (30.0)	10 (33.3)	

No statistically significant difference was observed in socio-demographic characteristics between groups ($p > 0.05$).

Table 2: Distribution of respondents according to obstetrical characteristics by group (Case=30, Control=30)

Obstetrical Characteristics	Case (N=30) n (%)	Control (N=30) n (%)	p-value
Gravida			
Primigravida	14 (46.7)	17 (56.7)	0.438
Multigravida	16 (53.3)	13 (43.3)	

No significant difference in gravida status was observed between groups ($p > 0.05$).

Table 3: Distribution of respondents according to family history of preterm birth by group (Case=30, Control=30)

Family History of PTB	Case (N=30) n (%)	Control (N=30) n (%)	p-value
Present	5 (16.7)	1 (3.3)	0.195
Absent	25 (83.3)	29 (96.7)	

No statistically significant difference was observed in family history of preterm birth between groups ($p = 0.195$).

Table 4: Distribution of respondents according to BMI by group (Case=30, Control=30)

BMI (kg/m ²)	Case (N=30) n (%)	Control (N=30) n (%)	p-value
Underweight (<18.5)	3 (10.0)	0 (0.0)	0.071
Normal (18.5–24.9)	11 (36.7)	18 (60.0)	
Overweight (25.0–29.9)	16 (53.3)	12 (40.0)	
Mean $\pm$ SD	24.23 $\pm$ 3.55	24.92 $\pm$ 2.08	0.36

No significant BMI difference was observed between the two groups ($p>0.05$).

Table 5: Distribution of mean ($\pm$ SD) maternal serum zinc levels by group (Case=30, Control=30)

Maternal Serum Zinc Level (mcg/dL)	Case (N=30)	Control (N=30)	p-value
Mean $\pm$ SD	68.13 $\pm$ 32.73	102.41 $\pm$ 60.97	0.009

Maternal serum zinc was significantly lower in the case group compared to the control group ($p=0.009$).

Table 6: Odds ratios (OR) and 95% confidence intervals (CI) for preterm birth according to serum zinc level (Case=30, Control=30)

Maternal Serum Zinc (mcg/dL)	Case (N=30) n (%)	Control (N=30) n (%)	p-value	Odds Ratio (95% CI)
<68 mcg/dL	20 (66.7)	9 (30.0)	0.001	4.667 (1.571–13.866)
$\geq$ 68 mcg/dL	10 (33.3)	21 (70.0)		

Women with serum zinc <68 mcg/dL had 4.7 times higher odds of preterm birth than those with zinc $\geq$ 68 mcg/dL (OR=4.667; 95% CI=1.571–13.866; $p=0.001$).

DISCUSSION

This case-control study was undertaken to compare maternal serum zinc concentrations between women who delivered preterm and those who delivered at term and to quantify the strength of association between zinc deficiency and preterm birth risk. The findings demonstrate a statistically significant reduction in serum zinc levels among women with preterm delivery and confirm a nearly fivefold increase in the odds of preterm birth when zinc levels fall below 68 mcg/dL.

The two study groups were well-matched with respect to socio-demographic characteristics. The majority of participants in both groups were between 21 and 30 years of age, had educational attainment up to the primary level, were housewives and belonged to the lower-middle income category. None of these demographic differences reached statistical significance, reducing the likelihood that socio-demographic confounding influenced the primary outcome. These findings parallel those of Wang *et al.*, who similarly reported no significant between-group differences in maternal age, pre-pregnancy BMI, or monthly income when comparing zinc-deficient and zinc-sufficient pregnant women in a Chinese cohort [17]. In contrast, Shaikh *et al.*, identified parity, infant sex and paternal education level as significant predictors of preterm birth in Pakistan, though their study design and setting differed considerably [20].

Regarding obstetric characteristics, multigravida women slightly predominated in the case group (53.3% vs. 43.3% in controls), a difference that was not statistically significant ($p=0.483$). This finding is consistent with a retrospective Indian study by Atiya and Patnaik (2020), in which multigravidas accounted for 52.81% of preterm deliveries [21]. Family history of preterm birth was more prevalent among cases (16.7% vs. 3.3% in controls), though the difference did not reach significance ($p=0.195$), possibly reflecting the relatively small sample size. BMI did not differ significantly between groups, with mean values of 24.23 $\pm$ 3.55 kg/m² in cases and 24.92 $\pm$ 2.08 kg/m² in controls. This is broadly consistent with a systematic review by McDonald *et al.*, which reported that the overall risk of preterm birth was similar across BMI categories, though the risk of induced preterm birth was elevated among overweight and obese women [22].

The primary finding of this study—a significantly lower mean maternal serum zinc in the preterm group (68.13 $\pm$ 32.73 mcg/dL) compared to the term group (102.41 $\pm$ 60.97 mcg/dL; $p=0.009$)—is consistent with the prevailing body of evidence. Wang *et al.*, demonstrated an inverse association between serum zinc concentration during pregnancy and the risk of preterm birth in a large Chinese population-based cohort [17]. Sultana *et al.*, whose data provided the basis for the sample size calculation in the present study, similarly reported lower serum zinc levels in mothers who delivered preterm compared to those who delivered at term in a Bangladeshi sample [23]. These findings are biologically plausible: zinc deficiency impairs immune surveillance, promotes cytokine-driven inflammation and activates matrix metalloproteinases that degrade

extracellular matrix components critical to fetal membrane integrity [14, 15].

The odds ratio analysis revealed that women with serum zinc below 68 mcg/dL had 4.667 times higher odds of preterm birth (95% CI: 1.571–13.866; $p=0.001$) compared to women with adequate levels. This is supported by Carmichael *et al.*, (2013), who reported a two-fold decrease in the risk of very preterm birth (<32 weeks) among women with dietary zinc intake above 8.0 mg/day relative to those with lower intakes [24]. Aydemir *et al.*, (2003) further documented that among neonates born preterm, maternal zinc levels averaged 67.7 ± 11.9 mcg/dL, a value closely approximating the preterm group mean observed in the current study [25].

Evidence from intervention trials similarly supports the clinical relevance of zinc adequacy during pregnancy. A Cochrane meta-analysis of 16 randomized controlled trials conducted by Ota *et al.*, reported a 14% reduction in preterm birth risk with zinc supplementation (RR 0.86; 95% CI: 0.76–0.97), particularly among women from low- and middle-income settings with a high burden of zinc deficiency [16]. Iqbal and Ali, in a recent umbrella review of meta-analyses, also confirmed a significant relationship between low maternal zinc status and adverse pregnancy outcomes including preterm birth [26].

Not all studies, however, have reported concordant findings. Hsu *et al.*, found no significant difference in dietary zinc intake between women who delivered preterm and those who delivered at term across all three trimesters [27]. Chiudzu *et al.*, in a Malawian case-control study, paradoxically documented elevated serum zinc concentrations in women with preterm birth, suggesting that population-specific factors—including dietary patterns, concurrent infections and measurement timing—may modulate the zinc-preterm birth relationship [19]. The discrepancies across studies likely reflect methodological heterogeneity in zinc measurement, dietary assessment methods, gestational timing of blood collection and differences in background rates of zinc deficiency.

The present study adds to the evidence base by demonstrating, in a Bangladeshi hospital-based sample, that low maternal serum zinc is independently associated with preterm birth. Given Bangladesh's high burden of preterm delivery and the widespread prevalence of nutritional deficiencies among pregnant women in this population, these findings have practical implications. Routine serum zinc screening during antenatal care, with targeted supplementation for deficient women, may represent a feasible, low-cost strategy to reduce preterm birth rates. Zinc supplementation has additionally been shown to have beneficial effects on neonatal immune function and early morbidity, further supporting its utility in maternal-neonatal care [28].

Limitations of the study

This study was conducted at a single tertiary-care institution with a relatively small sample size ($n=60$), limiting the generalizability of findings to the broader Bangladeshi population. Consecutive sampling may also introduce selection bias. Additionally, the short study period and single-center design precluded multivariate adjustment for all potential confounders.

CONCLUSION

Maternal serum zinc level was significantly lower in women with preterm birth compared to those with term delivery and zinc deficiency was associated with a nearly fivefold increase in preterm birth risk. These findings support the potential utility of serum zinc as a predictive marker for preterm birth and highlight the importance of adequate zinc nutrition during pregnancy. Routine zinc supplementation alongside standard antenatal micronutrient care warrants consideration as a preventive strategy, particularly in populations with a high burden of nutritional deficiency.

Conflicts of Interest: There are no conflicts of interest.

Ethical Approval: This study approved by the institutional ethical review committee.

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