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Correlation of Zinc and Copper Levels In Mothers and Cord Blood of Neonates With Prematurity and Intrauterine Growth Pattern

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Abstract

Background

Trace elements like zinc and copper are indispensable for human growth and development, exerting significant influence on a multitude of physiological processes. Acting as pivotal components for transcription factors and catalytic cofactors for enzymes, these elements play essential roles in cellular differentiation and maturation

Objective

The objective of this study was to study serum zinc and copper levels in mothers and neonates in relation to prematurity and intrauterine growth retardation (IUGR).

Methods

This was a cross-sectional study that included 100 mothers who met the inclusion criteria. Maternal history was recorded, and gestational age was estimated using the New Ballard scoring system. Maternal and cord blood samples were taken for zinc and copper analysis.

Results

The comparison of maternal copper and zinc levels between term and preterm neonates revealed a statistically significant difference with both trace elements found in less concentration in preterm when compared to the term patients ($p = 0.03$ for Zinc; 0.0001 for copper). We also report a statistically significant difference in maternal and cord blood copper and zinc levels in cases with IUGR compared to normal neonates.

Conclusion

The findings show that maternal zinc and copper levels are critical for the intrauterine growth of the fetus and for appropriate gestational age

Categories: Public Health, Obstetrics/Gynecology, Hematology
Keywords: trace elements, preterm delivery, intrauterine growth restriction (iugr), maternal copper, maternal zinc

Introduction

Infant mortality and morbidity risks rise as gestational age at birth decreases, particularly for very low-birth-weight (LBW) infants [1,2]. Preterm neonates, born before the 37th week of gestation, face elevated risks of poor outcomes due to incomplete micronutrient reserves, often resulting in low birth weight or being small for gestational age [3]. Zinc plays a crucial role in cell growth and development, being essential for RNA and DNA synthesis [4]. Severe zinc deficiency can lead to CNS impairments, including behavioral issues, decreased intelligence, and memory and learning difficulties [5].

In contrast, copper levels increase during pregnancy as gestational age progresses, driven by rising estrogen levels and ceruloplasmin production [6]. This ensures adequate serum copper levels for both the mother and the baby. Copper deficiency can negatively impact CNS and heart function during development, potentially leading to complications such as hearing loss and reduced motor function, which may persist despite replacement therapy [7].

Given the importance of zinc and copper in cell growth, maintaining sufficient levels of these elements is crucial for preterm and LBW neonates [1]. Maternal zinc restriction during fetal development in rodent models has been linked to intrauterine growth retardation [8]. However, studies have produced conflicting results regarding the impact of maternal zinc supplementation on outcomes such as fetal loss, fetal growth, and birth weight. Notably, the reduction of preterm delivery emerged as the only significant benefit of supplementation in previous research [2,3].

The present study aims to investigate serum zinc and copper levels in mothers and neonates in relation to prematurity and intrauterine growth retardation, shedding light on potential nutritional interventions to improve outcomes in at-risk neonates.

Materials And Methods

Study design and data collection

This was a cross-sectional study conducted at Dr. D. Y. Patil Medical College, Hospital & Research Centre, Pune, India. The study was approved by the Institutional Ethics Sub-Committee of Dr. D.Y. Patil Medical College, Hospital & Research Centre (approval number: I.E.S.C./W/52 /2024). A total of 100 mothers who met the inclusion criteria (given below) were selected. Before sample collection, patient/parental consent was obtained for the collection of maternal and cord blood samples for zinc and copper analysis. Maternal history was recorded, and gestational age was estimated using the New Ballard scoring system [9]. Birth weights were then plotted against gestational age using Fenton growth charts to determine if the neonates were small or appropriate for gestational age. Physical examinations of the newborns were conducted at birth, and those requiring further medical attention were admitted to the neonatal intensive care unit for appropriate management and monitoring.

Inclusion and exclusion criteria

The study's inclusion criteria encompassed mothers who delivered neonates at or after 32 completed weeks of gestation. Exclusion criteria included infants with congenital malformations or those born from multiple gestation pregnancies, as well as mothers with severe malnutrition (BMI less than 19) or with conditions such as gestational or overt hypertension, gestational or overt diabetes mellitus, chronic illness, severe anemia, or placental abnormalities. These criteria aimed to ensure a specific cohort for the study while excluding potential confounding factors that could affect the outcomes being investigated.

Laboratory testing

Zinc

This study assessed zinc levels using the endpoint nitro PAPS dye-binding method. The principle of this method involves the reaction of nitro PAPS with zinc in an alkaline solution, forming a purple-colored complex. The absorbance of this complex was then measured at 575 nm using a spectrophotometer. The reference value for serum zinc concentration in this study was set between 70-130 microgram per decilitre (µg/dL). The method demonstrated linearity up to 500 µg/dL of zinc concentration. Additionally, the sensitivity of the assay was determined to be 6.92 µg/dL, representing the minimum detectable concentration of zinc with an acceptable level of precision.

Copper

The estimation of copper concentration is conducted by measuring the absorbance of the product formed after reduced Cu^{2+} ions react with a chromogen (3,5-DiBr-PAESA), at 600 nm. The reference value for serum copper was established to be within the range of 95-126 µg/dL. The method exhibits linearity up to 100 micromoles per liter (µmol/L), indicating that the assay can accurately measure copper concentrations within this range. Regarding sensitivity, the minimum detectable concentration of Cu^{2+} with an acceptable level of precision was determined to be 1.97 µmol/L.

Under acidic conditions, ceruloplasmin (CER) bound to Cu^{2+} dissociates, resulting in the formation of free Cu^{2+}. Similarly, albumin bound to Cu^{2+} also dissociates under acidic conditions, leading to the release of Cu^{2+} ions. In the presence of a reducing agent, Cu^{2+} ions are reduced to Cuprous ions, which then react with a chromogen (3,5-DiBr-PAESA) to form a blue-colored complex. This complex is then measured to determine the concentration of Cu^{2+} in the sample.

Statistics

The data entry was done using Microsoft Excel (Microsoft Corporation, Redmond, Washinton, United States), followed by analysis utilizing SPSS for Windows, Version 16.0 (Released 2007; SPSS Inc., Chicago, United States). Qualitative data were represented in frequencies and percentages, while quantitative data were expressed in terms of mean and standard deviation. Nonparametric statistical methods, such as the Chi-square test, were used to determine significant associations between two qualitative variables. Unpaired and

ANOVA tests were utilized to assess the statistical significance between quantitative variables. A p-value of less than 0.05 was considered statistically significant.

Results

The majority of the study population (mothers) was within the age range of 19-28 years, comprising 83% of the total. Specifically, 42 patients (42%) were between 19 and 23 years of age, while 41 patients (41%) were between 24 and 28 years of age. Additionally, there were 15 patients (15%) in the age range of 29-34 years, and only two participants (2%) were older than 35 years. The mean age was 24.76±3.82 years. Among the study population, 49 patients (49%) were primiparous, while 51 patients (51%) were multiparous. This indicates an almost equal distribution between the two parity categories within the sample. Gestational age distribution among the study population was done; 16 women (16%) were in the gestational age range of 32-37 weeks, while the majority, comprising 84 women (84%), were in the range of 38-40 weeks. The mean gestational age for the entire sample was found to be 38.27±1.85 weeks. Among the study population, 16 cases (16%) were classified as preterm pregnancies, while the majority, consisting of 84 cases (84%), were categorized as term pregnancies. This showed a higher prevalence of term pregnancies within the study population. A total of 53 participants (53%) had a normal vaginal delivery (NVD), while the remaining 47 participants (47%) were delivered via lower segment cesarean section (LSCS).

Table *1* illustrates the distribution of birthweights among the neonates delivered by the participants in our study population (n=100) with each delivering a single baby. The mean birthweight for the sample population was calculated to be 2.76 kg, with a standard deviation of 0.51 kg.

Birthweight	Frequency	Percentage
1.5-2 kg	13	13%
2-2.5 kg	14	14%
2.5-3 kg	46	46%
>3 kg	27	27%

TABLE 1: Distribution of neonates based on birthweight (N=100)

Table *2* illustrates the length and head circumference of neonates in the study population.

	Minimum	Maximum	Mean SD	95% CI	Median
Length (cm)	46.40	52.50	49.04 ± 1.62	48.17-49.36	48.70
Head Circumference (cm)	33.7	37.80	36.04 ± 0.81	35.88-36.20	36.20

TABLE 2: Distribution of neonates based on length and head circumference (N=100)

The distribution of birthweights in the studied population revealed appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA). These findings highlight the predominance of infants with birthweights falling within the normal range for their gestational age (Table *3*).

Birthweights	Frequency	Percentage
Appropriate for Gestational Age	70	70%
Small for Gestational Age	27	27%
Large for Gestational Age	3	3%

TABLE 3: Distribution of neonates according to birthweight associated with age (N=100)

Table 4 shows the distribution of infants having intrauterine growth restriction (IUGR). This indicates that a majority of infants experienced normal growth during intrauterine development.

Incidence of IUGR	Frequency	Percentage
Yes	12	12%
No	88	88%

TABLE 4: Distribution of neonates based on incidence of IUGR (N=100)

IUGR: intrauterine growth restriction

The distribution of maternal zinc levels among the study population is shown in Table 5. The mean maternal zinc level was calculated to be 94.77 μg/dL, with a standard deviation of 12.76 μg/dL (Table 5).

Maternal zinc levels (μg/dL)	Frequency	Percentage
<87.9	20	20%
88 – 130	78	78%
>130	2	2%

TABLE 5: Distribution of study population based on maternal zinc levels (N=100)

The distribution of maternal copper levels among the study population is shown in Table 6. The mean maternal copper level was calculated to be 107.18 μg/dL, with a standard deviation of 11.74 μg/dL.

Maternal copper levels (μg/dL)	Frequency	Percentage
<95	15	15%
95 – 126	84	84%
>126	1	1%

TABLE 6: Distribution of study population based on maternal copper levels (N=100)

The distribution of cord blood zinc levels in the study population is shown in Table 7. The mean cord blood zinc level was calculated to be 138.14 μg/dL, with a standard deviation of 14.93 μg/dL.

Cord blood zinc levels	Frequency	Percentage
<124	12	12%
124 – 160	87	87%
>160	1	1%

TABLE 7: Distribution of study population based on cord blood zinc level (N=100)

The distribution of cord blood copper levels in the study population is shown in Table 8. The mean cord blood copper level was calculated to be 57.82 μg/dL, with a standard deviation of 18.65 μg/dL.

Cord blood copper levels (µg/dL)	Frequency	Percentage
<40	24	24%
40 – 90	73	73%
>90	3	3%

TABLE 8: Distribution of study population based on cord blood copper level (N=100)

The comparison of maternal zinc levels between term and preterm neonates revealed a statistically significant difference. The difference was found to be statistically significant (Table 9).

	Term	Preterm	p-value
Maternal zinc levels (µg/dL)	95.95 ±12.80	88.55 ± 10.90	p = 0.03*
Maternal copper levels (µg/dL)	111.03 ± 8.12	86.97 ± 5.16	p<0.0001*

TABLE 9: Association of maternal zinc and copper level and gestational age

*p-value less than 0.05 is considered significant

The comparison of maternal zinc and copper levels among neonates classified as AGA, SGA, and LGA revealed a statistically significant difference (Table 10).

	AGA	SGA	LGA	p-value
Maternal zinc (µg/dL)	95.49 ±12.50	92.31 ± 13.89	100.16 ±4.00	0.02*
Maternal copper levels (µg/dL)	110.87 ± 7.88	97.06 ± 14.05	112.23 ±14.58	0.0001*

TABLE 10: Association of maternal zinc and copper level and birthweight according to age

AGA: appropriate for gestational age; SGA: small for gestational age; LGA: large for gestational age

* p-value less than 0.05 is considered significant

The comparison of maternal zinc and copper levels between mothers with neonates diagnosed with IUGR and those without IUGR showed a statistically significant difference (Table 11).

	Yes	No	p-value
Maternal zinc levels (µg/dL)	84.78 ±12.39	95.58 ± 12.66	0.006*
Maternal copper levels (µg/dL)	85.63 ± 4.96	110.12 ± 9.20	< 0.0001*

TABLE 11: Association of maternal zinc and copper levels and incidences of IUGR

* p-value less than 0.05 is considered significant

IUGR: intrauterine growth retardation

The comparison of mean cord blood zinc and copper levels between neonates with IUGR and those born without IUGR revealed a statistically significant difference (Table 12).

	Yes	No	p-value
Cord blood copper levels (µg/dL)	115.23 ±15.48	141.26 ± 11.88	0.001*
Cord blood copper levels (µg/dL)	33.71 ± 4.10	61.11 ± 17.40	0.001*

TABLE 12: Association of cord zinc and copper levels and incidences of IUGR

* p-value less than 0.05 is considered significant

IUGR: intrauterine growth restriction

Discussion

The trace elements, such as zinc and copper are critical in human growth and development [10]. They play crucial roles in various physiological processes, serving as essential components for transcription factors and catalytic cofactors for enzymes involved in cell differentiation and maturation [11]. Zinc, for example, acts protectively against free radicals and is integral to intracellular processes like cell division and nucleic acid synthesis. Similarly, copper is a vital cofactor for oxidative and reductase enzymes [12].

Despite their significance, deficiencies in these trace minerals are not uncommon, particularly among preterm infants who may not receive adequate intrauterine fetal growth-related nutrients. Thus, understanding maternal mineral status during gestation becomes imperative for ensuring fetal and neonatal health.

In this study, we found that maternal copper and zinc levels were found to be significantly less in the cases of preterm birth when compared to term birth cases. A study by Nawfal et al. indicates a significant association between lower serum copper levels in mothers and a higher risk of developing PPROM [13]. Another study by Monangi et al. shows a negative association between maternal copper levels and gestational duration, as well as a positive association with the risk of preterm birth [14]. This suggests that higher maternal copper levels are linked to shorter gestational periods and an increased likelihood of experiencing preterm birth. In contrast, another study by Hao et al. suggests that elevated maternal copper levels during the first trimester of pregnancy could potentially heighten the risk of spontaneous preterm birth [15]. Several other studies have consistently shown the association of maternal serum copper and zinc levels with gestational age [16].

In this study, we found that maternal and cord blood cooper and zinc levels were significantly lower in the IUGR group. A similar study by Çelik et al. revealed significant differences in placenta zinc concentrations and the placenta zinc/copper ratio between the IUGR group and the control group, with the IUGR group exhibiting lower levels ($p < 0.05$) [17]. Furthermore, there was a notable correlation observed between placenta zinc concentrations and birth weight (p: 0.01, r: 0.31), suggesting a potential role of zinc in fetal growth. These results underscore the importance of adequate placental zinc levels in supporting optimal fetal development, with deficiencies possibly contributing to the development of IUGR. Abass et al., in their comparison study of maternal zinc and copper levels along with cord copper levels, reveal notable differences between newborns LBW and those with normal weight. Specifically, LBW newborns exhibit lower zinc and copper levels than their normal-weight counterparts. Additionally, cord copper levels are also diminished in LBW infants. These findings suggest a potential association between maternal trace element status and fetal growth [18]. Several other studies have attributed maternal zinc and copper levels to IUGR [19-21].

Although there have been studies on maternal and cord blood levels of zinc and copper, findings have been inconsistent. Therefore, this study aimed to measure zinc and copper levels in both maternal and cord blood samples and correlate these levels with gestational age and anthropometric measurements. Such investigations are crucial for providing healthcare professionals with essential data for appropriate management strategies.

Limitations

One significant limitation of this study is its relatively small sample size, which may impact the generalizability and reliability of the findings. Increasing the population size would enhance the statistical power of the study and allow for a more robust interpretation of the results. Additionally, this study only considered post-delivery cases, which means that it overlooks various intrauterine parameters that could potentially influence the outcomes. Including data on intrauterine parameters would provide a more comprehensive understanding of the factors contributing to the observed results.

Conclusions

This study highlights the critical role of trace elements, particularly zinc and copper, in fetal development and neonatal health. Our findings reveal significantly lower levels of these elements in maternal and cord blood in cases of preterm birth and IUGR. These deficiencies are linked to adverse outcomes, emphasizing the need for adequate maternal nutrition during pregnancy to support optimal fetal growth. The association between lower trace element levels and conditions like preterm birth and IUGR suggests that current nutritional guidelines and supplementation strategies may require reassessment to better address the needs of expectant mothers and their babies.

Understanding the exact mechanisms by which these trace elements influence fetal development and identifying the optimal levels required for healthy growth can help healthcare professionals develop more effective management strategies. Continued research efforts are crucial to refine supplementation guidelines and improve outcomes for preterm neonates and those at risk of IUGR.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Srinija Garlapati, Shailaja Mane, Amulya Dharmagadda, Kasireddy Sravanthi, Aryan Gupta, Nagaraja Venigalla

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Sub-Committee, Dr. D.Y. Patil Medical College, Hospital & Research Centre issued approval I.E.S.C./W/52 /2024. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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