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Association of Maternal Serum Zinc with Risk of Preeclampsia: A Comprehensive Systematic Review

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ABSTRACT

Background: Zinc is an essential trace mineral element vital for many physiological functions and plays an important role in growth, reproduction, and the immune system. Adequate zinc stores in the body are extremely important during periods of pregnancy. **Methods:** This systematic review focused on full-text English literature published between 2014 and 2024 using the PRISMA 2020 guidelines. Editorials and review pieces published in the same journal as the submission without a DOI were not accepted. The literature was compiled using PubMed, ScienceDirect, and SagePub, among other online venues. **Result:** Five publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles. **Conclusion:** serum zinc level in PE patients was significantly lower than that in healthy pregnancy women. A moderate amount of zinc supplementation may reduce the incidence of PE, which needs to be confirmed.

Keyword: Preeclampsia, zinc serum, maternal.

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INTRODUCTION

Preeclampsia (PE) is new–onset hypertension that develops after 20 weeks of gestation. It is characterized by proteinuria, and can progress to multiple organ dysfunction, including liver, kidney, and brain disease, and is a pregnancy–specific disease. The prevalence of PE is 3–5% globally and is estimated to cause at least 42,000 maternal deaths each year. In China, the incidence of PE is approximately 2.3%. PE can cause irreversible short–term and long–term effects on both the foetus and the mother. However, there is currently no cure for PE other than childbirth. Therefore, identifying the possible causes of PE and preventing its occurrence are crucial.[1,2]

Preeclampsia, the most common medical complication of pregnancy, is associated with oxidative stress. Oxidative stress is a condition of oxidant/antioxidant disequilibrium, in which increased reactive oxygen species (ROS) generate overwhelms antioxidant defense mechanisms that lead to oxidative damage of cellular molecules. One of the important contributors to the state of oxidative stress is exposure to excess toxic metals in the environment and the deficiency of trace elements like copper, manganese and zinc which are necessary for antioxidant defense mechanisms. In Saudi Arabia the incidence of preeclampsia is extrapolated to 13,876 out of a population of 25,795,938. It is characterized by development of high blood pressure (hypertension) and proteinuria after 20 weeks of gestation and affects about 5-8% of all pregnancies.[3,4]

PE is caused by multiple factors, and some studies have indicated that PE is associated with an imbalance of increased lipid peroxides (LPO) and decreased antioxidants. As an antioxidant trace metal, zinc deficiency may cause increasing lipid peroxidation. Many studies attempted to explore the relationship between the changes of serum zinc level in pregnant women and PE, but the results were conflicting. Some studies had discovered significantly lower levels of serum zinc in PE patients than in the control group. However, other studies found mean serum level of zinc was significantly higher in PE patients than in healthy pregnancy controls. Meanwhile, some studies found that the serum zinc concentrations were not significantly different between the PE patients and the healthy pregnancy controls. Therefore, we performed this meta-analysis to assess the relationship between serum zinc level and PE.[5,6]

Zinc (Zn) is one of the essential trace elements. As a micronutrient, it functions as a cofactor for up to 10% of proteins in living organisms, playing a vital role in a range of biological processes in the human body. Zn is involved in a range of signaling pathways, e.g., Nuclear Factor Kappa B (NF-κB) signaling, and Toll-like Receptor 4 (TLR4) signaling, carrying considerable clinical implications. Diseases such as breast cancer, tuberculosis, and cardiovascular diseases were associated with aberrant levels of serum Zn. Maternal serum Zn levels

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are usually measured *via* blood sampling from the maternal antecubital vein, reflecting the maternal homeostasis of Zn. During pregnancy, Zn exerts a key role in both maternal physiological adaptations and fetal development. The demand for Zn in fetal growth and placental function increases during the third trimester, and may lead to a lower level of Zn in maternal serum compared to healthy non-pregnant women. A significant lower levels of Zn may cause a series of dysfunctions in the biological process and higher risks of developing feto-maternal complications, such as gestational diabetes, preterm pre-labor rupture of membrane (PPROM), preterm birth, and low birth weight. The relationship between maternal serum Zn and preeclampsia were studied as micronutrients imbalance is believed a contributing factor of preeclampsia.[7–9]

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards were scrupulously followed by the work's author. The purpose of this was to make sure the study satisfied all the requirements. The chosen technique was carefully designed to ensure the accuracy and dependability of the investigation's findings.

Criteria for Eligibility

This study does a thorough evaluation of the last 10 years' worth of literature on association of maternal serum zinc with risk of preeclampsia. This study intends to improve and provide light on association of maternal serum zinc with risk of preeclampsia through a thorough examination of data. The primary goal of this paper is to highlight the significance of the noteworthy topics that have been identified across the literature.

To ensure the quality of the included information in this study, strict inclusion and exclusion criteria are applied. To be eligible for inclusion, papers must have been published in the English language between 2014 and 2024. Editorials, submissions without a DOI, previously published reviews, and duplicate journal entries are some of the exclusion criteria.

Search Strategy

The keywords used for this research is "association of maternal serum zinc with risk of preeclampsia". The Boolean MeSH keywords inputted on databases for this research are: *(((*"Preeclampsia*"[MeSH Terms] OR (*"Eclampsia*"[All Fields] AND* "Mineral*"[All Fields]) OR (*"Zinc*"[MeSH Terms] OR (*"Zinc Serum*"[All Fields] AND* "supplementation*"[All Fields]) AND (*"effects*"[MeSH Terms] OR* "supplement*"[All Fields] OR* "Risk factor*"[All Fields] OR* "Maternal*"[MeSH Subheading] OR "result"[All Fields] OR "prognosis"[All Fields])))*

Data retrieval

The writers thoroughly evaluated the abstract and title of each manuscript before beginning this systematic review in order to assess each one's significance. Just articles that met the inclusion criteria and

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aligned with the article's objectives were selected for further examination. Ultimately, a definitive result was obtained from a consistent pattern found over several analyses. Only full-text, English-language submissions were acceptable. Content that satisfied all pre-established inclusion criteria and directly related to the study's subject matter was included after the most stringent screening procedure. Studies that failed to satisfy these requirements were frequently ignored, and their conclusions were not taken into consideration. A thorough analysis was conducted on a plethora of information discovered throughout the research process, including titles, authors, publication dates, locations, study methodologies, and parameters.

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Quality Assessment and Data Synthesis

The research that was reported in the titles and abstracts of each article was independently assessed by the authors in order to determine which papers needed additional investigation. Going over each document that satisfied the pre-established requirements to be included in the review was the following stage. The selection of an article for inclusion in the review was based on the evaluation procedure's results. By accelerating the selection of articles for further evaluation, this criterion was able to accomplish the goal of facilitating a thorough analysis of previous research and the factors that qualified them for the review.

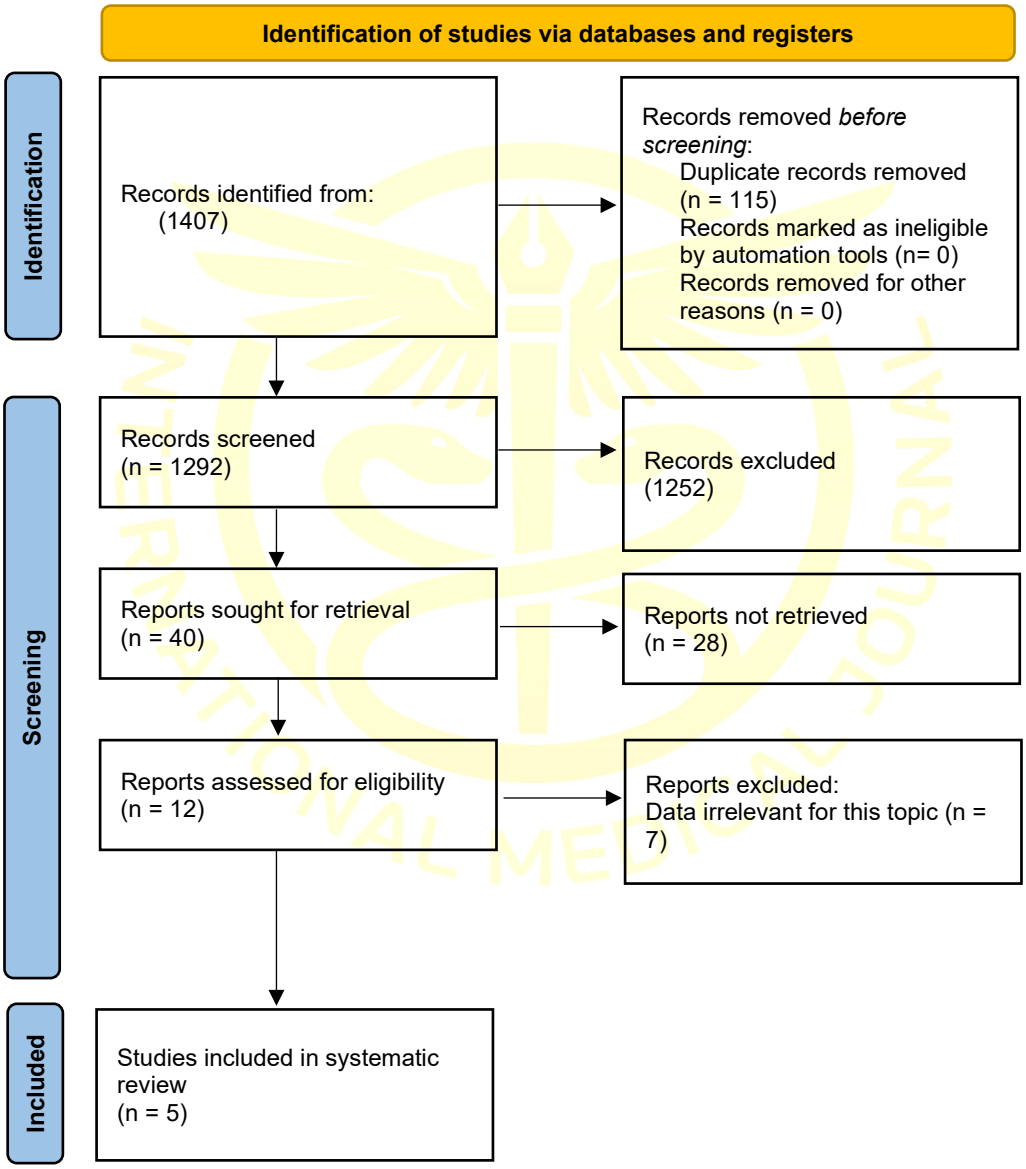


Figure 1. Article search flow chart

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RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered over 1407 publications. A thorough three-level screening strategy was used to identify only five papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Bilbeisi, AHE et al., 2023[10]	Palestina	This case-control study was conducted in 2022, in the three main Obstetrics and Gynecology departments in Gaza Strip, Palestine. One hundred sixty pregnant women, during the third trimester, aged ≥20 years, were selected using a convenient sampling method.	53	The participants' mean age was 30.7 ± 5.6 years. A total of 47 (58.8%) of cases and 6 (7.5%) of controls were insufficiently active; and the mean of blood pressure (mmHg) was 133.3 ± 11.9/85.11 ± 10.0 for cases and 112.8 ± 9.5/68.02 ± 7.2 for controls with significant differences between the two groups (*P* = <0.005). The mean serum zinc level (µg/dl) was 67.15 ± 16.5 for cases and 68.45 ± 18.0 for controls without significant differences between the two groups (*P* = 0.636). For newborns, the mean birth weight (g) was 2,904.6 ± 486 for cases, and 3,128.3 ± 501 for controls, and the mean Apgar score was 8.03 ± 0.62 for cases and 8.30 ± 1.17 for controls, with significant differences between the two groups (*P* = <0.005). Furthermore, 43 (53.8%) of cases have family history of hypertension; 5 (6.2%) were primiparous; 19 (23.8%) have previous caesarian section; 33 (41.2%) have history of preeclampsia; and 62 (77.5%) have edema, with significant differences

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				between the two groups (P = <0.005). Additionally, the total zinc dietary daily intake (mg/day) was 4.15 ± 2.10 for cases and 4.88 ± 3.02 for controls, with significant differences between the two groups (P = 0.041). After adjustment for confounding variables, participants in the case group have higher odds of having low total zinc dietary intake compared to those in the control group [OR = 1.185, 95% CI = (1.016–1.382), P = 0.030].
Uddin, SNM et al., 2023[11]	Bangladesh	The present study was conducted with 74 pre-eclampsia pregnant women (case) and 118 pregnant women having normal blood pressure (controls). Atomic Absorption Spectroscopy determined the serum level of trace components and electrolytes.	192	The researchers discovered notable differences in maternal age, gestational period, body mass index, systolic and diastolic blood pressure, hemoglobin, and creatinine level. Results of serum analysis revealed that calcium (52.06 ± 3.71 mg/L vs. 65.93 ± 2.57 mg/L, p < 0.05) and potassium (63.44 ± 5.33 mg/L vs. 102.54 ± 4.25 mg/L, p < 0.001) concentrations were substantially lower in the patient group than in control. Serum zinc (0.34 ± 0.02 mg/L vs. 0.52 ± 0.02 mg/L, p < 0.001) and iron (0.38 ± 0.03 mg/L vs. 0.46 ± 0.02 mg/L, p < 0.05) concentration were also considerably decreased in pre-eclampsia participants compared with a pregnant normotensive group. Pearson's correlation research results in the patient group revealed a connection between trace elements or macro

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				minerals. In addition, the systolic blood pressure was positively correlated with sodium ($r = 0.392$, $p < 0.01$) and negatively correlated with potassium ($r = -0.257$, $p < 0.05$) in the control group.
Kaprianti, T et al., 2022[12]	Indonesia	This observational study used case control design. The population of this study was all pregnant women with singleton pregnancy and 28–42 weeks of gestation who were treated at Department of Obstetrics and Gynecology dr. Mohammad Hoesin General Hospital Palembang from August 2020 to November 2020. The study was divided into 2 groups, a case group of 30 pregnant women with PE and a control group of 60 pregnant women	90	Both case and control groups had no meaningful differences in the general characteristics of the patient. There were significant differences in the maternal serum of average zinc level in both study groups (p = 0.013; 43.90 ± 15.79 µg/dL). The level of serum zinc which had the best sensitivity and specificity was 45.5 µg/dL.

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		without PE. Serum zinc level examination was performed on all samples which met the study criteria.		
Dumrongwongsiri, O et al., 2021[13]	Thailand	This is a prospective observational study, following pregnant women from the third trimester until child delivery. Pregnant women who attended the antenatal care clinic (ANC) at Ramathibodi Hospital, Bangkok, Thailand, were enrolled at 28–34 weeks gestation. Inclusion criteria were singleton pregnancy, plan to deliver the baby at Ramathibodi Hospital, and intention to breastfeed.	117	Zinc and iron intakes were estimated from a food frequency questionnaire. Serum zinc and ferritin were determined in maternal blood at enrollment and cord blood. Mean cord blood zinc and ferritin were 10.8 ± 2.6 µmol/L and 176 ± 75.6 µg/L, respectively. Cord blood zinc was associated with pre-pregnancy BMI (adj. ß 0.150; p = 0.023) and serum zinc (adj. ß 0.115; p = 0.023). Cord blood ferritin was associated with pre-pregnancy BMI (adj. ß −5.231; p = 0.009). Cord blood zinc and ferritin were significantly higher among those having vaginal delivery compared to cesarean delivery (adj. ß 1.376; p = 0.007 and 32.959; p = 0.028, respectively). Maternal nutritional status and mode of delivery were significantly associated with zinc and iron stores at birth. Nutrition during preconception and pregnancy should be ensured to build adequate stores of nutrients for infants.
Al-Sakarneh,	Jordan	A case-control study design was used to	30	Hcy levels were significantly higher among women with PE compared

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NA et al., 2021[14]		examine serum Zn and Hcy statuses, and their association to PE risk. Thirty pregnant women with PE 21∼35 years of age, and 30 matched healthy pregnant women were recruited from Amman, Jordan.		with controls (16.35±0.43 and 7.25±0.21 μmol/L, respectively; *P*<0.05). However, there was no significant difference in Zn levels between women with PE and controls (65.37±1.27 and 63.71±1.24 μg/dL, respectively; *P*>0.05). Blood levels of Hcy (μmol/L) were positively associated with systolic and diastolic blood pressure (β=3.54 and β=1.81, respectively; *P*<0.05), and Zn levels [odds ratios (OR)=0.84; 95% confidence intervals (CI): 0.71∼0.98] were significantly associated with PE risk (*P*<0.05). Although women with PE had significantly higher Hcy levels than controls, H-Hcy was not associated with increased PE risk. However, there was a strong association between severity of hypertension and serum Hcy levels, and serum Zn levels were inversely associated with H-Hcy. The likelihood of PE was significantly higher in women who were Zn deficient compared with healthy controls. To conclude, early management of H-Hcy and associated risk factors may be effective in decreasing the incidence of PE.

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Bilbeisi, AHE et al., 2023 showed the main risk factors of PIH among pregnant women in the Gaza Strip, Palestine are family history of hypertension, primiparous, previous caesarian section, history of preeclampsia, complaints of edema, high maternal BMI, physical inactivity, and low maternal dietary zinc intake. Furthermore, low maternal dietary zinc intake was associated with high levels of PIH. Moreover, having PIH could increase the risk of low birth weight and low Apgar scores. Therefore, reducing the main risk factors of PIH could reduce the adverse effect on both mother and birth outcomes. Further future studies with large sample size are recommended.[10]

Uddin, SNM et al., 2023 showed that calcium, potassium, iron, and zinc levels were lower, whereas sodium levels were higher in Bangladeshi pre-eclampsia patients compared to controls. These findings with Pearson's correlation and the inter-element relationship between the patient and a control subject results can act as critical indication factors for patients with pre-eclampsia in Bangladesh and, as a result, may require a higher intake of calcium, potassium, iron, and zinc for effective therapeutic intervention and reduce the intake of sodium.[11]

Kaprianti, T et al., 2022 showed there were significant differences in level of serum zinc between PE and non-PE patients (p = 0.013). The level of zinc serum of pregnant women with PE was lower than without PE. Based on the cut-off point curve of serum zinc level, the value that had the best sensitivity and specificity is 45.5 mcg/dL. There was a significant relationship between serum zinc level and PE. Pregnant women with serum zinc level ≤ 45.5 mcg/dL were significantly 3.2 times more risk towards PE than pregnant women with serum zinc levels > 45.5 mcg/dL (OR = 3,208 (CI95% 1,288–7,990; p = 0.020). There were no significant differences in the average age, age category, and gestational age. Further study should be conducted to provide zinc supplementation early in pregnancy to reduce the risk of preeclampsia.[12]

Dumrongwongsiri, O et al., 2021showed Zinc and iron deficiencies were highly prevalent among pregnant women in this study. Dietary intakes during pregnancy were problematic. Zinc storage of infants was related with maternal zinc level during pregnancy. Pre-pregnancy BMI was associated with cord blood zinc and ferritin concentrations. Vaginal delivery may provide an advantage for micronutrient transfer during active labor. Maternal nutrition during preconception and pregnancy affects some of the nutrient stores in infants. Prenatal iron supplementation has been universally recommended where iron deficiency is highly prevalent to prevent serious consequences of maternal death associated with child birth. In addition to iron supplementation, zinc supplementation may be needed in light of the high prevalence of zinc deficiency during pregnancy, and its significant contribution to the zinc store as reflected by cord blood zinc. Further study is needed to assess the magnitude of zinc deficiency in the population and effective intervention to improve both maternal zinc status and the infant store.[13]

Al-Sakarneh, NA et al., 2021 showed the serum Zn concentrations do not significantly differ between pregnant women with PE and healthy pregnant women. These results may be explained by the negative impact of iron on Zn absorption and status that could further exacerbate Zn status. In our study, approximately 63% of full cohort used supplements (calcium, iron, or multivitamins), which could explain why both pregnant women with PE and controls were at borderline of the normal range of the Zn cutoff level (i.e., 65.00

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μg/dL). However, elevated Zn in blood was significantly associated with H-Hcy in PE, and Hcy concentrations were positively correlated with plasma Zn concentrations in women with PE (r=0.588; P=0.003) but not healthy controls. In pregnant women with PE, a one unit increase in serum Zn was significantly associated with 0.18 μmol/L decrease in serum Hcy levels (P=0.02); however, there was no association between serum Zn and serum Hcy in controls or the full cohort (P>0.05).[14]

DISCUSSION

Preeclampsia (PE) is a multi-system disorder that onsets at 20 wks or later in pregnancy. It can affect pregnant women in many ways, such as causing hypertension, proteinuria, liver dysfunction, placental abruption, fetal growth restriction. It is a subtype of the hypertensive disorder spectrum in pregnancy, complicating around 5% of pregnancies worldwide. It remains one of the major causes of maternal, fetal and neonatal mortality, particularly in low-income and middle-income countries (LMICs). Despite many researchers devoted to this field, the etiology of preeclampsia is still largely unknown.[7,15]

Some scholars proposed that trace elements may play a vital role in developing preeclampsia. In spite of making up <0.1% in the human body, trace elements have a disproportional function in maintaining health. Overall, evidence suggests that micronutrient imbalances are associated with various disorders. This will be more prominent in pregnancy when maternal requirements are usually increased. Optimal supplementation can reduce a range of pregnancies complications, e.g., anemia, gestational diabetes, thyroid disorders, and miscarriage.[7]

Adequate maternal nutrition, particularly before and during pregnancy, is imperative to the health of both the mother and child. Poor nutrition in pregnancy may lead to inappropriate nutrient partitioning between the mother and fetus, which can be deleterious to the health of both. Each year, 3.5 million deaths in women and children are attributed to undernutrition. Zinc deficiency is predicted to be responsible for 1% of all deaths globally and 4.4% of deaths in children aged 6 months to 5 years. The World Health Organization (WHO) prioritized minimizing zinc deficiency in developing nations as part of the Millennium Development Goal 1: to eradicate extreme poverty and hunger. Therefore, understanding the effects of zinc deficiency on pregnancy and fetal growth is very important.[16,17]

Zinc is an essential component of over 1000 proteins including antioxidant enzymes, metalloenzymes, zinc-binding factors and zinc transporters. These are required for a variety of biological processes including carbohydrate and protein metabolism, DNA and RNA synthesis, cellular replication and differentiation, and hormone regulation. The importance of zinc to the growth of the fetus is demonstrated by the active transport of zinc across the placenta into the fetal circulation resulting in higher cord blood concentrations compared to those in the maternal circulation. Rodent models of severe maternal zinc deficiency show increased rates of fetal loss and congenital malformations in the surviving

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fetuses as well as reduced fetal growth, lower implantation rates and impaired placental growth, all highlighting the teratogenic effects of zinc deficiency in pregnancy.[16,18]

Zinc (Zn) is the second most abundant trace element next to iron which is essential for all living organisms. It exists as a divalent cation and is not redox active under physiological conditions, which explains why zinc performs different physiological roles in a variety of biological processes. Zn is served as the structural components and cofactors of different classes of enzymes. Zinc is an essential trace element for human nutrition that is an integral part of many enzyme systems like DNA polymerase complex. Zn is involved in different signaling pathways. Zn deficiency has been associated with different diseases like pre-eclampsia, different types of cancer, cardiovascular disease, skin disease, immunity, aging, and infection. Zn is important for normal pregnancy and fetal development and its deficiency during pregnancy or in early childhood period leads to stunting, mental retardation, and delayed sexual maturity.[19,20]

CONCLUSION

serum zinc level in PE patients was significantly lower than that in healthy pregnancy women. A moderate amount of zinc supplementation may reduce the incidence of PE, which needs to be confirmed.

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