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REVIEW PAPER

Association between zinc, copper, iron, calcium, magnesium, and preeclampsia development: a narrative review*

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Abstract

Preeclampsia is defined as hypertension and proteinuria or as hypertension and end-organ dysfunction with or without proteinuria, typically presenting after 20 weeks of gestation. This condition remains a leading cause of fetal and maternal morbidity worldwide. Its pathogenesis is associated with detrimental processes such as endothelial dysfunction, oxidative stress, and inflammation. The regulation of immune system activity, vascular health, and oxidative stress mitigation is influenced by minerals, which play a key role in pregnancy. Examples include zinc, copper, iron, calcium and magnesium. This narrative review aimed to establish a possible connection between the concentrations of these minerals in various biological samples (serum, urine, placenta and plasma) and the development of preeclampsia. Elevated dietary intake of these metals and the association between mineral intake and the risk of preeclampsia development were also considered. A literature search was conducted in scientific databases, including ScienceDirect and PubMed, to address the research question by collecting relevant studies published between 2014 and 2024. Evidence suggests that mineral status disturbances may contribute to oxidative stress, endothelial damage and inflammatory imbalance in preeclampsia. Specifically, zinc deficiency exacerbates oxidative stress, while higher copper concentrations are associated with increased oxidative damage. Elevated iron levels in both the diet and serum have been shown to contribute to ferroptosis through the generation of reactive oxygen species. Additionally, calcium and magnesium deficiencies have been reported to impair blood pressure regulation and vascular tone. The association between minerals and preeclampsia is complex and depends on multiple factors, including race, location, gestational age, maternal age, diet and ratios between elements.

Keywords: minerals, preeclampsia, pregnancy

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INTRODUCTION

Preeclampsia is a complex disorder diagnosed in 2-8% of pregnancies. This condition is highly dangerous, contributing to approximately 60,000 maternal deaths and >500,000 preterm births worldwide each year (Ma'ayeh and Costantine 2020). Preeclampsia is characterized by the onset of hypertension after 20 weeks of gestation, combined with proteinuria (>300 mg/day). In many cases, the condition is triggered by pregestational diabetes mellitus or a family history of preeclampsia. Both of these conditions can lead to maternal organ dysfunction, including renal insufficiency, as well as hematological and neurological complications (Huai et al. 2021). Although the exact mechanism of preeclampsia development remains unclear, key physiological processes that may contribute to its onset include abnormal placental development, uterine-placental vascular dysfunction, and an imbalance in proinflammatory cytokine levels (Hansson et al. 2015, Rana et al. 2019).

During pregnancy, fluctuations in concentrations of minerals may cause endothelial tissue dysfunction (Hansson et al. 2015). These findings have been emphasized in numerous recent publications emphasizing the importance of metal ions in preeclampsia (Shen PJ et al. 2015, Detlefs et al. 2022, Hao et al. 2024, Vásquez-Procopio et al. 2024).

Minerals are involved in the formation of antioxidant defense, the support of cellular metabolism, and the regulation of the immune system activity. The indicated processes play an important role in the inflammatory processes and the management of oxidative stress in preeclampsia (Muzyko et al. 2021). Calcium (Ca) and magnesium (Mg) are particularly important for bone growth, muscle function, and vascular tone regulation. In the context of preeclampsia, these minerals are directly involved in maintaining vascular health and blood pressure stability.

Despite the abundance of studies on the role of minerals in preeclampsia, determination of the underlying mechanisms remains inconclusive. In addition, certain studies have presented contradictory results, which could be attributed to the inadequate quality of the research conducted. While the roles of various minerals are well documented in the literature, the specific biomolecular mechanisms underlying preeclampsia are not yet fully understood. Therefore, clarifying the role of minerals in the development of this condition is of paramount importance.

This review aims to compile information on the significance of elemental analysis in preeclampsia based on literature published over the past decade (2014-2024). By examining the relationship between zinc (Zn), copper (Cu), iron (Fe), Ca, Mg levels in the maternal organism (serum/plasma, urine, placenta), this review seeks to identify not only potential but also definitive biomarkers of preeclampsia (Figure 1).

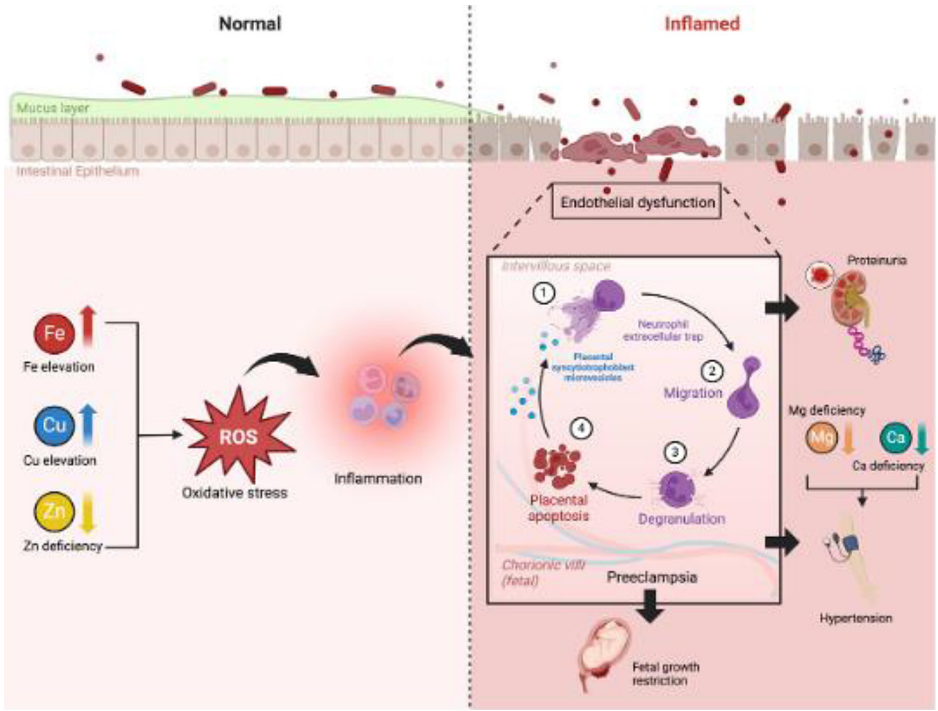

Fig. 1. Association of zinc, copper, iron, calcium, and magnesium with preeclampsia. BioRender was used for creation of this figure: Fe – iron, Cu – copper, Zn – zinc, Mg – magnesium, Ca – calcium, ROS – reactive oxygen species, 1,2,3,4 – the next stages of endothelial dysfunction

MATERIALS AND METHODS

A thorough literature search was conducted covering the period from 2014 to 2024. However, information from articles outside this timeframe was also considered when relevant. The PubMed and Scopus databases were used to obtain relevant articles based on the inclusion criteria. The keywords "pre-eclampsia" and "selected minerals" were used to collect studies focusing on the inclusion criteria. Individual search terms were combined using Boolean operators AND, NOT, and OR (Figure 2).

Inclusion criteria

The criteria for selecting studies were as follows:

1) all primary research designs and meta-analyses were considered;
2) studies analyzing specific chemical elements (Zn, Cu, Fe, Ca, Mg) about preeclampsia, whether individually or collectively, were included;

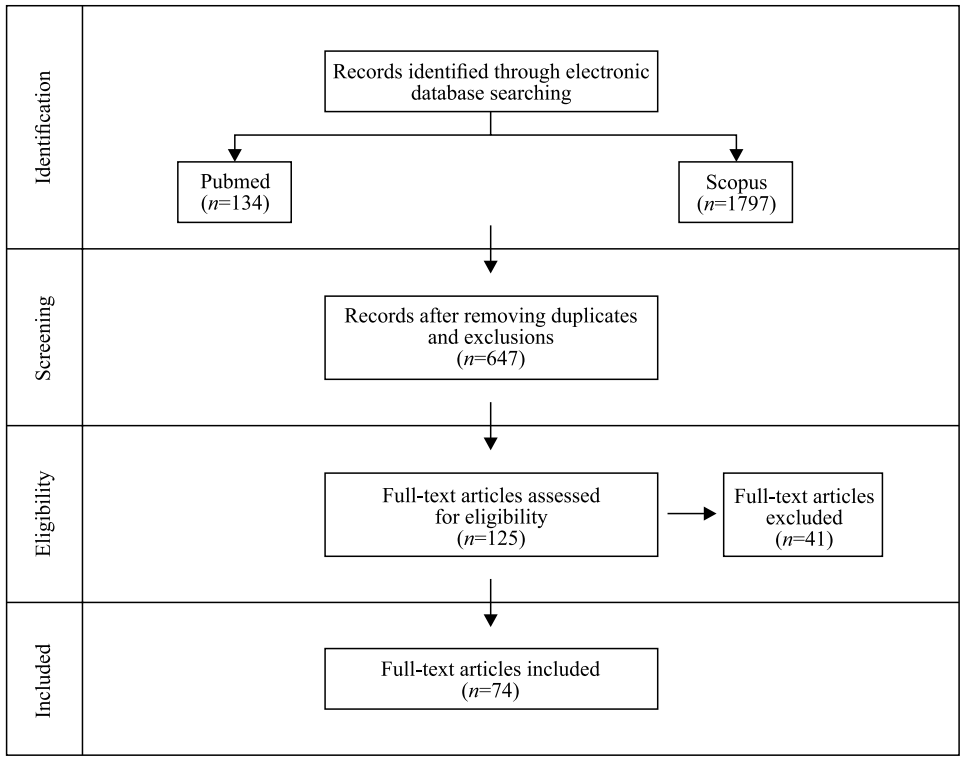

Fig. 2. Identification of inclusion and exclusion criteria for literature search strategy

3) no limitations were placed on the age of the study population;
4) studies covering cases of pregnant women at any stage of gestation were included;
5) research covering all severities of preeclampsia was considered. Experimental studies were included;
6) publications examining a variety of diets and biological samples, including serum, plasma, whole blood, amniotic fluid, placenta, umbilical cord blood, and urine, were deemed acceptable;
7) selected studies were required to reference “preeclampsia” and the specific chemical elements under investigation in their titles, abstracts, or keywords;
8) original research publications and meta-analyses were included, whereas narrative reviews, mini-reviews, letters, commentaries, and case studies were excluded.

Exclusion criteria

The exclusion criteria for this study were as follows:

1) papers not written in English were excluded;
2) articles outside the study period (2014-2024) were not considered;
3) papers lacking comprehensive data were omitted;
4) studies where full texts or crucial data were inaccessible were excluded;
5) duplicates, protocol studies, secondary analysis reports, and articles not related to minerals and preeclampsia were excluded.

RESULTS AND DISCUSSION

The role of minerals in the development of preeclampsia (PE) has been widely studied. The concentrations of the analyzed elements in women experiencing pregnancy complications have been thoroughly examined in blood serum/plasma, a key biomarker reflecting the body's elemental content, as well as in urine, placenta, and hair. The composition of blood serum/plasma plays a crucial role in ensuring the proper functioning and development of the placenta during this critical time. The concentration of minerals in urine, placenta, and hair shows the complete mineral balance in the maternal organism. The findings from various studies aimed at determining mineral status (as Zn, Cu, Fe, Ca, and Mg) in preeclampsia (PE) have shown considerable variability and inconsistency (Ma et al. 2015, Chen et al. 2022).

Zn and preeclampsia

Zn plays a critical role in various physiological processes during pregnancy, including DNA synthesis, cell division, and immune function. It is also essential for maintaining the body's antioxidant defense systems. This element is particularly important during pregnancy, as it supports fetal growth and development, and it helps modulate maternal immune responses, reducing the risk of adverse outcomes such as preeclampsia. PE is strongly associated with oxidative stress, a condition in which the body's antioxidant defenses are overwhelmed by reactive oxygen species – ROS (Ma et al. 2015).

Zn deficiency during pregnancy can exacerbate oxidative stress by impairing the activity of antioxidant enzymes, such as superoxide dismutase (SOD), which is crucial for neutralizing ROS. Studies have demonstrated that serum Zn levels are significantly lower in preeclamptic women compared to normotensive pregnant women. Meta-analyses and original studies have confirmed significantly lower Zn concentrations in serum and plasma among preeclamptic women compared to normotensive pregnant controls (Enebe et al. 2020, Guan et al. 2022, Pyla et al. 2024) Interestingly, meta--analyses indicate that this significant relationship is particularly relevant

to Asian populations. The analyses suggest that an important factor influencing the Zn-PE relationship is the location of the study and/or race of the subjects (Lang et al. 2022, Hao et al. 2024).

Kurlak et al. (2023) reported lower maternal Zn concentrations (serum, urine, placenta) in preeclamptic women and found an association between maternal Zn concentration and placental growth factor (PlGF) and FMS-like tyrosine kinase-1 (sFlt-1). Since PlGF and sFlt-1 are angiogenic markers, the significant association between Zn plasma levels and these parameters suggests that Zn plays a role in dysregulating the angiogenic balance in preeclampsia. Additionally, lower Zn levels in the placenta of preeclamptic women further support the connection between Zn and angiogenic disturbances in placental and trophoblast development, which directly impact fetal growth disorders (Zhu et al. 2016, Hao et al. 2024).

The positive effects of Zn ions on the regulation of oxidative stress, angiogenic imbalance, and inflammation were confirmed by Lang et al. (2022) in preeclamptic rats. Their findings suggest that PE may be mitigated by Zn supplementation (Keshavarz et al. 2017).

Zn's role in immune modulation is also significant in the context of preeclampsia. Zn deficiency affects T-cell function and cytokine production, potentially leading to an exaggerated inflammatory response. This imbalance can damage the vascular endothelium, a hallmark of PE, contributing to its progression. Moreover, Zn deficiency has been linked to abnormal placental development, a key factor in the pathogenesis of preeclampsia (Guan et al. 2022).

Despite the evidence linking Zn deficiency with PE, clinical trials evaluating the effectiveness of Zn supplementation in preventing or reducing the severity of the condition have yielded mixed results. While some studies suggest that Zn supplementation may offer potential benefits, further research is needed to establish the optimal dosage and timing for effective intervention (Elmugabil et al. 2016, Al-Jameil et al. 2017, Keshavarz et al. 2017, Gzhegotskyi and Sukhodolska 2019, Lewandowska et al. 2019, Enebe et al. 2020, Gul et al. 2022).

Despite the outlined connection between reduced Zn concentrations and preeclampsia, the effect of this mineral on the development of the condition remains inconclusive. The concentrations of serum Zn in PE patients have been investigated in several studies (Tesfa et al. 2011, Ma et al. 2015) with findings suggesting that Zn may be involved in the pathogenesis of the condition. However, in contrast to previously discussed studies, no statistically significant difference in serum Zn concentrations was observed between healthy and preeclamptic groups. Specifically, correlation analyses indicated no relationship between Zn levels and the disease (Chababa et al. 2016).

Notably, studies that failed to confirm a relationship between Zn concentration and PE were conducted in women in the third trimester. This suggests that the gestational week may be an important factor in determining

the association between Zn levels in serum/plasma and PE. Pyla et al. (2024) found no association between serum Zn levels and preeclampsia development, however, they suggested that a positive correlation between maternal Zn levels in serum and gestational age may play a protective role in late pregnancy.

In summary, key factors influencing the relationship between maternal Zn levels and PE include location, race, and gestational age. Monitoring Zn levels in pregnant women, particularly those at risk for preeclampsia, could serve as a promising strategy for early intervention and management. This approach may help mitigate the severity of preeclampsia and improve pregnancy outcomes by restoring immune balance and reducing oxidative stress.

Cu and preeclampsia

Cu is an essential trace element involved in various biological processes, including Fe metabolism, mitochondrial respiration, and connective tissue maintenance. It also plays a significant role in oxidative stress regulation, acting as both an antioxidant and a pro-oxidant. This dual role makes Cu particularly complex in the context of preeclampsia, a condition characterized by increased oxidative stress and endothelial dysfunction. The inconsistencies in Cu level findings across studies may reflect the heterogeneity of preeclampsia pathology and the diverse stages or severities of the disease observed in different populations (Elmugabil et al. 2016, Gzhegotskyi and Sukhodolska 2019).

Cu's antioxidant role is largely mediated through its function in superoxide dismutase (SOD), an enzyme responsible for neutralizing reactive oxygen species (ROS). In cases of Cu deficiency, SOD activity decreases, leading to a buildup of ROS, which contributes to the oxidative stress observed in preeclampsia. However, Cu can also function as a pro-oxidant, particularly when it catalyzes the formation of free radicals in the presence of hydrogen peroxide. This dual functionality complicates the interpretation of Cu levels in preeclampsia, as both elevated and reduced Cu concentrations may contribute to oxidative stress through different mechanisms (Keshavarz et al. 2017).

Several studies have reported higher Cu levels in serum and urine in preeclamptic women compared to healthy pregnant women (Gzhegotskyi, Sukhodolska 2019, Kurlak et al. 2023, Pyla et al. 2024).

These elevated levels may reflect an adaptive response to increased oxidative stress, as the body upregulates Cu-dependent enzymes like SOD to counterbalance heightened ROS production. However, excessive Cu levels can also contribute to inflammation and cardiovascular dysfunction in PE. Additionally, high Cu levels in blood may exacerbate oxidative Fe damage, particularly when Cu functions as a pro-oxidant under certain conditions (Gul et al. 2022, Zhong et al. 2022, He et al. 2024).

Pyla et al. (2024) found a positive correlation between maternal Cu levels in serum and maternal age, suggesting that elevated Cu levels with age may increase the risk of PE in older pregnant women. Similarly, Song et al. (2017) reported that higher serum Cu levels were significantly associated with PE risk in Asian populations.

Some studies have also found a positive correlation between Cu levels and the severity of PE (Gul et al. 2022, Pyla et al. 2024). In a study by Sak et al. (2020), Cu levels were elevated in maternal serum across different severities of preeclampsia, ranging from mild preeclampsia to severe preeclampsia and ultimately to HELLP syndrome (low platelet count syndrome), the most severe form of the condition. Elevated Cu levels are likely associated with increased oxidative stress resulting from pathophysiological changes in the placenta (Gul et al. 2022).

These findings suggest a strong involvement of Cu in the development of PE (Sak et al. 2020). This is further supported by the significant association between PE and elevated levels of Cu, Cu/Zn ratio, and MDA production in pregnant women (Rafeeinia et al. 2014).

In contrast, other studies have examined Cu levels in preeclamptic women, yielding mixed results. The observed reduction in Cu levels may indicate impaired antioxidant defense mechanisms, contributing to the oxidative stress and endothelial damage characteristic of preeclampsia (Gul et al. 2022, Zhong et al. 2022, Hao et al. 2024).

Some studies did not confirm a relationship between elevated maternal Cu levels and the risk of preeclampsia (Gul et al. 2022, Zhong et al. 2022). Conversely, other studies reported opposite findings, concluding that higher Cu levels are associated with a lower risk of PE (Chen et al. 2022). A meta-analysis conducted on over 5,000 pregnant women produced ambiguous results. While this analysis identified an association between Cu levels and PE, the relationship varied depending on region and economic development (Zhong et al. 2022).

Discrepancies in study findings may be influenced by geographic, dietary, and genetic factors, all of which can affect baseline Cu status in different populations. Additionally, the timing of sample collection (e.g., early vs. late pregnancy) and differences in the severity of PE among study participants could further contribute to the inconsistent findings. Some studies suggest that Cu levels fluctuate depending on disease progression, with early-stage PE showing elevated Cu levels due to an acute-phase response, followed by a decline in more severe cases as antioxidant reserves become depleted (Al-Hilli, Hasan 2015, Aouache et al. 2018).

The body's mineral status is also influenced by dietary intake. Interestingly, in the case of Cu, Liu et al. (2023) suggested a revised J-shaped relationship between Cu levels and PE risk.

Given these conflicting results, further research is needed to clarify the role of Cu in PE development. Future studies should focus on larger, more diverse populations, and account for factors such as dietary intake and

genetic variability. Additionally, longitudinal studies that track Cu levels throughout pregnancy could provide valuable insights into temporal changes in Cu metabolism and its potential role in the development and progression of PE (Elmugabil et al. 2016).

Fe and preeclampsia

Fe plays a critical role in several biological functions during pregnancy, including oxygen transport and cellular respiration. Research group highlights that optimal Fe concentrations during pregnancy are fundamentally important for supporting fetal development and maternal health. The transport of Fe between the mother and the child is regulated by the placenta. Similar to other nutrients, Fe follows a U-shaped risk curve, indicating that both high and low concentrations of Fe in the blood are dangerous. For instance, elevated Fe concentrations are dangerous since reactive Fe ions can produce ROS, leading to ferroptosis, a form of iron-dependent cell death. Conversely, low Fe levels can be detrimental to fetal health, as they reduce oxygen supply to developing cells. Some authors argue that ferroptosis in the placenta is commonly observed in PE. This process is driven by elevated active Fe ions, which promote excessive formation of ROS as intermediates in redox reactions. The accumulation of excess Fe levels leads to cell death and the development of various physiological disorders, including PE (Zhang et al. 2022).

Elevated maternal serum Fe and ferritin levels compared to normotensive pregnancies have been observed in multiple studies (Wahab et al. 2019, ElShahat et al. 2020, Ahmed et al. 2023, Li et al. 2024, Ortega et al. 2024, Pyla et al. 2024). Mobeen Rana et al. (2022) suggested that increased Fe and Cu levels in serum, along with decreased Zn concentrations, are indicators of PE.

The elevated serum Fe levels observed in preeclampsia are particularly concerning due to their role in catalyzing ROS formation via the Fenton reaction – a chemical process in which free Fe reacts with hydrogen peroxide, producing hydroxyl radicals, a highly reactive type of ROS. This increase in oxidative stress is a well-documented contributor to the pathogenesis of preeclampsia, exacerbating endothelial dysfunction, inflammation, and vascular damage – all key features of the disease (Grzeszczak et al. 2023).

Furthermore, oxidative damage caused by ROS can lead to lipid peroxidation, further impairing placental function and contributing to the clinical manifestations of preeclampsia, such as hypertension and proteinuria (Grzeszczak et al. 2023).

Elevated ferritin levels are not only a marker of Fe overload but also an indicator of ongoing inflammation. In preeclampsia, inflammation and oxidative stress are closely interconnected, with elevated ferritin levels supporting the idea that excess Fe contributes to an inflammatory environment, thereby worsening disease progression (Zhang et al. 2022).

The regulation of Fe metabolism during pregnancy is complex. Under normal conditions, Fe levels are carefully regulated to meet the increased

demands of the growing fetus while avoiding toxicity. However, in preeclampsia, this balance is disrupted, leading to Fe overload, which may be both a cause and a consequence of the oxidative stress and inflammation observed in the condition. The association between high Fe levels and preeclampsia raises concerns about Fe supplementation during pregnancy. For instance, excess Fe intake could potentially worsen the disease in susceptible women (Petry 2022, Zhang et al. 2022, Dwarkanath et al. 2024, Yang et al. 2024).

A meta-analysis confirmed higher ferritin and hepcidin levels in preeclamptic women compared to healthy controls (Bandyopadhyay et al. 2022). Hepcidin, a key regulator of Fe homeostasis and Fe availability, correlates with inflammation, similar to ferritin. In normal pregnancy, maternal hepcidin expression is suppressed during the second and third trimesters to increase Fe availability in the placenta. However, in PE, hepcidin upregulation may occur due to inflammation or oxidative stress (Bandyopadhyay et al. 2022).

Some authors suggest that increased hepcidin levels in PE may serve as a protective mechanism against Fe overload, thereby preventing oxidative stress (Shaji Geetha et al. 2022). Current study suggests independent of inflammation or oxidative stress, hormonal deregulation of maternal Fe bioavailability through decreasing placental erythroferrone (ERFE) that regulates Fe mobilization and control Fe transport in placenta to the fetus (Masoumi et al. 2023).

Other studies have found that lower Fe levels in the placenta and serum are associated with PE development (Uddin et al. 2023, Hao et al. 2024). Decreased Fe content in the placenta has been linked to an increased risk of PE with fetal growth restriction (Hao et al. 2024). Moreover, studies have observed increased expression of angiogenic proteins in Fe-deficient anemic pregnant women, leading to placental vascular changes and, consequently, preeclampsia (Venkata Surekha et al. 2019).

Zhu et al. (2022) reported that the relationship between ferritin and Fe levels in PE depends on the stage of pregnancy. They suggested that decreased ferritin levels in early pregnancy or elevated ferritin levels in late pregnancy accelerate ferroptosis and exacerbate PE. The authors concluded that high Fe status and ferroptosis may contribute to the development of PE in later pregnancy (Zhu et al. 2022).

Since many factors influence the Fe-ferritin-preeclampsia relationship, some studies have not found an association between Fe, ferritin, hepcidin, pro-hepcidin, and the risk of preeclampsia (Duvan et al. 2015, Zhang et al. 2022, Ahmed et al. 2023).

The elevation of serum Fe and ferritin levels in preeclamptic women remains inconsistent across studies. However, Fe has been shown to contribute to the pathogenesis of PE, primarily by promoting oxidative stress and inflammation. Further research is needed to fully understand the implica-

tions of these findings and to develop targeted strategies, particularly regarding Fe supplementation during pregnancy. Optimal management of Fe levels in pregnant women, especially those at risk for preeclampsia, is crucial for maternal and fetal health.

Ca and preeclampsia

Ca is essential for maintaining vascular tone and intracellular signaling. Hypocalcemia in preeclampsia, as observed in various studies, can impair smooth muscle function, contributing to hypertension. Ca levels are consistently found to be lower in preeclamptic women compared to healthy controls (Duvan et al. 2015, Khaing et al. 2017, Maduray et al. 2017, Woo Kinshella et al. 2022, Dwarkanath et al. 2024, Jaiswal et al. 2024).

Tabandeh et al. (2018) found significantly lower Ca levels in serum and higher levels in urine in preeclamptic women during the second trimester, suggesting increased Ca excretion during pregnancy. Reduced Ca levels may also hinder vasodilation, potentially exacerbating hypertension in preeclampsia. This physiological function of Ca suggests that Ca supplementation could help reduce the risk of preeclampsia in cases of Ca deficiency. This aligns with research showing that Ca supplementation in populations with low dietary Ca intake can significantly reduce the incidence of preeclampsia and its complications (Khaing et al. 2017, Woo Kinshella et al. 2022, Dwarkanath et al. 2024, Jaiswal et al. 2024).

Additionally, Ca levels are inversely correlated with preeclampsia severity, suggesting that hypocalcemia might predict the onset and progression of the condition (Vanaja et al. 2021). In an experimental model, low Ca intake was associated with an increased risk of preeclampsia development. Conversely, low-dose Ca supplementation was found to reduce the incidence of the condition by approximately 60% (Gatford et al. 2020).

A meta-analysis by Tang et al. (2015) confirmed the effectiveness of Ca supplementation in reducing PE incidence in women at risk of the condition and with low baseline Ca intake. Moreover, Ca may enhance the effectiveness of low-dose aspirin in preventing PE. Chen and Sun (2023) found in their meta-analysis that low-dose aspirin combined with Ca can effectively prevent PE, reduce preterm birth, and lower the risk of postpartum hemorrhage.

However, some studies have found no significant differences in serum Ca concentrations between preeclamptic and healthy pregnant women (Vafaei et al. 2015, Masoumi et al. 2023, Wadhwani et al. 2023).

In a large randomized placebo-controlled trial (RCT), Hofmeyr et al. (2018) found no significant reduction in PE incidence with Ca supplementation before and during early pregnancy. The effectiveness of Ca supplementation for PE prevention remains controversial. Results from multiple recent studies suggest that the impact of Ca on PE depends on several factors, including the stage of pregnancy, Ca intake, dosage, and timing of supplementation. However, the most critical factor appears to be Ca status in women before and during pregnancy.

The available evidence underscores the importance of monitoring Ca levels during pregnancy, particularly in women at risk of developing PE. Ca supplementation may provide a simple intervention to help mitigate preeclampsia risk, especially in populations with inadequate dietary Ca intake.

Mg and preeclampsia

In addition to Ca, Mg is another element essential for reproductive health. Mg is involved in over 300 enzymatic reactions, supporting neuromuscular function, cellular signaling, and vascular tone. Numerous studies have linked low Mg status in pregnant women to an increased risk of PE (Maduray et al. 2017, Eslamzadeh et al. 2023, Wadhwani et al. 2023, Hao et al. 2024, Pyla et al. 2024).

It is suggested that low Mg levels induce hypoxia and inflammatory responses, which are associated with the release of platelet-activating factor (PAF). PAF stimulates endothelial cell migration and angiogenesis and may also modulate blood pressure. Increased PAF levels and decreased Mg levels have been observed in pregnant women with PE (Chawla et al. 2023). Moreover, studies have found that Mg serum levels correlate negatively with maternal age and positively with gestational age (Pyla et al. 2024). This correlation suggests that Mg deficiency may increase the risk of PE, particularly in older pregnant women, as the risk of PE is known to increase with maternal age (Pyla et al. 2024). Liu et al. (2023) suggested that higher dietary intake of Mg (along with Ca, Fe, and Zn) during pregnancy is associated with lower odds of developing PE. Similarly, higher Mg levels in whole blood during the second trimester have been associated with a reduced risk of PE (Chen et al. 2022). Mg supplementation is beneficial in reducing the pathophysiological consequences of PE (Gatford et al. 2020, Vanaja et al. 2021).

Several mechanisms have been proposed to explain Mg's role in regulating blood pressure and placental angiogenesis. Studies indicate that Mg can reduce the concentrations of sFlt-1 and endoglin, block the activity of the brain N-methyl-D-aspartate receptors, decrease the extent of inflammation mediators, activate nitric oxide synthases, block the activity of arginases and limit the formation of free radicals and improve uterine blood flow and reduce fetal growth restriction (Chiarello et al. 2018, Fondjo et al. 2023).

Preventive and therapeutic effects of Mg salts in preeclamptic women confirm the potential role of Mg in blood pressure regulation in PE. However, some randomized clinical trials have shown that Mg supplementation does not prevent PE, even in women with hypomagnesemia (De Araújo et al. 2020). It has been suggested that Mg supplementation may be more beneficial in severe PE than in mild PE (Fondjo et al. 2023) and that its effects are more pronounced in late gestational weeks (30-34 weeks) compared to earlier weeks (26-30 weeks) – Xing et al. 2024.

Other studies indicate that a low Ca-to-Mg ratio in serum may serve

as a significant indicator of PE risk, as it is associated with nerve damage, impaired smooth muscle function in blood vessels, and vasoconstriction (Adhipurnawan Winarno et al. 2021).

Table 1

Association between Zn, Cu, Fe, Ca and Mg and preeclampsia

Sample	Zn	Cu	Fe	Ca	Mg	References
Serum	↓	X	X	X	X	(Ma et al. 2015)
Serum	↓	↑	↑	↓	-	(Pyla et al. 2024)
Placenta	↓	↓	↓	↓	↓	(Hao et al. 2024)
Plasma	↓	↑	X	X	X	(Kurlak et al. 2023)
Urine	~	↑	X	X	X	(Zhu et al. 2016)
Plasma	↓	↓	X	X	X	(Keshavarz et al. 2017)
Serum	↓	↑	↓	↓	↓	(Al-Jameil et al. 2017)
Serum	~	~	X	↓	↑	(Elmugabil et al. 2016)
Serum	↓	↑	X	X	X	(Lewandowska et al. 2019)
Serum	~	↑	X	X	X	(Gul et al. 2022)
Serum	~	↑	X	X	X	(He et al. 2024)
Serum	X	↑	X	X	X	(Sak et al. 2020)
Serum	~	X	X	X	X	(Chababa et al. 2016)
Serum	↓	↓	↑	X	X	(Al-Hilli and Hasan 2015)
Serum	~	↑	X	X	X	(Rafeeinia et al. 2014)
Serum	X	X	↑	X	X	(Wahab et al. 2019)
Serum	X	X	~	X	X	(Ahmed et al. 2023)
Serum	↓	X	↓	↓	X	(Uddin et al. 2023)
Serum	↓	↑	↑	X	X	(Mobeen Rana et al. 2022)
Serum	X	X	↑	X	X	(Jana et al. 2018)
Serum	X	X	↑	X	X	(ElShahat et al. 2020)
Serum	X	X	X	↓	↓	(Vanaja et al. 2021)
Serum	X	X	X	↓	↓	(Wadhwani et al. 2023)
Serum	~	X	X	↓	~	(Vafaei et al. 2015)
Serum	↑	↓	X	↓	↓	(Maduray et al. 2017)
Hair	↑	~	~	~	~	(Maduray et al. 2017)
Serum	X	X	X	↓	↓	(Eslamzadeh et al. 2023)
Serum	X	X	X	↓	↓	(Adhipurnawan Winarno et al. 2021)
Diet	X	X	X	↓	↓	(Kinshella et al. 2022)
Serum	X	↑	X	X	X	(Song et al. 2017)
Urine	↓	X	X	↑	X	(Tabandeh et al. 2018)
Urine	↓	↓	X	↓	↓	(Yu et al. 2019)
Plasma	↑	↑	X	X	X	(Salima et al. 2022)
Plasma	↓	X	X	X	X	(Ilechukwu et al. 2021)

Data are presented as: (↑) increase significant; (↓) decrease significant; (~) no differences; (X) not analyzed

CONCLUSIONS

The available studies indicate that the role of minerals in PE development is complex and depends on health, nutritional, and environmental factors. The relationship between trace elements and PE is influenced by geographic location, race, disease stage, gestational age, maternal age, diet, and element ratios. It appears that adequate mineral intake and optimal maternal nutritional status may play a crucial role in reducing PE risk. Recent studies provide further support for this hypothesis.

Author contributions

R.C. – methodology, visualization, writing – original draft preparation, writing – review and editing, J.S. – conceptualization, funding acquisition, investigation, supervision, writing – review and editing.

Conflicts of interest

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

REFERENCES

Adhipurnawan Winarno, G.N., Pribadi, A., Maruli, H.J., Achmad, E.D., Anwar, R., Mose, J.C., Nisa, A.S., and Trianasari, N. (2021) 'Ratio of serum calcium to magnesium levels on pregnancy with and without preeclampsia', *Medical Science Monitor*, 27, available: https://doi.org/10.12659/MSM.932032

Ahmed, Y.I.B., Yagoub, H.S., Hassan, M.A., Adam, I., and Hamdan, H.Z. (2023) 'Maternal serum iron status, hepcidin and interleukin-6 levels in women with preeclampsia', *Frontiers in Physiology*, 14, available: https://doi.org/10.3389/fphys.2023.1049994

Al-Hilli, N., Hasan, A. (2015) 'The Association of Serum Iron, Zinc, and Copper Levels with Preeclampsia', available: http://www.medicaljb.com

Al-Jameil, N., Tabassum, H., Ali, M.N., Qadeer, M.A., Khan, F.A., and Al-Rashed, M. (2017) 'Correlation between serum trace elements and risk of preeclampsia: A case controlled study in Riyadh, Saudi Arabia', *Saudi Journal of Biological Sciences*, 24(6), 1142-1148, available: https://doi.org/10.1016/j.sjbs.2015.02.009

Aouache, R., Biquard, L., Vaiman, D., and Miralles, F. (2018) 'Oxidative stress in preeclampsia and placental diseases', *International Journal of Molecular Sciences*, available: https://doi.org/10.3390/ijms19051496

De Araújo, C.A.L., De Sousa Oliveira, L., De Gusmão, I.M.B., Guimarães, A., Ribeiro, M., and Alves, J.G.B. (2020) 'Magnesium supplementation and preeclampsia in low-income pregnant women - A randomized double-blind clinical trial', *BMC Pregnancy and Childbirth*, 20(1), available: https://doi.org/10.1186/s12884-020-02877-0

Bandyopadhyay, A., Ahamed, F., Palepu, S., Ghosh, T., and Yadav, V. (2022) 'Association of serum hepcidin with preeclampsia: A systematic review and meta-analysis', *Cureus*, available: https://doi.org/10.7759/cureus.26699

Chababa, L., Mukosha, M., Sijumbila, G., Vwalika, B., Author, C., and Chababa, L. (2016) Relationship between Serum Zinc Levels.

Chawla, N., Shah, H., Huynh, K., Braun, A., Wollocko, H., and Shah, N.C. (2023) 'The role of platelet-activating factor and magnesium in obstetrics and gynecology: Is there crosstalk between pre-eclampsia, clinical hypertension, and HELLP syndrome?', *Biomedicines*, available: https://doi.org/10.3390/biomedicines11051343

Chen, W.Y., Sun, S.F. (2023) 'Clinical efficacy of low-dose aspirin combined with calcium in preventing preeclampsia: A systematic review and meta-analysis', *Medicine (United States)*, available: https://doi.org/10.1097/MD.0000000000034620

Chen, Y., Ou, Q.X., Chen, Y., Zhu, Q.L., Tan, M.H., Zhang, M.M., Wu, S.Z., and Xu, H.Y. (2022) 'Association between trace elements and preeclampsia: A retrospective cohort study', *Journal of Trace Elements in Medicine and Biology*, 72, available: https://doi.org/10.1016/j.jtemb.2022.126971

Chiarello, D.I., Marín, R., Proverbio, F., Coronado, P., Toledo, F., Salsoso, R., Gutiérrez, J., and Sobrevia, L. (2018) 'Mechanisms of the effect of magnesium salts in preeclampsia', *Placenta*, 69, 134-139, available: https://doi.org/10.1016/j.placenta.2018.04.011

Detlefs, S.E., Jochum, M.D., Salmanian, B., McKinney, J.R., and Aagaard, K.M. (2022) 'The impact of response to iron therapy on maternal and neonatal outcomes among pregnant women with anemia', *American Journal of Obstetrics and Gynecology MFM*, 4(2), available: https://doi.org/10.1016/j.ajogmf.2022.100569

Duvan, C.I., Simavli, S., Keskin, E.A., Onaran, Y., Turhan, N.O., and Koca, C. (2015) 'Is the level of maternal serum prohepcidin associated with preeclampsia?', *Hypertension in Pregnancy*, 34(2), 145-152, available: https://doi.org/10.3109/10641955.2014.988350

Dwarkanath, P., Muhihi, A., Sudfeld, C.R., Wylie, B.J., Wang, M., Perumal, N., Thomas, T., Kinyogoli, S.M., Bakari, M., Fernandez, R., Raj, J.-M., Swai, N.O., Buggi, N., Shobha, R., Sando, M.M., Duggan, C.P., Masanja, H.M., Kurpad, A. V., Pembe, A.B., and Fawzi, W.W. (2024) 'Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy', *New England Journal of Medicine*, 390(2), 143-153, available: https://doi.org/10.1056/nejmoa2307212

Elmugabil, A., Hamdan, H.Z., Elsheikh, A.E., Rayis, D.A., Adam, I., and Gasim, G.I. (2016) 'Serum calcium, magnesium, zinc and copper levels in sudanese women with preeclampsia', *PLoS ONE*, 11(12), available: https://doi.org/10.1371/journal.pone.0167495

ElShahat, A.M., Ibrahim, Z.M., Kishk, E.A., Basuony, R.A., and Taha, O.T. (2020) 'Increased serum ferritin levels in women with preeclampsia', *Journal of Clinical Obstetrics and Gynecology Research*, 1(1), available: https://doi.org/10.52338/directive.2020.1001

Enebe, J.T., Dim, C.C., Ugwu, E.O., Enebe, N.O., Meka, I.A., Obioha, K.C., Eleje, G.U., and Nwagha, U.I. (2020) 'Serum antioxidant micronutrient levels in pre-eclamptic pregnant women in Enugu, south-East Nigeria: A comparative cross-sectional analytical study', *BMC Pregnancy and Childbirth*, 20(1), available: https://doi.org/10.1186/s12884-020-03081-w

Eslamzadeh, A., Kashani, S.M. amin, Asadi, N., Bazmi, S., Rezaei, S., Karimimoghadam, Z., Nowrouzi-Sohrabi, P., and Tabrizi, R. (2023) 'Serum calcium and magnesium levels in women presenting with pre-eclampsia: A systematic review and meta-analysis based on observational studies: serum calcium and magnesium levels in women with pre-eclampsia', *Galen Medical Journal*, 12, available: https://doi.org/10.31661/gmj.v12i.3151

Fondjo, L.A., Sarpong, D., Owiredu, W.K.B.A., Opoku, S., Adu-Bonsaffoh, K., and Teviu, E. (2023) 'Effect of magnesium sulfate treatment on mediators of endothelial dysfunction and electrolytes in mild and severe preeclampsia: A case-control study', *Health Science Reports*, 6(5), available: https://doi.org/10.1002/hsr2.1232

Gatford, K.L., Andraweera, P.H., Roberts, C.T., and Care, A.S. (2020) 'Animal Models of Preeclampsia: Causes, Consequences, and Interventions', *Hypertension*, available: https://doi.org/10.1161/HYPERTENSIONAHA.119.14598

Grzeszczak, K., Łanocha-Arendarczyk, N., Malinowski, W., Ziętek, P., and Kosik-Bogacka, D. (2023) 'Oxidative Stress in Pregnancy', *Biomolecules*, available: https://doi.org/10.3390/biom13121768

Guan, D.-X., Gorini, F., Ogechi Bede-Ojimadu, O., and Zheng, Y. (2022) 'Maternal serum zinc level is associated with risk of preeclampsia: A systematic review and meta-analysis', available: https://www.crd.york.ac.uk/prospero/

Gul, A.Z., Atakul, N., Selek, S., Atamer, Y., Sarıkaya, U., Yıldız, T., and Demirel, M. (2022) 'Maternal serum levels of zinc, copper, and thiols in preeclampsia patients: a case-control study', *Biological Trace Element Research*, 200(2), 464-472, available: https://doi.org/10.1007/s12011-021-02660-y

Gzhegotskyi, M., Sukhodolska, N. (2019) 'Lead, cadmium, copper and zinc content in women's blood during the third trimester of uncomplicated and complicated gestation', *Experimental and Clinical Physiology and Biochemistry*, 2019(3), 5-11, available: https://doi.org/10.25040/ecpb2019.03.005

Hansson, S.R., Nääv, Å., and Erlandsson, L. (2015) 'Oxidative stress in preeclampsia and the role of free fetal hemoglobin', *Frontiers in Physiology*, available: https://doi.org/10.3389/fphys.2014.00516

Hao, Y., Yu, W., Wu, J., Yue, Y., Wu, Y., Huang, H., and Wu, W. (2024) 'Reduction in placental metal and metalloid in preeclampsia: A case – control study', *Nutrients*, 16(6), available: https://doi.org/10.3390/nu16060769

He, J., Pu, Y., Du, Y., Liu, H., Wang, X., He, S., Ai, S., and Dang, Y. (2024) 'An exploratory study on the association of multiple metals in serum with preeclampsia', *Frontiers in Public Health*, 12, available: https://doi.org/10.3389/fpubh.2024.1336188

Hofmeyr, G.J., Lawrie, T.A., Atallah, Á.N., and Torloni, M.R. (2018) 'Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems', *Cochrane Database of Systematic Reviews*, available: https://doi.org/10.1002/14651858.CD001059.pub5

Huai, J., Lin, L., Juan, J., Chen, J., Li, B., Zhu, Y., Yu, M., and Yang, H. (2021) 'Preventive effect of aspirin on preeclampsia in high-risk pregnant women with stage 1 hypertension', *Journal of Clinical Hypertension*, 23(5), 1060-1067, available: https://doi.org/10.1111/jch.14149

Ilechukwu, O., Onuegbu, J., Olisekodiaka, J., and Ezeani, C. (2021) 'Evaluation of plasma selenium, zinc and malondialdehyde levels in newly diagnosed preeclamptic women at a teaching hospital', *The Ulutas Medical Journal*, 7(2), 86, available: https://doi.org/10.5455/umj.20210422011242

Jaiswal, V., Joshi, A., Jha, M., Hanif, M., Arora, A., Gupta, S., Shah, M., Deb, N., Peng Ang, S., Aujla, S., Patel, N., Habib, A., and Ghadvaje, G. (2024) 'Association between calcium supplementation and gestational hypertension, and preeclampsia: A Meta-analysis of 26 randomized controlled trials', *Current Problems in Cardiology*, available: https://doi.org/10.1016/j.cpcardiol.2023.102217

Jana, S., Mukhopadhyay, M., Nath Bandyopadhyay, S., Jana, T., Pramanik, S., Sangeeta, D., and Pramanik, J.((2018) 'Preeclampsia is associated with elevated iron and ferritin in third trimester of pregnancy: A cross sectional observational study from a tertiary center at kolkata', *Journal of Medical Science and Clinical Research,* available: https://doi.org/10.18535/jmscr/v6i2.184

Keshavarz, P., Nobakht M. Gh, B.F., Mirhafez, S.R., Nematy, M., Azimi-Nezhad, M., Afin, S.A., Esmaily, H., Pourali, L., Hakak, A.M., Soukhtanloo, M., Mirteimouri, M., Ghomian, N., and Ferns, G.A. (2017) 'Alterations in lipid profile, zinc and copper levels and superoxide dismutase activities in normal pregnancy and preeclampsia', *American Journal of the Medical Sciences*, 353(6), 552-558, available: https://doi.org/10.1016/j.amjms.2017.03.022

Khaing, W., Vallibhakara, S.A.O., Tantrakul, V., Vallibhakara, O., Rattanasiri, S., McEvoy, M., Attia, J., and Thakkinstian, A. (2017) 'Calcium and vitamin D supplementation for preven-

tion of preeclampsia: A systematic review and network meta-analysis', *Nutrients*, available: https://doi.org/10.3390/nu9101141

Kinshella, M.L.W., Omar, S., Scherbinsky, K., Vidler, M., Magee, L.A., von Dadelszen, P., Moore, S.E., Elango, R., Poston, L., Mistry, H.D., Volvert, M.L., Lopez, C.E., Moore, S., Tribe, R., Shennan, A., Salisbury, T., Chappell, L., Craik, R., Temmerman, M., Etyang, A.K., Wanyonyi, S., Omuse, G., Okiro, P., Mwashigadi, G., Sevene, E., Boene, H., Tchavana, C., Macete, E., Carillho, C., Quimice, L., Maculuve, S., Russell, D., Baratt, B., Lawn, J., Blencowe, H., Filippi, V., Silver, M., Makanga, P.T., Makacha, L., Dube, Y., Nyapwere, N., Mlambo, R., D'Alessandro, U., Roca, A., Martinez-Alvarez, M., Jah, H., Diallo, B., Sesay, A.K., Touray, F., Sillah, A., Noble, A., Papageorghiou, A., Cartwright, J., Whitley, G., Krishna, S., Townsend, R., Khalil, A., Singer, J., Li, J., Bone, J., Pickerill, K., Sandhu, A., Domena, T., and Stones, W. (2022) 'Maternal nutritional risk factors for pre-eclampsia incidence: findings from a narrative scoping review', *Reproductive Health*, available: https://doi.org/10.1186/s12978-022-01485-9

Kurlak, L.O., Scaife, P.J., Briggs, L. V., Broughton Pipkin, F., Gardner, D.S., and Mistry, H.D. (2023) 'Alterations in antioxidant micronutrient concentrations in placental tissue, maternal blood and urine and the fetal circulation in pre-eclampsia', *International Journal of Molecular Sciences*, 24(4), available: https://doi.org/10.3390/ijms24043579

Lang, Q., Wei, J., Tian, M., Wei, S., Yu, X., Zhao, C., Zhang, J., and Huang, B. (2022) 'Attenuated effect of zinc gluconate on oxidative stress, inflammation, and angiogenic imbalance in pre-eclampsia rats', *Life Sciences*, 310, available: https://doi.org/10.1016/j.lfs.2022.121055

Lewandowska, M., Sajdak, S., Marciniak, W., and Lubiński, J. (2019) 'First trimester serum copper or zinc levels, and risk of pregnancy-induced hypertension', *Nutrients*, 11(10), available: https://doi.org/10.3390/nu11102479

Li, P., Wang, H., Chen, T., Chen, G., Zhou, Z., Ye, S., Lin, D., Fan, D., Guo, X., and Liu, Z. (2024) 'Association between iron status, preeclampsia and gestational hypertension: a bidirectional two-sample Mendelian randomization study', *Journal of Trace Elements in Medicine and Biology*, 127528, available: https://doi.org/10.1016/j.jtemb.2024.127528

Liu, Y., Wang, X., Fu, W., Cao, Y., Dou, W., Duan, D., Zhao, X., Ma, S., and Lyu, Q. (2023) 'The association between dietary mineral intake and the risk of preeclampsia in Chinese pregnant women: a matched case – control study', *Scientific Reports*, 13(1), available: https://doi.org/10.1038/s41598-023-43481-4

Ma, Y., Shen, X., and Zhang, D. (2015) 'The relationship between serum zinc level and preeclampsia: A meta-analysis', *Nutrients*, available: https://doi.org/10.3390/nu7095366

Ma'ayeh, M. and Costantine, M.M. (2020) 'Prevention of preeclampsia', *Seminars in Fetal and Neonatal Medicine*, 25(5), available: https://doi.org/10.1016/j.siny.2020.101123

Maduray, K., Moodley, J., Soobramoney, C., Moodley, R., and Naicker, T. (2017) 'Elemental analysis of serum and hair from pre-eclamptic South African women', *Journal of Trace Elements in Medicine and Biology*, 43, 180-186, available: https://doi.org/10.1016/j.jtemb.2017.03.004

Masoumi, Z., Hansson, L.R., Hansson, E., Ahlm, E., Mezey, E., Erlandsson, L., and Hansson, S.R. (2023) 'Assessing erythroferrone and iron homeostasis in preeclamptic and normotensive pregnancies: A retrospective study', *Placenta*, 133, 10-18, available: https://doi.org/10.1016/j.placenta.2023.01.008

Mobeen Rana, A., Shahzad, M., Iftikhar, B., Ullah, Z., Shaheen, B., and Hussain, S. (2022) 'Serum iron, copper and zinc levels in preeclampsia and normotensive primigravida females', *Pakistan BioMedical Journal*, 276-281, available: https://doi.org/10.54393/pbmj.v5i5.440

Muzyko, E.A., Laschenova, L.I., Tkacheva, G.A., and Perfilova, V.N. (2021) 'Role of trace elements during pregnancy', *Trace Elements in Medicine (Moscow)*, 22(1), 21-31, available: https://doi.org/10.19112/2413-6174-2021-22-1-21-31

Ortega, M.A., Garcia-Puente, L.M., Fraile-Martinez, O., Pekarek, T., García-Montero, C.,

Bujan, J., Pekarek, L., Barrena-Blázquez, S., Gragera, R., Rodríguez-Rojo, I.C., Rodríguez--Benitez, P., López-González, L., Díaz-Pedrero, R., Álvarez-Mon, M., García-Honduvilla, N., De León-Luis, J.A., Bravo, C., and Saez, M.A. (2024) 'Oxidative stress, lipid peroxidation and ferroptosis are major pathophysiological signatures in the placental tissue of women with late-onset preeclampsia', *Antioxidants*, 13(5), available: https://doi.org/10.3390/antiox13050591

Petry, C.J. (2022) 'Iron supplementation in pregnancy and risk of gestational diabetes: A narrative review', *Nutrients*, available: https://doi.org/10.3390/nu14224791

Pyla, K.K., Ilaka, V.D., Penmetsa, P., Kiran Kumar, P.V.S.N., and Yerramilli, S.P. (2024) 'Exploring the complex interplay of trace elements and their association with the risk of development of pre-eclampsia in pregnancy: a case-control', *Biological Trace Element Research*, 202(10), 4410-4417, available: https://doi.org/10.1007/s12011-023-04030-2

Rafeeinia, A., Tabandeh, A., Khajeniazi, S., and Marjani, A.J. (2014) Send Orders for Reprints to Reprints@benthamscience.net serum copper, zinc and lipid peroxidation in pregnant women with preeclampsia in Gorgan, The Open Biochemistry Journal.

Rana, S., Lemoine, E., Granger, J., and Karumanchi, S.A. (2019) 'Preeclampsia: Pathophysiology, Challenges, and Perspectives', *Circulation Research*, 124(7), 1094-1112, available: https://doi.org/10.1161/CIRCRESAHA.118.313276

Sak, S., Barut, M., Çelik, H., Incebiyik, A., Ağaçayak, E., Uyanikoglu, H., Kirmit, A., and Sak, M. (2020) 'Copper and ceruloplasmin levels are closely related to the severity of preeclampsia', *Journal of Maternal-Fetal and Neonatal Medicine*, 33(1), 96-102, available: https://doi.org/10.1080/14767058.2018.1487934

Salima, S., Daundy, K.H., Mose, J.C., Pramatirta, A.Y., Suardi, D., and Pusianawati, D. (2022) 'Comparison levels of copper, zinc, and Cu/Zn ratio of in pre-eclampsia and normal pregnancy', *Open Access Macedonian Journal of Medical Sciences*, 10(B), 2392-2398, available: https://doi.org/10.3889/oamjms.2022.10891

Shaji Geetha, N., Bobby, Z., Dorairajan, G., and Jacob, S.E. (2022) 'Increased hepcidin levels in preeclampsia: a protective mechanism against iron overload mediated oxidative stress?', *Journal of Maternal-Fetal and Neonatal Medicine*, 35(4), 636-641, available: https://doi.org/10.1080/14767058.2020.1730322

Shen PJ, Gong B, Xu FY, and Luo Y (2015) 'Four trace elements in pregnant women and their relationships with adverse pregnancy outcomes', *European Review for Medical and Pharmacological Sciences*, 19, 4690-4697

Song, X., Li, B., Li, Z., Wang, J., and Zhang, D. (2017) 'High serum copper level is associated with an increased risk of preeclampsia in Asians: A meta-analysis', *Nutrition Research*, available: https://doi.org/10.1016/j.nutres.2017.01.004

Tabandeh, A., Eshghinia, S., Joshaghani, H.R., Azarian, M., and Besharat, S. (2018) 'Serum and urinary levels of micronutrients in preeclamptic and healthy pregnant women: A case-control study', Original Research Article JCBR.

Tang, R., Tang, I.C., Henry, A., and Welsh, A. (2015) 'Limited evidence for calcium supplementation in preeclampsia prevention: A meta-analysis and systematic review', *Hypertension in Pregnancy*, 34(2), 181-203, available: https://doi.org/10.3109/10641955.2014.988353

Tesfa, E., Nibret, E., and Munshea, A. (2011) 'Maternal serum zinc level and pre-eclampsia risk in African women: a systematic review and meta-analysis', *Biological Trace Element Research*, 199, 4564-4571, available: https://doi.org/10.1007/s12011-021-02611-7/Published

Uddin, S.M.N., Haque, M., Barek, M.A., Chowdhury, M.N.U., Das, A., Uddin, M.G., and Islam, M.S. (2023) 'Analysis of serum calcium, sodium, potassium, zinc, and iron in patients with pre-eclampsia in Bangladesh: A case – control study', *Health Science Reports*, 6(2), available: https://doi.org/10.1002/hsr2.1097

Vafaei, H., Dalili, M., and Hashemi, A. (2015) 'Serum concentration of calcium, magnesium and zinc in normotensive versus preeclampsia pregnant women: A descriptive study in women of kerman province of Iran', *Iran J Reprod Med.,* 2015 Jan, 13(1), 23-26.

Vanaja D, Chikkagowdra, S., and Banu, R. (2021) 'Association of serum calcium and magnesium levels in pre-eclampsia: A case control study', *International Journal of Clinical Obstetrics and Gynaecology*, 5(1), 77-79, available: https://doi.org/10.33545/gynae.2021.v5.i1b.795

Vásquez-Procopio, J., Torres-Torres, J., Rojas-Lima, E., Espino-y-Sosa, S., Solis-Paredes, J.M., Sánchez-Martínez, M., Tolentino-Dolores, M.C., Perichart-Perera, O., Missirlis, F., and Estrada-Gutierrez, G. (2024) 'Maternal metal ion status along pregnancy and perinatal outcomes in a group of Mexican women', *International Journal of Molecular Sciences*, 25(23), available: https://doi.org/10.3390/ijms252313206

Venkata Surekha, M., Singh, S., Sarada, K., Sailaja, G., Balakrishna, N., Srinivas, M., and Uday Kumar, P. (2019) 'Study on the effect of severity of maternal iron deficiency anemia on regulators of angiogenesis in placenta', *Fetal and Pediatric Pathology*, 38(5), 361-375, available: https://doi.org/10.1080/15513815.2019.1587120

Wadhwani, N., Dangat, K., Randhir, K., Poddar, A., Joshi, P., Pisal, H., Kadam, V., Bakshi, R., Chandhiok, N., Lalwani, S., Mehendale, S., Wagh, G., Gupte, S., Sachdev, H.S., Fall, C., and Joshi, S. (2023) 'Longitudinal assessment of calcium and magnesium levels in women with preeclampsia', *Biological Trace Element Research*, 201(7), 3245-3255, available: https://doi.org/10.1007/s12011-022-03440-y

Wahab, Dr.A.T.A. Al, Jasim, R.N., and Fridawi, Dr.A.A.M. (2019) 'Elevated serum iron levels in pregnant women with preeclampsia', *International Journal of Clinical Obstetrics and Gynaecology*, 3(4), 06-08, available: https://doi.org/10.33545/gynae.2019.v3.i4a.282

Woo Kinshella, M.L., Sarr, C., Sandhu, A., Bone, J.N., Vidler, M., Moore, S.E., Elango, R., Cormick, G., Belizan, J.M., Hofmeyr, G.J., Magee, L.A., and von Dadelszen, P. (2022) 'Calcium for pre-eclampsia prevention: A systematic review and network meta-analysis to guide personalised antenatal care', *BJOG: An International Journal of Obstetrics and Gynaecology*, available: https://doi.org/10.1111/1471-0528.17222

Xing, B., Dai, X., Gao, G., Liu, L., and Zhang, Y. (2024) 'Magnesium sulfate improves blood flow of uterine, umbilical, and fetal middle cerebral arteries in women with severe preeclampsia at 30-34 gestational weeks', *Hypertension in Pregnancy*, 43(1), 2404459, available: https://doi.org/10.1080/10641955.2024.2404459

Yang, X., Wei, J., Sun, L., Zhong, Q., Zhai, X., Chen, Y., Luo, S., Tang, C., and Wang, L. (2024) 'Causal relationship between iron status and preeclampsia-eclampsia: a Mendelian randomization analysis', *Clinical and Experimental Hypertension*, 46(1), available: https://doi.org/10.1080/10641963.2024.2321148

Yu, Q., Sun, X., Zhao, J., Zhao, L., Chen, Y., Fan, L., Li, Z., Sun, Y., Wang, M., and Wang, F. (2019) 'The effects of zinc deficiency on homeostasis of twelve minerals and trace elements in the serum, feces, urine and liver of rats', *Nutrition and Metabolism*, 16(1), available: https://doi.org/10.1186/s12986-019-0395-y

Zhang, Y., Lu, Y., and Jin, L. (2022) 'Iron Metabolism and Ferroptosis in Physiological and Pathological Pregnancy', *International Journal of Molecular Sciences*, available: https://doi.org/10.3390/ijms23169395

Zhong, Z., Yang, Q., Sun, T., and Wang, Q. (2022) 'A global perspective of correlation between maternal copper levels and preeclampsia in the 21st century: A systematic review and meta-analysis', *Frontiers in Public Health*, available: https://doi.org/10.3389/fpubh.2022.924103

Zhu, Q., Zhang, L., Chen, X., Zhou, J., Liu, J., and Chen, J. (2016) 'Association between zinc level and the risk of preeclampsia: a meta-analysis', *Archives of Gynecology and Obstetrics*, 293(2), 377-382, available: https://doi.org/10.1007/s00404-015-3883-y

Zhu, X., Jiang, R., Ying, X., Li, Z., and Jiang, P. (2022) 'The role of ferritin and iron dextran in exacerbating preeclampsia in an L-NAME-treated rat model', *Annals of Translational Medicine*, 10(16), 889-889, available: https://doi.org/10.21037/atm-22-3675