




DOI: 10.38136/jgon.1117596

Is there any connection between zinc deficiency and adverse obstetric outcomes in pregnancy?**Gebelikteki çinko eksikliği ile kötü obstetrik sonuçlar arasında bir bağlantı var mı?**UĞUR DEĞER¹GÖKÇE TURAN²NURULLAH PEKER³ Orcid ID:0000-0002-8451-4214 Orcid ID:0000-0002-2443-1927 Orcid ID:0000-0002-3285-9990¹ Department of Obstetrics and Gynecology, Gelişim University, İstanbul, Turkey² Department of Obstetrics and Gynecology, Gazi University, Faculty of Medicine, Ankara, Turkey³ Department of Obstetrics and Gynecology, Dicle University, Faculty of Medicine, Diyarbakır, Turkey**ÖZ**

Amaç: Bu çalışmanın amacı gebelikteki çinko eksikliğinin maternal ve fetal sonuçları üzerindeki etkisini araştırmaktır.

Gereç ve Yöntemler: Bu çalışma Ocak 2020 ile Aralık 2020 tarihleri arasında ikinci basamak bir hastanede yapıldı. Tüm hastaların demografik verileri, doğum sırasındaki çinko, hemoglobin (Hb), hematokrit (Hct) düzeyleri, oligohidramnios, preterm doğum, preeklampsi, preterm prematür membran rüptürü (PPROM), intrauterin gelişme geriliği (IUGR) gibi kötü gebelik sonuçları kaydedildi. Maternal serum çinko değeri <56 µg/dL çinko eksikliği olarak kabul edilirken, maternal serum çinko düzeyi ≥56 µg/dL normal olarak kabul edildi. Çinko eksikliği olan grup ile çinko düzeyi yeterli olan grubun, maternal ve neonatal sonuçları karşılaştırıldı.

Bulgular: Bu hastaların 36'sında (%35,2) çinko eksikliği bulundu. Çinko seviyesi yeterli olan grubun ortalama çinko düzeyi 74 µg/dL (56-120), çinko düzeyi eksik olan grubun ortalama çinko düzeyi 50 µg/dL (36-55) (p:0.000) idi. Çinko eksikliği olan grupta PPRM ve preterm doğum oranları anlamlı olarak daha fazla bulundu (sırasıyla p=0,031, p=0,039). Çinko eksikliği olan grubun 1.ve 5. dakika APGAR skorları ise anlamlı olarak daha düşüktü (sırasıyla p=0,002 ve p=0,001). Çinko eksikliği PPRM riskini 1,7 kat, preterm doğumu 0,479 kat anlamlı olarak artırıyordu (sırasıyla; OR=1.713, %95 CI=0.662-0.824, p=0.043; OR=0.479, %95 CI=0.209-0.095, p=0.041).

Sonuç: Özetle, bu çalışma gebelerdeki çinko seviyesinin maternal ve neonatal sonuçlarını araştırdı ve çinko eksikliği olan gebelerde preterm doğum ve PPRM görülme oranı daha fazla idi. Sonuç olarak, gebelere özellikle gebeliğin üçüncü trimesterinde verilen çinko takviyesi çinko eksikliğine bağlı olumsuz perinatal sonuçları azaltacaktır.

Anahtar kelimeler: Maternal serum, Çinko, Preterm doğum, Gebelik

ABSTRACT

Aim: The present study aims to examine the effects of zinc deficiency on maternal and fetal outcomes during pregnancy.

Materials and methods: The study was carried out in a secondary care hospital between 2020 January and 2020 December. Demographic data of all patients, zinc, hemoglobin (Hb), hematocrit (Hct) levels at birth and adverse pregnancy outcomes such as oligohydramnios, preterm delivery, preeclampsia, preterm premature rupture of membranes (PPROM), intrauterine growth retardation (IUGR) were recorded. Maternal serum zinc levels of <56 µg/dL were considered deficient, whereas maternal serum zinc levels of ≥56 µg/dL were considered normal. Maternal and neonatal outcomes of the zinc-deficient group and the zinc-sufficient group were compared.

Results: Zinc deficiency was found in 36(35.2%) of these patients. The group with sufficient zinc levels had a mean zinc level of 74 µg/dL (56-120), while the group with zinc deficiency had a mean zinc level of 50 µg/dL (36-55) (p:0.000). The rates of PPRM and preterm delivery were significantly higher in the zinc-deficient group (p=0.03, p=0.039, respectively). The zinc-deficient group had significantly lower 1st and 5th minute APGAR scores (p=0.002, p=0.001, respectively). Zinc deficiency significantly increased the risk of PPRM by 1.7 times and preterm birth by 0.479 times (OR=1.713, 95% CI=0.662-0.824, p=0.043; OR=0.479, 95% CI=0.209-0.095, p=0.041, respectively).

Conclusion: The results of this research indicate that pregnant women who were zinc deficient had a higher rate of preterm delivery and PPRM. In conclusion, zinc supplements given to pregnant women, particularly during the third trimester of pregnancy, will reduce the negative perinatal outcomes associated with zinc deficiency.

Keywords: Maternal serum, Zinc, Preterm birth, Pregnancy

Sorumlu Yazar/ Corresponding Author: Uğur Değer

Adres: Assistant Professor, Department of Obstetrics and Gynecology, Gelişim University, İstanbul, Turkey

E-mail: ugurdeger21@hotmail.com

Başvuru tarihi : 16.05.2022

Kabul tarihi : 04.08.2022

INTRODUCTION

Zinc is a structural component required for cell growth, differentiation, and development, and plays an important role in normal growth and development as a cofactor of several enzymes in human metabolism (1). Furthermore, zinc has a role in vital functions such as reproduction and embryogenesis, nucleic acid synthesis, and gene expression. Because of these effects, it has been shown to be extremely important during periods of increased cell production, such as infancy, childhood, adolescence, and pregnancy (2). The zinc requirement during pregnancy, particularly in the third trimester, is approximately twice that of non-pregnant women (3). It has been demonstrated that pregnant women in developing countries consume diets with low mineral and vitamin density, indicating that zinc deficiency is a major issue in both developed and developing countries (4,5).

Since zinc plays an important role in growth and development, low zinc intake during pregnancy may result in poor pregnancy outcomes such as increased maternal mortality, low birth weight fetus, prolonged delivery, spontaneous abortion, and prematurity (6). It has been discovered that low zinc levels during pregnancy, in particular, have a negative impact on late fetal development (6).

While it is still unclear whether maternal serum zinc concentration during pregnancy is associated with preterm birth, a recent meta-analysis found that low zinc levels during pregnancy may have some association with high perinatal mortality (7). Furthermore, it was discovered that maternal zinc supplementation reduced preterm births by 14% (7). A randomized controlled trial, on the other hand, discovered that maternal zinc supplementation had no effect on gestational age (8).

The aim of the present study is to look into the effects of zinc deficiency on maternal and fetal outcomes during pregnancy.

MATERIALS AND METHODS

This descriptive-cross-sectional study was carried out in a secondary care hospital between 2020 January and 2020 December. The study included 102 patients who had their pregnancy follow-ups and deliveries at our hospital. The study was conducted retrospectively, and approval was obtained from the ethics committee (ethics committee number: 09.05.2022/003). All patients were asked to sign an informed consent form. All procedures were carried out in accordance with the institutional

and/or national research committee ethical standards, as well as the Helsinki Declaration of 1964 and its subsequent amendments or comparable ethical standards.

The study excluded pregnant women with a history of low birth weight, multiple pregnancies of twins or more, a history of pre-eclampsia and eclampsia, known uterine cervical abnormalities, antenatal bleeding in their current pregnancy, and known maternal disease.

Demographic data of all patients, zinc, hemoglobin (Hb), hematocrit (Hct) levels at birth and adverse pregnancy outcomes such as oligohydramnios, preterm delivery, preeclampsia, preterm premature rupture of membranes (PPROM), intrauterine growth retardation (IUGR) were recorded. Anthropometric measurements of babies, including birth weight, were taken within one hour of birth, and the Apgar score was measured in the delivery room by an experienced nurse. The height and weight as well as the first and fifth minute APGAR scores of the newborns were all recorded. Maternal serum zinc levels of <56 g/dL were considered deficient, while maternal serum zinc levels of ≥ 56 g/dL were considered normal (9). The zinc-deficient group was designated as the study group, while the zinc-sufficient group was designated as the control group, and demographic data, maternal and neonatal outcomes were compared between the two groups.

IUGR was defined as a birth weight that was less than the 10th percentile of the birth weight-for-gestational age reference curve. PPRM was defined as a disruption of membrane integrity before 37 weeks of gestation. Preterm birth (late preterm birth) was defined as a birth occurring between 34 and 37 weeks of gestation. Preeclampsia was defined as systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg in two measurements taken at least four hours apart, as well as proteinuria of ≥ 300 mg in 24-hour urine or a urine Protein/Creatinine Ratio of ≥ 0.3 or 1+ proteinuria as measured with a Urine Stick after the 20th gestational week in a pregnant woman who previously had normal blood pressure. Oligohydramnios was defined as amniotic fluid with a depth of less than 2 cm in the deepest vertical pocket and less than 5 cm in the vertical measurement of 4 quadrants.

Blood was drawn from patients who had been hospitalized after giving birth and centrifuged at 3000 rpm for 15 minutes to determine serum zinc levels. Plasma was isolated and stored at -20°C . All samples were analyzed after collection. The concentration of zinc in the blood was determined using flame atomic absorption spectroscopy (AAS) on a Perkin-Elmer 1100B

device.

Statistical Analysis

Continuous variables were represented by the median (minimum-maximum), while categorical data were represented by numbers and percentages. The Kolmogorov-Smirnov Goodness of Fit Test was used to analyze the normality of continuous variables. Because the continuous variables did not fit a normal distribution, the Mann-Whitney U test was used in the comparisons between the two groups. Logistic Regression Analysis was used to determine whether low zinc was a risk factor for certain conditions (Binary) (Enter method). To compare categorical data, the Chi-square Test (or, if necessary, the Fisher's Exact Test) was used. The IBM SPSS Package Program version 22.0 was used for the analyses (IBM Corporation, Armonk, NY, USA). Significance level was taken as $p < 0.05$.

The study initially included 132 patients from 2020 January to 2020 December. Following the exclusion of patients who did not meet the inclusion criteria, 102 patients were included within the study. While 36 (35.2%) of these patients were zinc deficient, 66 (64.7%) had adequate zinc levels. Table-1 shows the demographic information for the patients.

Table 1. Comparison of selected maternal and neonatal characteristics of the groups

		Deficiency(<56), (n=36)	Sufficiency(\geq 56), (n=66)	<i>p</i>
RESULTS				
<i>Maternal characteristics</i>				
Age (year) ***		30 (23-42)	30 (22-42)	0.855*
Parity***		0 (0-2)	0 (0-6)	0.893*
Abort (n,%)	No	26 (72.2%)	44 (66.7%)	0.658**a
	Yes	10 (27.8%)	22 (33.3%)	
BMI (kg/m ²) ***		24.9 (19.4-33.5)	24 (20-34.1)	0.385*
Hgb (mg/dl)		11 (9-13)	12 (10-14)	0.288*
Hct (mg/dl)		36 (29-39)	36 (30-42)	0.075*
Zinc (μ g/dL)		50 (36-55)	74 (56-120)	0.000*
Type of childbirth (n,%)	NVD	14 (38.9%)	42 (63.6%)	0.022**a
	CS	22 (61.1%)	24 (36.4%)	
Birth Week ***		37.5 (34-39)	36 (34-39)	0.115*
<i>Neonatal features</i>				
Birth Weight ***		2830 (2170-3844)	2825 (1950-3844)	0.914*
Birth Weight (n,%)	<2500 gr	9 (25.0%)	24 (36.4%)	0.275**a
	2500-4000 gr	27 (75.0%)	42 (63.6%)	
Baby height ***		47 (43-50)	48 (45-52)	0.870*
APGAR 1 ***		8 (7-9)	9 (7-9)	0.002***
APGAR 5 ***		9 (8-10)	10 (9-10)	0.001*
		*Mann Whitney U test ** Chi-square Test (*Fisher's Exact Test) ***[median (min-max)]		

When the demographic data of the groups were compared, there was no statistical difference between the pregnant women with and without zinc deficiency in terms of age, parity, abortion, BMI, Hb, Hct, and mean weeks of delivery. The group with sufficient zinc levels had a mean zinc level of 74 µg/dL (56-120), while the group with zinc deficiency had a mean zinc level of 50 µg/dL (36-55) ($p:0.000$). Table-2 shows the poor pregnancy outcomes of the groups. While there was no difference in rates of preeclampsia, oligohydramnios, or IUGR between the two groups, rates of PPROM and preterm delivery were significantly higher in the zinc-deficient group ($p=0.031$ and $p=0.039$, respectively). When the newborn characteristics of the groups were compared, there was no difference in birth weights or birth heights, but the zinc-deficient group had significantly lower 1st and 5th minute APGAR scores ($p=0.002$ and $p=0.001$, respectively). The researchers used a univariate logistic regression analysis to see if zinc deficiency was a risk factor for preterm birth and PPROM (Table-3)

Table 3. Univariate logistic regression analysis to determine whether zinc deficiency is a risk factor for preterm birth and PPROM.,

	B	SE	OR (Exp β)	95% CI	p
Preterm birth	0.737	0.422	0.479	0.209-0.095	0.041*
PPROM	0.693	0.619	1.713	0.662-0.824	0.043*
* Binary Logistic Regression (Enter method)					
** OR=Odds Ratio, CI=Confidence Interval, SE=Standard error					

Zinc deficiency was found to increase the risk of PPROM by 1.7 times, and this increase was statistically significant (OR=1.713, 95% CI=0.662-0.824, $p=0.043$). Furthermore, zinc deficiency was found to increase preterm birth 0.479 times, which was statistically significant (OR=0.479, 95% CI=0.209-0.095, $p=0.041$) (Table-3).

Table 3. Univariate logistic regression analysis to determine whether zinc deficiency is a risk factor for preterm birth and PPROM.

	B	SE	OR (Exp β)	95% CI	p
Preterm birth	0.737	0.422	0.479	0.209-0.095	0.041*
PPROM	0.693	0.619	1.713	0.662-0.824	0.043*
* Binary Logistic Regression (Enter method)					
** OR=Odds Ratio, CI=Confidence Interval, SE=Standard error					

DISCUSSION

It was discovered in the present study that pregnant women with zinc deficiency had a higher rate of preterm labor and PPROM than those who did not have a zinc deficiency. Additionally, the zinc-deficient group had lower APGAR scores and a significantly increased likelihood of PPROM and preterm delivery.

Many women in low- and middle-income countries are malnourished and are deficient in essential micronutrients. These micronutrients are particularly vital during pregnancy when the energy and nutritional requirements of both the mother and the developing fetus are increased. Because zinc is essential for fetal growth and development, zinc deficiency can result in complications such as preterm or low birth weight delivery.

A 14% reduction in preterm births was found in those who received maternal zinc supplementation, according to several systemic reviews (7,10,11). In another study that looked at the effects of low, medium, and high zinc levels on maternal and neonatal outcomes in pregnant women, the incidence of preterm birth was found to be 7.3%, 6.0%, and 3.1% in the low, medium, and high zinc groups, respectively. Pregnant women with low and moderate zinc levels have a higher risk of preterm birth than those with high zinc levels, according to research (12). Although the mechanism of the relationship between zinc in pregnancy and preterm birth is still unknown, it has been suggested that zinc may have anti-inflammatory properties (7). It has been demonstrated that zinc supplementation reduces the inflammatory effects on wound healing, and that it has an anti-inflammatory effect (13). In other studies, placental inflammation has been linked to preterm birth, and zinc supplementation has been shown to reduce this inflammation (14–16). The present study discovered that mothers with zinc deficiency had a higher rate of preterm birth, and that zinc deficiency increased preterm birth by 0.479 times.

One study that looked at the effects of sociodemographic data on zinc levels, such as maternal age, monthly income, and parity, found that these factors had no effect on zinc levels (9). However, the same study found that zinc levels in pregnant women with BMIs of <18.5 were found to be significantly lower than those with BMIs ranging from 18.5 to 24.9. Another recent study determined that zinc supplementation may be beneficial in controlling metabolic disorders and may be effective in improving poor pregnancy outcomes due to its beneficial effects on glycemic outcomes and lipid profiles in obese patients (17). The demographic data of the patients in the present study differed in no way; however, the present study did have fewer patients than the sample study.

It is debatable whether zinc deficiency during pregnancy raises the risk of low birth weight (LBW) and small for gestational age (SGA) babies. According to some studies in the literature, increased oxidative damage and inflammatory parameters play a role in the pathophysiology of IUGR (17). They also claimed that zinc consumption reduces inflammation and oxidative stress. As a result, zinc consumption has beneficial effects on inflammation and oxidative stress, and zinc supplementation may be beneficial in lowering the risk of IUGR in zinc-deficient women (17). Maternal zinc deficiency during pregnancy has been linked to an increased risk of LBW and SGA delivery in a large population-based birth cohort study involving 3,187

pregnant women (9). A recent meta-analysis of 25 randomized controlled trials involving over 18,000 pregnant women and their infants found that zinc supplementation had no effect on the risk of LBW and SGA infants (18). According to the same meta-analysis, there is insufficient evidence that zinc supplementation during pregnancy improves maternal or neonatal outcomes, but improving pregnant women's overall nutritional status, particularly in low-income areas, should be a top priority. The incidence of IUGR in the present study was comparable between the zinc deficient and zinc sufficient groups. These disparities in research findings may be due to the fact that the methods used to assess zinc deficiency are insufficiently sensitive and specific.

Zinc concentrations in low-income women between 16 and 22 weeks of pregnancy have been found to decrease as the gestational week progresses (4). McMichael et al. (19) reported that maternal serum zinc concentrations had a negative correlation with gestational age at birth, whereas Lao et al. reported that there was no such relationship between zinc plasma level and gestational week (20). The present study included zinc levels in pregnant women between 34 and 37 weeks. However, both maternal and neonatal outcomes reported in the literature could be attributed to zinc levels measured at different trimesters of pregnancy.

When the relationship between zinc deficiency and APGAR scores in newborns is investigated in the literature, there are contradictory findings. While Tmura et al. found no relationship, and no difference was found between zinc levels and APGAR scores in a study evaluating its effect, Mukherjee et al. stated the opposite (21). APGAR levels were significantly higher in the zinc-sufficient group in our study.

The literature is also divided on the relationship between maternal zinc nutrition and pregnancy-induced hypertension and preeclampsia. Even though some researchers claim that maternal plasma zinc concentrations are significantly lower in women with preeclampsia than in those who do not have preeclampsia (22), other authors claim that there is no such relationship (4). The pathophysiology of preeclampsia is linked to increased oxidative stress, according to studies on the relationship between oxidative stress, antioxidant enzymes, and preeclampsia (23,24). In this study, no significant relationship between plasma zinc concentrations and preeclampsia rates was found, which is consistent with the literature. However, the patient population in this study was smaller than in previous studies. Despite this, the belief is that these findings are more

significant because they were obtained during the third trimester of pregnancy.

According to the literature, a decrease in the intake of nutrients such as thiamine, riboflavin, vitamins A, C, and E, copper, and zinc is associated with preterm birth and a higher risk of PPRM (25). Recent evidence reveals that PPRM is linked to biochemical processes such as collagen degradation in the extracellular matrix of the amnion and chorion, as well as apoptosis in fetal membranes and that this problem is caused by nutrient deficiencies that disrupt collagen structure (25). Furthermore, using food or dietary supplements as antioxidants in membrane rupture is a PPRM prevention strategy because trace minerals like zinc play a role in collagen biosynthesis and the stability of the chorionic and amniotic layers. They also protect the body from oxidative stress (26). In accordance with this data, the incidence of PPRM was higher in the zinc-deficient group, with zinc deficiency increasing PPRM by 1.7 times in the present study. Another study found that plasma zinc concentrations in women with PPRM were significantly lower than in controls, lending credence to our findings (27). On the contrary, it was discovered in a study looking into the effect of zinc supplementation in preventing PPRM that zinc sulfate intake had no effect on PPRM prevention (28). Similarly, researchers discovered that zinc supplementation had no effect on the incidence of PPRM in a study of 196 women who were 19-20 weeks pregnant (29).

The current study had several limitations. The first is that the study had a small number of patients and was conducted in a single location. Second, the causes of low maternal serum zinc levels were not investigated. Third, no information was provided about environmental factors such as infection or low socioeconomic status, which could lead to complications such as preterm birth, PPRM, or IUGR. However, we believe that our study will contribute to the literature because many causes and outcomes are still unknown, and there are few studies on this subject in the literature.

CONCLUSION

In summary, this study looked at the maternal and neonatal outcomes of zinc levels in pregnant women, and found that the incidence of preterm delivery and PPRM was higher in pregnant women who were zinc deficient. In conclusion, the belief is that zinc supplements given to pregnant women, particularly during the third trimester of pregnancy, will reduce the negative perinatal outcomes related to zinc deficiency. However, more

multicenter studies with more patients are required to fully understand the maternal and neonatal consequences of zinc deficiency.

REFERENCES

- Hirano T, Murakami M, Fukada T, Nishida K, Yamasaki S, Suzuki T: Roles of Zinc and Zinc Signaling in Immunity: Zinc as an Intracellular Signaling Molecule. *Adv Immunol.* 2008; 97:149–76.
- Osendarp SJM, West CE, Black RE: The need for maternal zinc supplementation in developing countries: An unresolved issue. *J Nutr.* 2003; 133.
- Mistry HD, Kurlak LO, Young SD, Briley AL, Broughton Pipkin F, Baker PN, et al.: Maternal selenium, copper and zinc concentrations in pregnancy associated with small-for-gestational-age infants. *Matern Child Nutr.* 2014; 10:327–34.
- Tamura T, Goldenberg RL, Johnston KE, DuBard M: Maternal plasma zinc concentrations and pregnancy outcome. *Am J Clin Nutr.* 2000; 71:109–13.
- Shah D, Sachdev HPS: Effect of gestational zinc deficiency on pregnancy outcomes: summary of observation studies and zinc supplementation trials. *Br J Nutr.* 2001; 85:S101–08.
- Khadem N, Mohammadzadeh A, Farhat AS, Valaee L, Khajedaluae M, Parizadeh SMR: Relationship between low birth weight neonate and maternal serum zinc concentration. *Iran Red Crescent Med J.* 2012; 14:240–44.
- Ota E, Mori R, Middleton P, Tobe-Gai R, Mahomed K, Miyazaki C, et al.: Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev.* 2015; 2015.
- Caulfield L, Zavaleta N, Figueroa A, Leon Z: Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. *Journal of Nutrition.* 1999;129:1563-68
- Wang H, Hu Y-F, Hao J-H, Chen Y-H, Su P-Y, Wang Y, et al.: Maternal zinc deficiency during pregnancy elevates the risks of fetal growth restriction: a population-based birth cohort study OPEN. *Nat Publ Gr.* 2015.
- Mori R, Ota E, Middleton P, Tobe-Gai R, Mahomed K, Bhutta ZA: Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev.* 2012.
- Mahomed K, Bhutta Z, Middleton P: Zinc supplementation for improving pregnancy and infant outcome. *Cochrane*

Database Syst Rev. 2007.

12. Zhang C, Xu YY, Tao FB, Xu DX: Maternal serum zinc concentration during pregnancy is inversely associated with risk of preterm birth in a Chinese population. *J Nutr.* 2016; 146:509–15.
13. Lim Y, Levy M, Bray TM: Dietary Zinc Alters Early Inflammatory Responses during Cutaneous Wound Healing in Weanling CD-1 Mice. *J Nutr.* 2004; 134:811–16.
14. Defranco EA, Jacobs TS, Plunkett J, Chaudhari BP, Huettner PC, Muglia LJ: Placental pathologic aberrations in cases of familial idiopathic spontaneous preterm birth. *Placenta.* 2011; 32:386–90.
15. Andrews WW, Goldenberg RL, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC: The Alabama Preterm Birth study: polymorphonuclear and mononuclear cell placental infiltrations, other markers of inflammation, and outcomes in 23- to 32-week preterm newborn infants. *Am J Obstet Gynecol.* 2006; 195:803–08.
16. Chen Y-H, Zhao M, Chen X, Zhang Y, Wang H, Huang Y-Y, et al.: Zinc Supplementation during Pregnancy Protects against Lipopolysaccharide-Induced Fetal Growth Restriction and Demise through Its Anti-inflammatory Effect. *J Immunol.* 2012; 189:454–63.
17. Mesdaghinia E, Naderi F, Bahmani F, Chamani M, Ghaderi A, Asemi Z: The effects of zinc supplementation on clinical response and metabolic profiles in pregnant women at risk for intrauterine growth restriction: a randomized, double-blind, placebo-controlled trial. *J Matern Neonatal Med.* 2021; 34:1382–88.
18. Carducci B, Keats EC, Bhutta ZA: Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev.* 2021; 2021.
19. Higashi A, Tajiri A, Matsukura M, Matsuda I: A prospective survey of serial maternal serum zinc levels and pregnancy outcome. *J Pediatr Gastroenterol Nutr.* 1988; 7:430–33.
20. Lao TT, Chin RKH, Mak YT, Swaminathan R, Lam YM: Plasma and erythrocyte zinc and birth weight in pre-eclamptic pregnancies. *Arch Gynecol Obstet.* 1990; 247:167–71.
21. Mukherjee MD, Sandstead HH, Ratnaparkhi M V., Johnson LK, Milne DB, Stelling HP: Maternal zinc, iron, folic acid, and protein nutrition and outcome of human pregnancy. *Am J Clin Nutr.* 1984; 40:496–507.
22. Yasodhara P, Ramaraju LA, Raman L: Trace minerals in pregnancy 1. Copper and zinc. *Nutr Res.* 1991; 11:15–21.
23. Demir ME, Ulas T, Dal MS, Eren MA, Aydogan H, Yalcin S, et al.: Oxidative stress parameters and ceruloplasmin levels in patients with severe preeclampsia. *Clin Ter.* 2013; 164.
24. Dey M, Arora D, Narayan N, Kumar R: Serum cholesterol and ceruloplasmin levels in second trimester can predict development of pre-eclampsia. *N Am J Med Sci.* 2013; 5:41–46.
25. Carmichael S, Yang W, Shaw G: Maternal dietary nutrient intake and risk of preterm delivery. *Am J Perinatol.* 2013; 30:579–88.
26. Noor S, Nazar AF, Bashir R, Sultana R: Prevalence of PPRM and its outcome. *J Ayub Med Coll Abbottabad.* 2007; 19:14–17.
27. Rahmanian M, Jahed FS, Yousefi B, Ghorbani R: Maternal serum copper and zinc levels and premature rupture of the foetal membranes. *J Pak Med Assoc.* 2014; 64:770–74.
28. Shahnazi M, Khalili AF, Azimi S: Effect of zinc supplement on prevention of PPRM and improvement of some pregnancy outcomes in pregnant women with a history of PPRM: A randomized double-blind controlled trial. *Iran Red Crescent Med J.* 2017; 19:41931.
29. Aminisani N, Ehdaivand F, Shamshirgaran SM, Mohajery M, Pourfarzi F, Sadegh