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ORIGINAL ARTICLE

How Important Is Maternal Serum Zinc Level and Supplementation?

Maternal Serum Çinko Seviyesi ve Takviyesi Ne Kadar Önemli?

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Abstract

Introduction: Zinc is found in metalloenzymes and is an important trace element for fetal and maternal health. Its deficiency may cause pregnancy complications. The prevalence of zinc deficiency also differs due to different food sources. Our aim in conducting this study was to evaluate the relationship between serum zinc levels and pregnancy complications in our pregnant population.

Methods: This is a retrospective study conducted on 201 patients. Serum zinc levels obtained for various reasons during pregnancy were evaluated. The relationship between the pregnancy complications that occur in patients and the zinc levels was examined. In addition, the effects of zinc-containing vitamin supplementation on serum zinc levels were also checked. The primary endpoint of the study was to evaluate the relationship between serum zinc levels and pregnancy complications. The secondary endpoint was to investigate the effects of supplemental vitamins on serum zinc levels and pregnancy complications according to trimesters.

Results: According to trimesters, the mean zinc values were 72 mg/dL, 66.1 mg/dL, and 63 mg/dL, respectively. It was observed that the rate of zinc deficiency increased as the gestational week progressed. Among the patients, 49.7% did not take any vitamin supplements containing zinc, and 50.3% took supplements. The zinc level was found to be higher in patients who took zinc-containing vitamin supplements than in patients who did not take any supplements. However, a statistically significant difference was observed in terms of zinc levels between patients who received and did not take supplements only in the third trimester (p=0.003). Pregnancy complications were recorded: abortion in 7 patients (3.4%), intrauterine growth retardation in 10 patients (5.1%), preterm delivery in 12 patients (6.1%), pre-eclampsia in 17 patients (8.7%), oligohydramnios in 17 patients (8.7%), and gestational diabetes mellitus developed in 16 (8.2%) patients. A statistically significant correlation was observed only between oligohydramnios and second trimester zinc level (p=0.035).

Discussion and Conclusion: Zinc deficiency, which increases with the advancing gestational week, improves significantly with zinc supplementation, especially in the last trimester. Despite the significant relationship between the second trimester zinc level and oligohydramnios, zinc supplementation does not seem to have a significant effect on pregnancy outcomes.

Keywords: Oligohydramnios; Preeclampsia; Pregnancy; Zinc

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Healthy fetal development is closely related to the nutritional status of the mother. In fetal life, with intense cell growth and differentiation, nutritional elements that are effective, especially on DNA replication, become more important.[1] Zinc is an essential trace element in this regard as it is found in about 300 enzymes, including the polymerase enzyme required for DNA replication. Through these enzymes, zinc plays a vital role in protein metabolism and nucleic acid synthesis. It is known that zinc is present in approximately 500 peptides in the formation of aldolases and phosphatases and various proteins. The special zinc ring formed by zinc and these peptides is called the zinc finger motif because of its shape. Thanks to this motif structure, zinc is responsible for the ability of many transcription factors to bind to DNA. These zinc proteins are involved in the coding and transmission of genetic material.[2]

Circulating zinc levels decrease when maternal intake of zinc, which is essential for normal fetal growth and development, is insufficient even for a short time. Moreover, zinc cannot be stored and must be consumed regularly to replace losses.[3] According to WHO, the daily zinc requirement for women is around 6.5 mg/day. Additional zinc requirement for fetal and placental tissues during pregnancy must be met by increased intake and from maternal tissues. Therefore, the daily requirement for zinc during pregnancy ranges from 7.3 to 13.3 mg.[2]

Severe zinc deficiency is embryotoxic and teratogenic, causing abnormal fetal development.[2] Zinc has antioxidant properties and improves immunity and normal placentation. Many studies have shown that there is a risk of preeclampsia, preterm birth, low birth weight (LBW), or premature rupture of membranes when zinc level decreases.[2,4] However, a few studies show that zinc deficiency does not have a significant effect on pregnancy complications.[5–8]

Although severe zinc deficiency is now considered rare, mild to moderate deficiency is relatively common worldwide. Previous studies show that approximately 33%–73% of pregnant women have a zinc deficiency.[9,10] This difference is due to the regional nutritional habits and the difference in the amount of zinc in the food. Using a model that correlates pregnant women's zinc intake with the recommended intake, Caulfield estimated that 82% of pregnant women worldwide have insufficient zinc intake.[11]

In this study, we investigated the rate of pregnant patients with insufficient zinc levels and the relationship between serum zinc levels and pregnancy complications. In addition, we wanted to evaluate the effect of the multivitamin drug containing 7.5 mg of zinc, which the Ministry of Health provided to pregnant women as a routine supplement after the 12th week in Turkey, on the zinc level of pregnant women by accessing the drug use information from the file records of the patients.

Table 1. Demographic characteristics of the patients and mean zinc values according to trimesters

Characteristics (n=201)	
Age, mean (min–max)	29.8 (20–46)
Primipara/multipara	87/114
VD/CS	89/112
Zinc levels, mean (min–max)	
First trimester	72 (36.3–154.3)
Second trimester	66.1 (37.3–147.7)
Third trimester	63 (39.2–135.6)

VD: Vaginal delivery; CS: Cesarean section.

Materials and Methods

After the approval of the local ethics committee (Lokman Hekim University non-interventional clinical research ethics committee, date: December 28, 2020, decision no.: 2020089), we retrospectively analyzed 201 patients who applied to the Obstetrics and Gynecology Department of Etlik Lokman Hekim Hospital for pregnancy follow-up between October 2019 and October 2020. The study was conducted in accordance with the Helsinki Declaration Principles.

Inclusion criteria: All pregnant women who had a zinc test in all three trimesters, regardless of age and parity.

Exclusion criteria: Patients with a history of severe eating disorders and malabsorption problems that may impair zinc absorption and intake.

The files of the patients were examined, and the zinc tests were compared with the reference value. Serum zinc value of <60 mg/dL was considered low and ≥60 mg/dL was considered normal. In addition, from the patient files, age, parity, weeks of pregnancy when zinc test was performed, multivitamin use during pregnancy, delivery type, newborn height and weight, and presence of pregnancy complications [abortion, intrauterine growth retardation (IUGR), preeclampsia, preterm labor, gestational diabetes mellitus (GDM), and oligohydramnios] were recorded.

Statistical Analysis

The data were analyzed using Windows SPSS 22 (Statistical Package for Social Sciences, Inc., Chicago, IL, USA). Categorical variables were expressed as percentages. Numerical variables were presented with mean, minimum, and maximum. The Chi-squared test was used in the analysis. Values

Table 2. Hyaluronidase treatment interferences study and percent recovery of all spiked synovial fluid

	n (+supp)	% (+supp)	n (-supp)	% (-supp)	n (total)	% (total)	χ^2	p
First trimester	24	48	26	52	50	24.9	0.027	0.870
Second trimester	48	51.6	45	48.4	93	47.9	0.086	0.789
Third trimester	51	42.1	70	57.9	121	62.4	**9.005**	**0.003**

+supp: Taking zinc-containing vitamin supplements; -supp: Not taking any zinc-containing vitamin supplements.

Table 3. Relationship of pregnancy complications with serum zinc levels

	First trimester zinc deficiency		χ^2	p	Second trimester zinc deficiency		χ^2	p	Third trimester zinc deficiency		χ^2	p
	n	%			n	%			n	%		
IUGR	3	6.4	0.191	0.707	4	4.3	0.266	0.750	7	5.8	0.261	0.746
GDM	5	10.8	2.119	0.167	3	3.2	2.697	0.101	6	5	0.834	0.373
Preeclampsia	3	6.4	0.439	0.767	6	6.5	1.194	0.275	11	9.1	0.043	0.835
Preterm labor	1	2.1	1.760	0.300	4	4.3	1.093	0.296	6	5	0.834	0.373
Oligohydramnios	3	6.4	0.439	0.767	4	4.3	**4.448**	**0.035**	9	7.4	0.706	0.401

IUGR: Intrauterine growth retardation; GDM: Gestational diabetes mellitus.

of $p<0.05$ were accepted as statistically significant. To evaluate the difference in zinc values of patients according to trimesters, one-way ANOVA and Tukey's HSD multiple comparison tests were performed. The power of the study was calculated considering previous studies, and the current sample size is 0.60.

Results

A total of 201 patients with a mean age of 29.8 years were included in the study. Among pregnant women, 43.2% of the patients were primipara, and 56.8% were multipara. According to trimesters, the mean zinc values were 72 mg/dL, 66.1 mg/dL, and 63 mg/dL, respectively. There was no significant relationship between zinc levels and age and parity in any of the trimesters ($p>0.05$). Of the patients, 44.2% delivered vaginally (VD) and 55.8% delivered by cesarean section (CS). Indications of patients with CS: 49.1% previous history of CS, 15.1% CPD, 12.5% nonprogressed labor, 11.6% developed breech. The mean newborn weight was 3265 g (1610–4140), and the length was 49.9 cm (41–56). Among participants, 100 (49.7%) of them did not take any vitamin supplements containing zinc, and 50.3% took supplements. The average time to start zinc therapy in patients taking supplements was 12 weeks of gestation. Among pregnancy complications, abortion was reported in 7 patients (3.4%), IUGR in 10 patients (5.1%), preterm delivery in 12 patients (6.1%), preeclampsia in 17 patients (8.7%), oligohydramnios in 17 patients (8.7%), and GDM in 16 (8.2%) patients. The demographic data of the patients are summarized in Table 1.

The zinc values of the patients showed a significant difference according to the trimesters ($F(2–586)=19.086$; $p=0.05$). Tukey's HSD multiple comparison test was performed to determine between which groups there were significant differences. According to the results of the multiple comparison test, the difference between the first trimester zinc values ($\chi=72.05$) and the second trimester ($\chi=64.67$) and third trimester zinc values ($\chi=61.55$) in favor of the measurements made in the first trimester was found.

The zinc level was found to be higher in the patient group that took zinc-containing vitamin supplements than the group that did not take the supplement. However, a statistically significant difference was observed between the patients who took supplements and those who did not, in terms of zinc levels only in the third trimester ($p=0.003$). The proportions of patients with low zinc levels according to the trimesters and the variation in zinc levels by trimesters between patients who received and did not take supplements are shown in Table 2.

It was observed that there was no statistically significant relationship between the risk of abortion and the first trimester zinc levels ($p=0.369$). As a result of the analysis, no statistically significant relationship was observed between other pregnancy complications and zinc deficiency, but a statistically significant relationship was observed between the presence of oligohydramnios and the zinc level in the second trimester ($p=0.035$). There was no significant difference in pregnancy complication rates between the patient groups that received and did not receive supplements. In

Table 4. Relationship of pregnancy complications with supplementation status

	+supp		-supp		χ^2	p
	n	%	n	%		
IUGR	3	3.1	7	7.3	1.775	0.211
GDM	6	6.1	6	6.1	0.001	0.971
Preeclampsia	10	10.2	7	7.3	0.514	0.473
Preterm labor	9	9.2	3	3.1	3.068	0.080
Oligohydramnios	12	12.2	5	5.2	3.003	0.083

IUGR: Intrauterine growth retardation; GDM: Gestational diabetes mellitus; +supp: Taking zinc-containing vitamin supplements; -supp: Not taking any zinc-containing vitamin supplements.

the analysis performed to determine the relationship between LBW and zinc deficiency and supplementation, the Chi-squared statistical value could not be interpreted because the number of pores with the expected frequency value below 5 exceeded 20% (50%) of the total number of pores. The relationship between serum zinc levels and pregnancy complications and the distribution of complications in the groups are shown in Tables 3 and 4.

Discussion

A healthy diet during pregnancy is essential for healthy fetal development.[1] The deficiency of some nutrients has more negative effects on fetal development. Zinc is an important trace element because it is present in the structure of enzymes necessary for protein synthesis.[2] Dietary zinc intake is required daily. However, daily dietary zinc intake and deficiency vary between different geographic regions due to differences in dietary sources and nutritional habits.[12] Previous studies showed that approximately 33%–73% of pregnant women have a zinc deficiency.[9,10] In another study on zinc deficiency according to trimester, the prevalence of zinc deficiency in the first trimester was 1.5%, but this ratio was 15.9% in the second trimester.[13] In another study investigating the prevalence of zinc deficiency at different gestational weeks, zinc deficiency was reported to increase gradually with increasing gestational age. However, the results were not statistically significant. In the same study, it was stated that increasing age and parity had an effect on serum zinc levels, and a significant inverse relationship was observed between parity and zinc level (p=0.07).[14] As a result of our study, we observed that zinc deficiency increased in the following weeks in trimesters, in line with other studies (24.9%, 47.9%, and 62.4%, respectively, according to trimesters). However, we did not observe a significant relationship between zinc levels and age and parity in any trimester (p>0.05).

In a few studies evaluating the effect of zinc supplementation on zinc deficiency, huge differences such as 35% vs 81% were observed, but no effect was observed in some others.[7,9] In a meta-analysis conducted in 2012, it was stated that the most consistent result showing the effect of zinc supplementation was the increase in maternal serum zinc status in late pregnancy.[5] In our study, we observed that the difference between serum zinc levels of the patients who took supplements was not significant in the first two trimesters (p=0.870 and p=0.769, respectively), but there was a statistically significant difference between the two groups in the third trimester (p=0.003).

In a recent study evaluating the serum zinc concentrations between patients diagnosed with missed abortion and healthy pregnant women, no significant relationship was found between the two groups (p=0.441).[6] In our study, abortion occurred in 7 patients (3.4%). Of these patients, 4 had normal zinc levels and 3 showed low zinc levels. No significant relationship was observed between zinc level and abortion (p=0.369).

Due to its effects on placentation and protein synthesis, zinc is likely to affect fetal weight. Different results have been obtained in studies conducted to evaluate this effect. In a controlled study, zinc levels were found to be lower in mothers of newborns with LBW compared with mothers of newborns with ideal birth weight.[10] In another study investigating the correlation between maternal serum and umbilical cord blood zinc levels and newborn weight in the first and second trimesters, the risk of LBW increased in the low-level serum zinc group in the first trimesters (RR 1.51, 95% CI 1.05–2.19), but it was observed that there was no statistically significant relationship between serum zinc levels and cord blood zinc level and LBW risk in the second trimester (p>0.05).[13] A meta-analysis of 23 studies showed that both maternal zinc status and cord blood zinc were inversely related to LBW, and maternal zinc status was significantly associated with cord blood zinc.[15] In a cross-sectional study conducted on 200 patients who were given or not given zinc supplementation during pregnancy, newborn birth weight was found to be higher in the group with zinc supplementation.[9] However, in a systematic analysis including 9000 pregnant women, it was shown that zinc supplementation and its level did not have a positive effect on birth weight.[7] In our study, due to the low number of LBW newborns, a statistically appropriate evaluation could not be made between zinc level and supplementation and the risk of LBW.

In a systematic review, different studies with different results regarding the association between serum zinc levels and the risk of preterm birth were reported.[12] In a study conducted on 3081 pregnant women in China, the inci-

dences of preterm birth were found to be 7.3%, 6.0%, and 3.1% among subjects with low, medium, and high zinc levels, respectively, and according to the results of the study, it was stated that there was an inverse correlation between serum zinc levels and the risk of preterm birth.[16] In another study conducted by giving zinc supplementation to pregnant women who previously gave birth, it was observed that there was no relationship between zinc levels and the risk of preterm birth.[17] As a result of our study, no significant relationship was observed between serum zinc levels and preterm labor (p>0.05).

As a result of 21 randomized controlled studies on the effect of zinc supplementation on preterm birth, a 14% reduction in preterm birth was observed in patients who took zinc supplements compared with those who did not take the supplement.[18] In the WHO report on nutrition during pregnancy, it was reported that maternal zinc supplementation in regions with zinc deficiency may reduce the risk of preterm birth with its reducing effect on maternal infection.[19] However, as a result of our previous study to evaluate the effect of zinc deficiency and supplementation on urinary tract infection, which is one of the most common infectious causes of preterm birth, we found that zinc deficiency or supplementation had no effects on urinary tract infection.[20] In our study, no difference was observed between the groups that received or did not receive supplements in terms of preterm labor (p=0.080).

Studies examining the relationship between low serum zinc levels in pregnancy and the risk of preeclampsia reported conflicting results. In a study conducted on serum trace elements among preeclamptic, eclamptic, and normotensive pregnant women, serum zinc levels were found to be significantly higher in preeclamptic pregnant women than in eclamptic pregnant women and borderline low in normotensive pregnant women.[21] In another study in which serum zinc levels and superoxide dismutase activity were evaluated, significantly lower zinc and superoxide dismutase activity were observed in preeclamptic patients compared with normotensive pregnant women.[22] In another similar study, the mean plasma zinc level was found to be significantly higher in preeclamptic patients compared with controls (p<0.05).[23] In a review evaluating 21 randomized controlled studies involving more than 17,000 mothers and their babies, it was observed that there was no significant difference in terms of preeclampsia risk between the groups that received and did not receive zinc supplementation (RR 0.83, 95% CI 0.64–1.08).[18] As a result of our study, no significant relationship was observed between serum zinc levels and supplementation and preeclampsia in any trimesters.

In a study examining the relationship between maternal serum and placental zinc levels and IUGR, placental zinc level was found to be lower in cases with IUGR than in normal pregnancies, but no relationship was observed in terms of maternal serum zinc level.[24] In a systematic review conducted by the same researchers, a significant inverse relationship was found between the risk of IUGR and maternal zinc level.[15] In our study, no significant relationship was observed between zinc levels or zinc supplementation and IUGR in any trimesters.

As a result of a study in which dietary zinc intake and serum zinc level were evaluated in hypoglycemic and hyperglycemic pregnant women, it was observed that the amount of dietary zinc and serum zinc level were lower in patients with impaired glucose tolerance and gestational hyperglycemic patients.[25] In addition, no relationship was found in another study investigating the effect of serum zinc level and dietary zinc intake on GDM in early pregnancy.[26] As a result of our study, no significant relationship was observed between the three trimester zinc levels or the use of zinc supplements and GDM (p>0.05).

Although the data about the relationship between zinc levels and oligohydramnios are limited in the literature, in a study comparing the serum and amniotic fluid zinc levels of patients who developed oligohydramnios or premature rupture of membranes during pregnancy, serum and amniotic fluid zinc levels in the group with oligohydramnios was found to be significantly lower compared with the control groups.[27] In our study, we observed a statistically significant relationship between low serum zinc levels in the second trimester and oligohydramnios (p=0.035). However, no significant relationship was observed between first and third trimester zinc levels and oligohydramnios (p=0.767 and p=0.401, respectively). There was no difference in terms of oligohydramnios between the two groups that received and did not receive any zinc supplementation (p=0.083).

Limitations

Although we have a sufficient sample size, the number of newborns with preterm labor and LBW among the patients who gave birth is not sufficient because our center had a second-step neonatal intensive care unit at the time of the study. In advanced centers, where high-risk pregnancy follow-ups can be performed, the results will be more realistic.

However, we hope that it will shed light on future studies because it is the first study to investigate the relationship between oligohydramnios and zinc deficiency.

Conclusion

Zinc is a trace element that is expected to be effective in the course of pregnancy, complications, and fetal development with its enzymatic functions. As a result of our study, although serum zinc values decrease in the following weeks of pregnancy, no significant relationship was observed between zinc levels and pregnancy complications other than the increase in the risk of oligohydramnios due to zinc deficiency in the second trimester. Although vitamin supplements containing zinc significantly corrected zinc deficiency in the last trimester of pregnancy, this supplement does not seem to have a significant effect on pregnancy outcomes. It can be suggested that, in pregnant women with oligohydramnios, especially in the second trimester, serum zinc levels should be evaluated.

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