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Role of Copper and Zinc in Full-term Pregnancy and İts Effect on Apgar Score

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Authors' contributions

This work was carried out in collaboration among all authors. Authors HY, HUY and BE did the concept. Author HY did the supervision. Authors HUY and HY did the materials. Authors BE and HY did the data collection and processing. Authors HY, HUY and BE did the analysis and ınterpretation. Authors HY and BE did the writing. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Our aim in this study; is to determine zinc, copper and copper/zinc ratios in third-trimester pregnant women with a new laboratory method.
Methods: In this research conducted on 59 pregnant women in the last trimester, Those diagnosed with preeclampsia, preterm birth, postmaturity, and gestational diabetes were excluded from the study. In pregnant blood serums, zinc and copper levels were studied on fully automatic analyzers with a new method. The new technique kits used in the study are Rel Assay Diagnostics brand. The zinc ion reacted with 5-Br-PAPS and gave an absorbance at a wavelength of 548 nm in direct proportion to the total zinc level. The copper ion reacted with 3,5-DiBr-PAESA and showed absorbance at 572 nm in direct proportion to the total copper level. Zinc and copper measurements

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were made in this way by the colourimetric method. Additionally, copper/zinc ratios were calculated. In addition, determined the APGAR (Activity-Pulse-Grimace-Appearance-Respiration) score of the babies. Statistical studies of the obtained data were performed at $p<0.05$ significance level.

Results: Zinc and copper parameters; No statistically significant relationship was found in the analyzes performed with gestational age, gestational week, birth weight, APGAR score, gravida and the number of living children ($p>0.05$). In addition, it was observed that there was no difference in zinc and copper/zinc ratios in the evaluations made according to the gender of the baby ($p>0.05$). On the other hand, copper levels in pregnant women; were found to be significantly higher in female fetuses (200.72±36.36) than in males (164.17±42.47) ($p<0.001$).

Conclusion: Although the copper values of pregnant women with female fetuses are significantly higher, these results require more comprehensive studies. On the other hand, there is not relationship between zinc, copper and copper/zinc values and APGAR scores.

Keywords: Third trimester; pregnancy; zinc; copper; copper/zinc.

1. INTRODUCTION

Although correct and healthy nutrition is critical during pregnancy, it is possible to detect this situation with test parameters. Among these tests is copper, zinc values and copper/zinc ratio in blood serum. Of course, the nutritional needs of individuals are different. Factors such as body size and the presence of pregnancy bring about energy consumption differences. Therefore, reference levels for the adequacy of diets are also set for pregnant women. The reference and recommended intakes for zinc and copper in pregnant women are shown in the table (Table 1). However, these tables may differ slightly in European countries [1].

Table 1. Recommended dietary allowances and acceptable intakes for Zn and Cu

	Zn (mg)	Cu (mg)
Pregnant	11	1000
Lactating	12	1300

***Source**: Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine Dietary Reference [1]*

When zinc and copper are not taken in sufficient amounts in the diet, metabolic function losses and various diseases occur as a result (Table 2). A higher-than-normal serum copper level is defined as hypercupremia, and a low level is defined as hypocupremia. Copper, which is effective in the mobilization of iron, participates in redox reactions as a trace element. In addition, copper is included in the structure of enzymes necessary for the use of iron in the formation of haemoglobin and is necessary for the activities of these enzymes. Copper deficiency is encountered in various malabsorption syndromes and causes cardiovascular disease symptoms. Again, copper deficiency is seen in Menkes disease, which is a rare, X-linked neurodegenerative disease. The daily Zn requirement is up to 15 mg. Most of the dietary Zn is absorbed from the small intestine by active transport. Zinc absorption requires a "zinc-binding exocrine ligand" secreted by the pancreas [2]. In its deficiency, regression in growth and skeletal development, hepatosplenomegaly, acrodermatitis enteropathica, skin rashes in infants, and decreased sense of taste and smell. Zinc; It participates in the structure of carbonic anhydrase, alcohol dehydrogenase, glutamate dehydrogenase, kidney phosphatase, carboxypeptidase, and uricase enzymes. It improves ischemic conditions by providing enlargements in cerebral vessels and coronary arteries. If you are in the zinc-deficient nutrition server, Acrodermatitis enteropathica and susceptibility to infections, in addition, various subclinical conditions arise [1].

A healthy life is accepted as an essential assurance in the process of successful pregnancies. Reducing the risks of negativity for the mother and fetus in a problem-free pregnancy and subsequent life makes it necessary for this process to start before pregnancy [4]. In addition, there are many studies and studies describing the importance of diet and nutrition in pregnancy [5,6,7].

Many biochemical markers are being investigated to establish reference ranges for various tests and to evaluate pregnancy trimesters (first, second and third) in healthy pregnant women [8,9,10].

Table 2. Zn, Cu Functions and deficiency disease

	Zn (mg)	Cu (mg)
Functions	Function as prosthetic groups in Enzymes	Function as prosthetic groups in enzymes
Deficiency Disease	Acrodermatitis Enteropathica.Prenteral Nutrition. Infectious Disease.Subclinical Effects of Deficiency	Menkes Syndrome. Malabsorption Syndromes. Cardiovascular Disease

Source: This table has been adapted from the Tietz section IV chapter [3]

A systematic review examining the APGAR score and maternal and perinatal pregnancy risks highlighted the heterogeneous characteristics of the results of many studies on this topic [11]. In addition, the APGAR system is still widely used in clinics for neonatal scoring for decades [12]. However, there is no study in which the APGAR scoring system and pregnant zinc and copper values are evaluated together.

In our study, the blood serum in the third trimester of pregnancy determined zinc, copper and copper/zinc ratio. Used a newly described method for zinc and copper measurements; caught the postnatal APGAR (Activity-Pulse-Grimace-Appearance-Respiration) score of the babies by scoring. Our study is a first in the literature considering the measurement techniques of the zinc and copper test.

2. MATERIALS AND METHODS

The ethics committee of the study was recruited from Sakarya University (24.09.2018 date, 216 numbers). Fifty-nine pregnant women in the last trimester of pregnancy and who had a singleton pregnancy were included in the study. Accepted 37-40 weeks for the definition of the previous trimester. Pregnant women who were diagnosed with preeclampsia, preterm labour, postmaturity, and gestational diabetes during the study were excluded from the study. Exclusion criteria were gastroctaemia, small bowel resection, peptic ulcus, psychiatric disease, pregnancy toxaemia, bronchial asthma, active hepatitis, cancer, chronic renal failure, and heart failure. In addition to the test parameters values examined in the research, it also looked at the baby's sex, APGAR-1, APGAR-5, gestational age, number of living children and fetal gender.

2.1 Laboratory Process in the Study

For zinc and copper detection, venous blood was drawn into special tubes with clot activator while patients were fasting (dark blue capped trace element tubes, BD vacutainer trace element testing). After the blood was drawn, it was inverted 8-10 times and the samples were transferred to the laboratory following the cold chain. Subsequently, the samples were subjected to refrigerated centrifugation (4000 rpm for 10 minutes). The obtained sera were stored in capped Eppendorf tubes (isolab centrifuge tubes 2.0 ml) at -80. Rel Assay Diagnostics kit was used on the fully automatic AU 680 analyzer (serial number: 2016024580, Tokyo, Made In Japan) on a working day. The zinc ion in the sample reacted with 5-Br-PAPS and gave absorbance at 548 nm wavelength in direct proportion to the total zinc level. The copper ion reacted with 3,5-DiBr-PAESA and showed absorbance at 572 nm wavelength in direct proportion to the total copper level. Zinc and copper measurements were made in this way by the colourimetric method (Table 3). In the study, the APGAR score of all babies was scored after delivery and determined.

Table 3. Performance of the tests used in the research

	Normal Range	Linearity	Accuracy	Precision %CV
Zinc (µg/dL)	60-120	4-1000^{q}	0.98^{Z}	2.32
Copper (µg/dL)	110-312^{X}	3-600^{q}	0.97^{Y}	1.85

^{X}: Pregnancy, ^{Y}: Correlation coefficient (r), ^{Z}: Correlation coefficient (r), ^{q}: Low-High

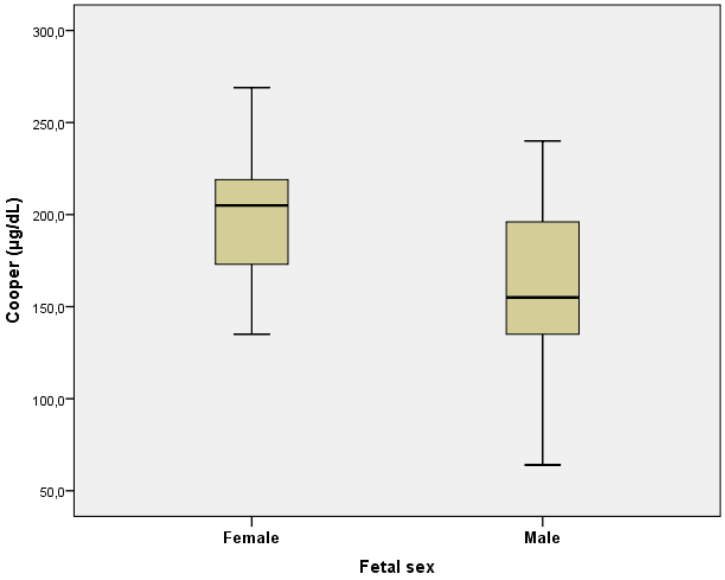
3. RESULTS

While there was no statistically significant difference between the zinc levels and zinc/copper ratios between the male and female genders in the evaluation made according to the fetus gender, the copper levels were found to be significantly higher in the pregnant women with a female fetus (Table 4, $p>0.05$).

Table 4. Comparison of Cu, Zn and Cu/Zn values according to fetus gender

	Girl Fetus	Male Fetus	P
Zinc	86,64±23,81	80,38±24,40	0,346
Copper	200,72±36,36	164,17±42,47	0,001
Zinc/Copper	2,49±0,80	2,23±0,78	0,233
N	25	29	

Student's t test was performed. P<0.05 was considered significant.



Graphic 1. Comparison of copper levels by fetal sex (p=0.001)

Table 5. Relationship of gestational age, number of living children, APGAR-1 and 5 with test parameters

	Zinc		Copper		Copper/Zinc	
	r	**p**	**r**	**p**	**r**	**p**
Age	0,156	0,259	0,081	0,559	-0,115	0,407
Living children	0,010	0,941	-0,059	0,672	-0,062	0,656
APGAR-1	-0,067	0,628	0,190	0,170	0,202	0,143
APGAR-5	-0,051	0,714	0,178	0,198	0,189	0,170

Pearson korelasyon analizi yapılmıştır. P<0.05 was considered significant

As a result of the correlation analysis of zinc, copper and Zinc/copper parameters with gestational age, the number of living children, and APGAR (1 and 5) parameters at the first and fifth minutes determined that there was no significant correlation between them (Table 5 and Graphic 1; p<0.05).

4. DISCUSSION

The use of Apgar scoring in clinical studies has been going on for a long time and is still used in many studies. One of the most recent is a retrospective cohort study [12]. Their work, like ours, evaluated Apgar scores of newborns at the 1st and 5th minutes. However, our study, perhaps for the first time in the literature, investigated the role of copper and zinc in term pregnancy and its effect on the Apgar score.

Squitti et al. [13] It has long been known that elevated serum copper levels decrease the antioxidant system and correlate with poor neuropsychological performance and medial temporal lobe atrophy [14]. Indeed, examined serum levels of zinc, copper and iron in 1165 adults. This study showed that high serum zinc, copper and iron levels are associated with the risk of metabolic syndrome, BMI and the number of metabolic factors independent of insulin resistance. In our study, serum copper levels were found to be significantly higher in women

who were pregnant with a girl (Gao et al., 2020). In a study whose data were taken from the 2011-2016 National Health and Nutrition Examination surveys, it was stated that copper induces oxidative stress and zinc counteracts oxidative stress. On the other hand, the same study indicated that causality deserves more confirmation.

Zhang et al., [15] In fertile women aged 18-44 years from a representative population in China, research was done on Zn, Cu and Cu/Zn ratios. A total of 191 women who gave birth to healthy children participated with a strict set of inclusion criteria. Determined baseline biological indicators and basic levels in the whole blood of the included women. After they evaluated the data they obtained, They concluded that "the Zn, Cu and Cu/Zn ratios in plasma and whole blood of fertile women can be used as an indicator to evaluate the reference range, element deficiency and overload status".Our study, using a new method in zinc and copper measurements and with the results obtained, examined the relationship between APGAR scores, number of living children, and fetus gender.

Giddens, [16] A study investigating dietary food intake in the second and third trimesters of pregnancy compared dietary standards in adolescent and adult pregnant women. According to them, The diets of 59 pregnant adolescents and 97 pregnant adults were inadequate and below the recommended dietary intakes, including zinc. It is seen in our work and their work that; Continuous nutritional monitoring of pregnant adolescents and pregnant adults is required, including nutritional guidance highlighting food sources of zinc vitamins [17-22].

5. CONCLUSION

With zinc, copper and copper/zinc values in pregnant women in the third trimester, There does not appear to be a relationship regarding APGAR scores. Similarly, there is no relationship between age and the number of living children. On the other hand, the fact that the copper values were significantly higher in pregnant women with female fetuses was seen as a result that requires further research.

6. LIMITATIONS AND STRENGTHS

The limitation of the study is the lack of Examination of lifestyle and healthy nutrition in pregnant women. On the other hand, the Examination of zinc, copper and copper/zinc ratio in the third trimester with a new method for the first time can be stated as the strength of the research.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICS APPROVAL

Approval for the study was obtained from the Sakarya University Faculty of Medicine Ethics Committee (24.09.2018 date, 216 numbers). Fifty-nine pregnant women in the last trimester of pregnancy and who had a singleton pregnancy were included in the study. Accepted 37-40 weeks for the definition of the previous trimester and the Declaration of Helsinki conducted the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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