Original article

The Evaluation of the Effect of Prenatal Copper Supplementation on Pregnancy Outcomes in Pregnant Women with Cupper Deficiency

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Abstract:

Introduction: Copper (Cu) is an essential trace element for the body and seems to play an important role in the final outcome of a successful pregnancy. Some studies have shown an increase in serum levels of copper in pathological pregnancies during the first trimester. This study aimed to evaluate the effect of copper supplementation in pregnant women was designed with copper deficiency on pregnancy outcomes.

Methods: This double-blind randomized controlled clinical trial on pregnant women with gestational age of 16-12 weeks was conducted during 2014-2015. The copper levels measured in pregnant women, then 120 qualified mothers have serum levels of copper at less than normal baseline values (120 µg / dL) have been selected. Data analysis with statistical software SPSS-21 and chi-square and independent t-test were done.

Findings: Of the 120 cases studied, 20 patients (16.6% of the total) had premature rupture of membranes which 6 women were in the case and 14 women were in the control group and statistical tests showed a significant difference between the two groups (P=0.025). Also among the 120 cases studied, 23 patients (19.1% of total) with pre-eclampsia which 8 women were in the case and 15 women were in the control group and statistical tests showed a significant difference between the two groups (P=0.034). Other variables include spontaneous abortion, preterm delivery, placental abruption, low birth weight, intrauterine growth restriction, and intrauterine fetal death there was no significant difference between the two groups.

Conclusion: Based on our findings, supplementation containing copper in pregnant women can reduce the risk of pre-eclampsia and premature rupture of the fetal membranes that Both can be serious consequences, such as infection of membranes, miscarriage or intrauterine death or life-threatening for the mother.

Keywords: Pregnancy, Copper serum level, Premature rupture of membranes

Introduction:

Rare elements are the basic constituents of biological processes, including oxidative processes. Copper (Cu) is one of the rare and essential elements of the body that is known in the building of many metalloenzymes that undergo oxidation and resuscitation (metalloenzymes) (1). The metabolic pathways in the human body include many biochemical reactions, mainly catalyzed by enzymes. These protein enzymes naturally require precursors for their biological activity. Some elements such as copper, iron, and zinc act as vital factors for the major activity of enzymes and are responsible for biochemical oxidation and regeneration in metabolic pathways (2). Studies have shown that copper plays an important role in the final outcome of a successful pregnancy. During pregnancy, the amount of copper gradually increases with an increase in the amount of estrogen and progesterone in the circulation from an initial pre-pregnancy level (about 120 μg/dL). In several studies, the average serum copper level at the end of the third trimester of pregnancy was reported between 220-170 μg / dL (3).

It has recently been reported that serum copper levels in pathologic pregnancies during the first trimester are relatively lower than normal pregnancies. There is also a significant increase in serum copper levels in pathologic pregnancies during the first trimester (4). However, no specific data on postpartum complications and copper levels have been reported. On the other hand, copper deficiency in the mother was shown to cause deficiency in the fetus and cause serious consequences such as impairment in the cognitive development of the infant during the first 6 months of life, immunological complications in the fetus, low birth weight (LBW), intrauterine growth restriction (IUGR), prematurity, spontaneous abortion, intrauterine fetal death (IUFD), prolonged labor, low birthweight (SGA), premature rupture of membranes (PROM), cleft palate , Fetal neural tube defect (NTD). In pregnancy, due to increased estrogen, the serum levels of ceruloplasmin increase, which leads to an increase in maternal serum copper concentrations (1).

Studies have shown that many metabolic disorders result from copper deficiency, which is an essential part of the daily diet. Copper is not only a critical factor, it is essential for the development of the fetus, and consequently a decrease in the serum copper level with fetal defects. Copper is directly involved in pregnancy outcomes, and this period of prenatal life is accompanied by a defect in copper metabolism in the fetus and mother.(5,6)In 2006, Zhang et al examined the relationship between copper and PROM. For this purpose, 100 pregnant women were enrolled with PROM and were divided into three groups: 37-42 weeks, 36-34 weeks, and 33-28 weeks, based on the gestational age. 100 pregnant women without PROM who were matched for gestational age were selected as control group. The results of this study showed that in preterm pregnant women, the decrease in serum copper and amniotic fluid was directly related to PROM (5). Also, in 2010, Moghaddam-Banaem et al. Examined the relationship between serum and cord

blood levels of zinc, copper, magnesium, iron, and calcium with low birth weight. This cross-sectional study was performed on 344 pregnant women and their newborns. Serum concentrations of iron, zinc, copper, magnesium, and calcium were measured in mother and cord blood samples. The results of this study showed that low birth weight in mothers with more calcium deficiency was observed and the remaining elements, including copper, did not show a relationship with low birth weight (6).

The growing embryo receives copper for growth and development through the placenta, and changes in the level of copper in pregnant mothers directly affect the condition of the embryo before birth. Some metabolic abnormalities in pregnancy interfere with the proper distribution of copper through the placenta, and this should be considered in assessing copper status during pregnancy (7). According to a study conducted in Golestan province, the mean serum copper concentration in normal pregnant mothers was 201.08 ± 82.66 μg / dl in preterm and preterm pregnancies (8).

According to various and sometimes contradictory reports on the effects of copper on pregnancy outcomes and the possibility of early detection and prevention of adverse maternal and fetal complications due to changes in serum copper levels, this study aimed to investigate the effect of copper supplementation in pregnant women with deficiency Copper was designed for pregnancy outcomes.

Methods:

This study was a double-blind, randomized, controlled clinical trial and was conducted on pregnant women referred to Sayyad Shirazi Hospital in Gorgan during 2014-2015. Due to the lack of similar studies, this pilot study was performed on 120 pregnant mothers with copper deficiency. In order to divide the samples into two groups, the first pregnant mother was in the intervention group and the second mother in the control group and this process continued until the end of the sampling. In this study, the samples were available from 357 pregnant women and They were selected in the second trimester of pregnancy and have a gestational age of 12 to 16 weeks. The inclusion criteria included Nulliparity, age 18-35, second trimester of pregnancy, and satisfaction to participate in the study. Exclusion criteria include Twin and multi-threaded, history of any systemic disease, administration of any supplementation other than iron supplementation and folic acid, known sensitivity to copper supplements, polyhydramnios, embryonic anomalies, smoking, alcohol, and drugs abuse. The samples were also excluded if the prescribed supplements were not used regularly There is an allergy to them.

At the beginning and the end of the study, serum copper levels in pregnant women were measured. It was determined that 132 mothers (36.9% of the total number of subjects) had lower serum copper levels and, finally, 120 mothers who had the level The serum copper levels were lower than normal values (80 μg/dL) (3). The subjects were randomly divided into intervention and

control groups (each group included 60). The two groups were matched in terms of maternal age, gestational age, number of pregnancies, number of births, iron supplementation, and zinc supplementation and BMI.

After obtaining a history and careful clinical examination, a form containing demographic characteristics and pregnancy was completed for each of the mothers. Then, to the case group, a supplement of minerals containing 2 mg of copper (prepared from Al-Hawi Pharmaceuticals Company, Tehran, Iran) was given once a day until the end of pregnancy and for the control group also, the copper minerals supplement (prepared By Al-Hawaii Pharmaceuticals Company, Tehran, Iran) was given once a day until the end of pregnancy. The method of blinding has been that the pregnant mothers who received the drug and the prescriber were not aware of the nature of the drug according to the same characteristics of the drug in the two groups and the only doctor and presenter of the plan are aware of the prescribing.

The final outcomes of the pregnancy that were studied in this study included spontaneous abortion, premature rupture of membranes (PROM), preterm labor (PTL), Placental abruption, preeclampsia, low birth weight (LBW), intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD). At the end of the study period, the serum copper level was re-measured for the case and control group and the two groups were compared in terms of the outcomes. Measurement of serum copper level was done by Atomic Absorption Spectrophotometer (AAS) at Sayyad Shirazi Hospital.

Statistical Analyses:

The collected data were analyzed by SPSS software version 21 after encoding and logging. The mean, mean, standard deviation and percentage were used to describe the data. To compare the mean serum copper level between two groups, a t-test was used and chi-square ($\chi 2$) test was used for comparison between groups. The significance level of the tests was less than 0.05.

Findings:

In this study, a total of 120 pregnant women were evaluated in two groups of 60 people. The mean age of the subjects in the control group was 26.1 years and the mean age of the subjects was 27.3 years.

After a primary review of the serum copper level before the intervention, it was determined that the mean serum copper level in the case group was 63.31±10.11 μg/dl with a maximum of 78 and minimum 38.5 and The mean serum copper level in the control group was 64.96±9.27 μg / dl with a maximum of 79.7 μg/dl and minimum of 38.9 μg/dl.

Also, the serum copper level in the serum of the subjects after the intervention was as follows: the mean serum copper level in the case group was 86.14±7.68 μg/dl with a maximum of 110 μg/dL and at least 54 μg/dL and The mean serum copper level in the control group was 63.65±8.27 μg/dl with a maximum of 78.9 and minimum of 45.4 μg/dL.

In 120 subjects that studied 7 (5.8% of total) had abortions, 3 of them (5% of case group and 2.5% of all subjects) in case group and 4 patients (6.6% of the control group and 3. 3% of the total subjects) were in the control group and statistical tests did not show a significant difference between the two groups (P>0.05). Also, 20 (16.6% of the total) had premature rupture of membranes, 6 patients (10% of the case group and 5% of the total subjects) in the case group and 14 patients (23.3% of the Control group and 11.6% of the total subjects) were in the control group. Significant differences were found between the two groups (P=0.025).

11 pregnant women (9.1% of the total) had preterm labor, 4 of them (6.6% of the case group and 3.3% of the total subjects) in the case group and 7 (11.6% of the control group and 5.8% of the total subjects) were in the control group. The statistical tests did not show a significant difference between the two groups (P> 0.05).

23 patients (19.1% of the total) had pre-eclampsia, 8 cases (13.3% of the case group and 6.6% of the total subjects)were in the case group and 15 patients (25% of The control group and 12.5% of the total subjects) were in the control group. Significant differences were observed between the two groups (P=0.034). Four infants (3. 3% of the total) had low birth weight, which 2 (3.3% of the case group and 1.6% of the total subjects)were in the case group and 2 (3.3% of the control group and 1.6% of the total subjects were in the control group. The statistical tests did not show a significant difference between the two groups (P>0.05).

A total of 120 subjects 2 had Placental abruption (1.6% of the total) that both of them were in the control group and 1 (0.8% of the total) had intrauterine growth restriction, which was in the control group Which has not been statistically significant. No cases of intrauterine death have been reported in the case and control group, of course, have not been statistically analyzed.

Discussion:

Pregnancy is a very important stage in the life of any woman with Fertility possibility, of course, its implications are important. The most important reasons for this period, which generally lasts from 37 to 42 weeks, are the importance of maternal and fetal health until the end of the pregnancy.

During pregnancy, there may be many physiological and pathological events for the mother and fetus that can sometimes be risky for them. With regard to the issues mentioned, one of the most important health policy frameworks in each country is maternal and fetal health policies, so that healthy and capable mothers can develop healthy development for the community as well as healthy children.

Copper is one of the rare but important elements in the body. Its deficiency due to its metabolic role in the body can lead to changes in the development of the fetus and cause many disorders, including negative effects on cognitive mechanisms, immunological ability and negative impact on other The organs. Thus, the importance of the lack of this metal in the body, especially in the developing embryo, highlights. The purpose of this study was to determine the effect of copper

supplementation on pregnant women with copper deficiency in pregnancy outcomes.

Based on the results of this study, there were significant differences between the two case and control groups after copper and non-copper supplements in two cases, one of the prevalences of preeclampsia and the frequency premature rupture of membranes, both in The case group was less than control. In fact, this study showed that the use of copper supplements could reduce the risk of preeclampsia and premature rupture of membranes (13).

In 2006, Zhang et al. Examined the relationship between copper and PROM. In this study, it was found that in pregnant women between the ages of 33 and 28 weeks, serum copper and amniotic fluid copper decreased between the two groups. The result showed that in preterm pregnant women, the decrease in serum copper and amniotic fluid was directly related to PROM (14). The results of this study were consistent with our study, which showed that supplementation with copper can reduce the frequency of premature rupture of membranes. Also ,In a study by Liu et al., changes in levels of copper, zinc, calcium, and magnesium in natural pregnant women during the different pregnancy periods were investigated in 2010, and the results of this study showed that changes in copper, calcium and magnesium levels There was a statistically significant difference between the three times studied in pregnancy and zinc in the middle and late gestation and postpartum, and in fact, the levels of these elements in pregnant women were lower than non-pregnant women. This study can indicate the use of the fetus in the body. In our study, the average serum copper levels in pregnant women in the control group decreased at the end of the study compared to the beginning, which was consistent with the study by Liu et al. (11).Also, in a study by Moghaddam-Banaem et al in 2010, the association between serum zinc, copper, magnesium, iron, calcium, and cord blood levels with low birth weight was studied. Copper deficiency was found in 53.5% of samples but did not show any relation to low birth weight. These results are in fact consistent with the results of our study on the lack of correlation of copper deficiency with low birth weight (12).

Conclusions:

Based on our findings, administration of copper supplements for pregnant women can reduce the preeclampsia and premature rupture of membranes, which can lead to dangerous outcomes such as uterine infections, abortions and/or intrathoracic deaths or dangers for women Pregnant women.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Tables and Charts:

Figure.1: Mean serum copper level before and after intervention

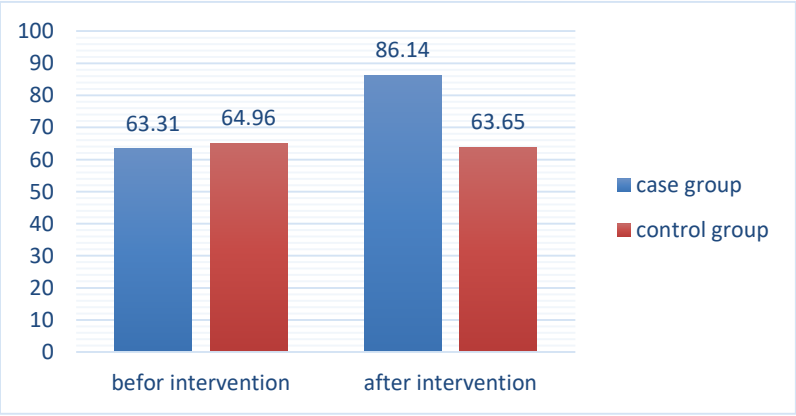

Figure.2: Study of pregnancy outcomes in two groups

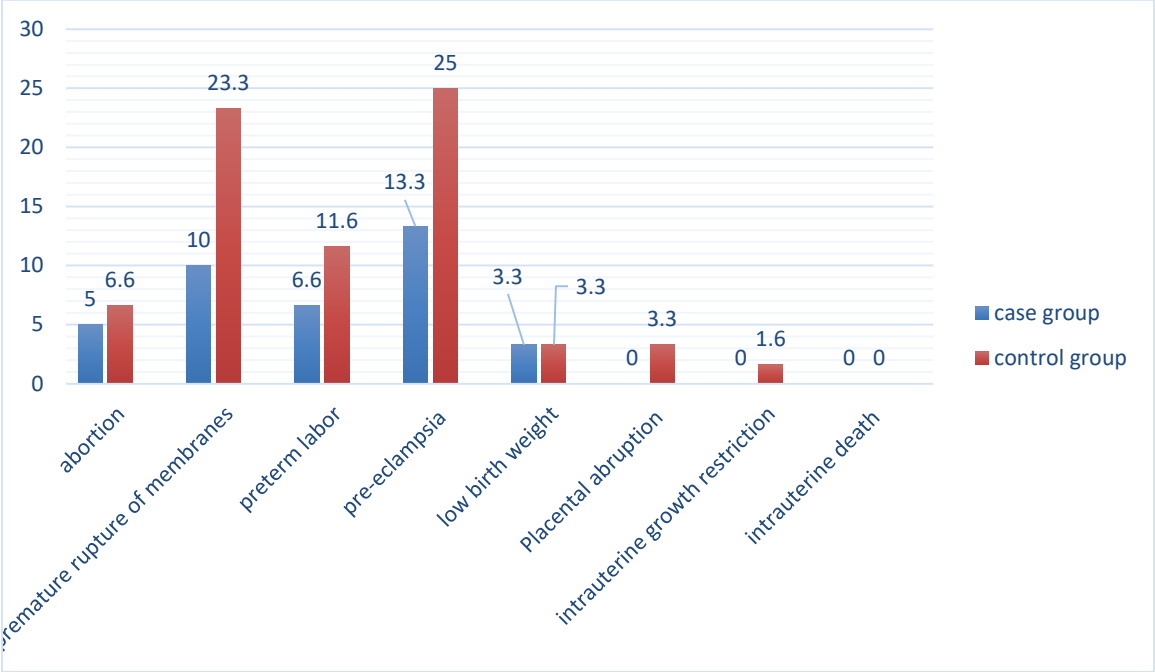

Figure.3: Study of pregnancy outcomes in two groups

	Case - group	Control- group	total	p-value
abortion	3 (5 %)	4 (6.6 %)	7 (5.8 %)	P> 0.05
premature rupture of membranes	6 (10 %)	14 (23.3 %)	20 (16.6 %)	***P = 0.025***
preterm labor	4 (6.6 %)	7 (11.6 %)	11 (9.1 %)	P> 0.05
pre-eclampsia	8 (13.3 %)	15 (25 %)	23 (19.1 %)	***P = 0.034***
low birth weight	2 (3.3 %)	2 (3.3 %)	4 (3.3 %)	P> 0.05
Placental abruption	0	2 (3.3 %)	2(1.6 %)	-
had intrauterine growth restriction	0	1(1.6 %)	1 (0.8 %)	-

intrauterine fetal death	0	0	0	-