

# Variations of Serum Copper Values in Pregnancy

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## SUMMARY

**Introduction** Copper is essential micronutrient and has an important role in the human body. The serum copper increases during pregnancy and is doubled at full term. Lower levels of serum copper in pregnancy are connected with some pathological conditions.

**Objective** The aim of this study was to estimate the levels of serum copper in normal and pathological pregnancies, comparing them with values of serum copper in non-pregnant women, to determine if serum copper is lower in some pathological pregnancies and if this is of some importance.

**Methods** A total of 2170 plasma samples for copper analyses were made in the following groups: healthy non-pregnant women; healthy pregnant women from the 5<sup>th</sup>-40<sup>th</sup> gestational week, during the first delivery stage and during the first three postpartum weeks, in pregnant women with habitual abortion, imminent abortion, abortion in progress, missed abortion (9<sup>th</sup>-24<sup>th</sup> weeks), missed labour and premature rupture of membranes (29<sup>th</sup>-40<sup>th</sup> weeks). Levels of serum copper were determined by colorimetric technique of bathocuproin with disulphate as a chromogen.

**Results** Serum copper values in non-pregnant women range from 11.6-25.8 µmol/L. In healthy pregnant women, there is a constant trend of the increase of serum copper. The mean serum copper values revealed three significant peaks at the 22<sup>nd</sup>, 27<sup>th</sup> and 35<sup>th</sup> gestational week. Serum copper values in the patients with some pathological pregnancies in relation to the serum copper values of the healthy pregnant women were significantly lower.

**Conclusion** Serum copper values can be used as an indicator of some pathological pregnancies.

**Keywords:** serum copper; pregnancy; missed labour; spontaneous abortion; premature rupture of membranes

## INTRODUCTION

Copper is essential micronutrient and is required for the formation of many enzymes, with important role in the human body. It has an important role in pregnancy for the formation of a wide variety of enzymatic and other processes within the developing foetus. During pregnancy, many changes occur in copper levels and transport in both mother and foetus. The serum copper increases in early pregnancy and continues to rise to reaching levels at full term approximately twice those found in non-pregnant women. Maternal age does not influence copper serum levels [1].

Some analyses have shown substantially lower plasma concentrations of copper in pathological conditions diagnosed during the first trimester of pregnancy (spontaneous abortion, threatened abortion, missed abortion and blighted ovum). No significant differences in maternal plasma blood copper concentrations have been found in pathological conditions (threatened abortion, threatened preterm delivery and pyelonephritis) diagnosed in the second trimester of pregnancy. Tendencies to higher plasma copper concentrations, however statistically insignificant, can be observed in other pathological conditions during the third trimester (gestosis, intrauterine growth retardation, preterm labour) [2].

Copper is delivered to the developing foetus via specific transporters in the placenta that are

regulated by the mother's estrogen and insulin levels. These findings have implications for better understanding of preeclampsia, intrauterine growth retardation, the development of babies born to mothers with gestational diabetes and some genetic disorders [3].

## OBJECTIVE

Aims of this study were: 1) to estimate levels of serum copper values in healthy non-pregnant women, healthy pregnant women and to find out if there is a change in serum copper levels during normal pregnancy, delivery and the postpartum period, and if so, to determine the level of significance compared with the serum copper values in healthy non-pregnant women; 2) to determine if there is a significant difference between the mean serum copper levels in different weeks of gestational age of healthy pregnant women with normal course of pregnancy; 3) to find out if there is a change of serum copper levels in some pathological pregnancies (habitual abortion, imminent abortion, abortion in progress, missed abortion, missed labour and premature rupture of membranes) and if so, at which significant level compared with serum copper values in healthy pregnant women with normal pregnancy course and in healthy non-pregnant women; 4) to determine if there is a significant difference in serum copper values

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between the investigated pathological pregnancies; and 5) after having acquired all previous results, to estimate the influence of serum copper levels on the outcome of pregnancy and its significance for the prediction and control of some pathological pregnancies.

## METHODS

A total of 2170 maternal plasma samples for copper analyses were made in the following groups of women:

Control group – a: Healthy non-pregnant women (N=31) of fertile age with no therapy administered for at least 6 months before investigation and during the investigation.

Control group – b: A total of 1240 serum copper determinations were performed in healthy pregnant women with normal course of pregnancy with no hormonal therapy applied, with no diseases (pregnancy related or not related to pregnancy) of either genital or some other organs. The patients were distributed into groups of 31 women in each gestational week from the 5<sup>th</sup>-40<sup>th</sup> gestational week; in the first delivery stage (term delivery with intact membranes and the average cervical dilation of 4-5cm N=31), and in the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> week postpartum (delivery completed at term and no obstetric intervention applied, 7, 14 and 21 days after delivery; 31 women in each week). Women were not followed longitudinally.

Groups with pathological pregnancies: Serum copper was analyzed in every week from the 9<sup>th</sup>-24<sup>th</sup> weeks of pregnancy in women with habitual abortion (more than 3 spontaneous abortions, normal clinical findings, whereas the reason for hospitalization was a “burdened” obstetric history, N= 165) ; imminent abortion (small amount of bleeding from the uterus, slight lower abdominal pain, cervix closed, N=177); abortion in progress (cervix completely opened, embryo and trophoblast protruding from the cervix, with blood taken immediately after the completed spontaneous abortion, N=178); missed abortion (non-viable embryo/foetus, N=190). Serum copper was estimated in every week from the 29<sup>th</sup>-40<sup>th</sup> weeks of gestational age in women with missed labour (vaginal delivery, stillborn foetus over 1000 g of weight, with no signs of either maceration or foetal malformations, blood taken before the delivery, N=31) and women with premature rupture of membranes (blood samples obtained 24-48 h after membrane rupture in vital pregnancy, N=158). Women with abortion in progress, missed abortion and missed labour were, at some point in the study, formed as a group of „pathological pregnancies with bad outcome”.

In all investigated patients gestational age was determined by ultrasound. Blood samples were obtained from the cubital vein in the morning, on an empty stomach.

The copper content of blood serum was determined by colorimetric technique of bathocuproin with disulphate as a chromogen.

Data were analyzed with descriptive statistical methods and the t-test by SPSS program (testing significance of correlation coefficient, SD for ungrouped data, percentage structure of arithmetical median values, standard errors,

t-test for two unrelated groups with different number of cases and others.).

## RESULTS

In healthy non-pregnant women, serum copper values ranged from 11.6-25.8  $\mu\text{mol/L}$  (mean value 20.15  $\mu\text{mol/L}$ ).

In healthy pregnant women with normal course of pregnancy, there was a constant trend of the increase of the mean serum copper values comparing to the mean serum copper values in healthy non-pregnant women. The results of t-test ( $t=4.66$ ) suggested a high statistical significance ( $p<0.01$ ) in the period between the 7<sup>th</sup> gestational week and 4<sup>th</sup> postpartum week. Analyses showed three significant peaks ( $p<0.01$ ) of the serum copper levels at the 22<sup>nd</sup>, 27<sup>th</sup> and 35<sup>th</sup> weeks of pregnancy, while maximal values were recorded in the interval between the 38<sup>th</sup> and 40<sup>th</sup> weeks of pregnancy.

There was a decrease of the mean serum copper values of 9% during the first stage of delivery comparing to the mean serum copper values in healthy pregnant women during the 40<sup>th</sup> week of pregnancy ( $p<0.05$ ).

During the first postpartum week, the decrease of mean serum copper values of 15.8% was recorded in relation to the mean serum copper values of the pregnant women during the first delivery stage ( $p<0.01$ ). On the basis of the trend of decrease of the mean serum copper values after delivery, it could be concluded with a high probability (95.45%) that during the 5<sup>th</sup> postpartum week, the mean serum copper values would decrease to the level of those obtained in healthy non-pregnant women.

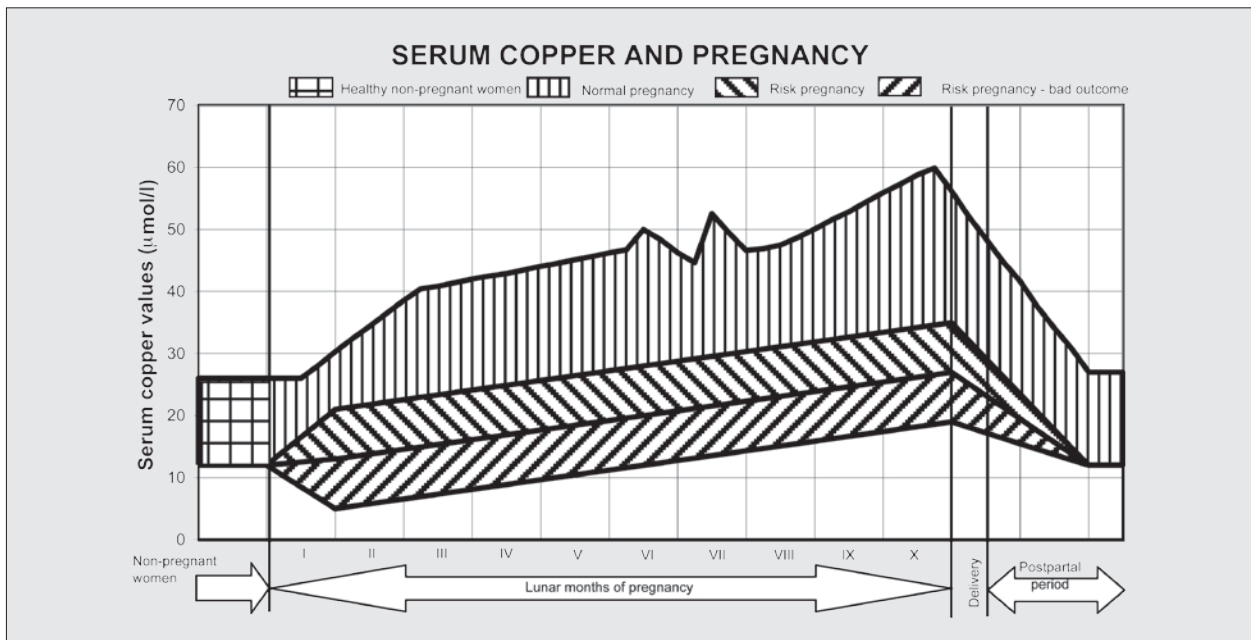
The mean values obtained in the serum of healthy pregnant women with a normal course of pregnancy represented the standard course. Dispersion of individual serum copper values within a range of  $\pm 2$  SD can represent the standard of the general trend of serum copper values in normal pregnancy.

In pathological pregnancies (habitual abortion, imminent abortion, missed abortion, missed labour, spontaneous abortion, premature rupture of membranes) the mean serum copper values were significantly lower ( $p<0.01$ ) comparing with the mean values obtained in the serum of healthy pregnant women with a normal course of pregnancy. There was no statistical significant difference ( $p>0.05$ ) in the trend of mean serum copper values between analyzed pathological pregnancies.

Therefore, the trends of serum copper values in the patients with the above mentioned pathological conditions during the 1<sup>st</sup>-40<sup>th</sup> gestational week could be presented by common tabular values (Table 1), i.e. the common graph

**Table 1.** Variations of serum copper values through trimesters of pregnancy in normal and pathological pregnancies

Pregnancy	Serum copper value ( $\mu\text{mol/l}$ )		
	I trimester	II trimester	III trimester
Normal	24-43	30-52	35-60
Pathological	17-25	22-30	27-35
Pathological with bad outcome	<17	<22	<27



**Graph 1.** Variations of serum copper values through trimesters of pregnancy in normal and risk- pathological pregnancies

(Graph 1). For better overview in the table (Table 1), pregnancy was divided in three trimesters, and pathological pregnancies with bad outcome (abortion in progress, missed abortion and missed labour) are shown separately, because of lower serum copper levels in these conditions (although not statistically significant).

## DISCUSSION

Copper (Cu) is an oligoelement which is a constitutional part of each cell. Its biological value could be compared with hormones, vitamins and ferments. Atomic weight of copper is 63.57, specific weight 8.93-8.95, and atomic number 29. About 96% of plasma copper is firmly bound to ceruloplasmin.

In physiological and pathological conditions, the increase of serum copper values is varying in dependence on the increase of serum ceruloplasmin and its surplus is excreted through urine. Copper plays the main biochemical role being a component of metalloenzymes and metalloproteinase. A common characteristic of enzymes containing copper is their ability of using elementary oxygen as a substrate for oxidation and hydroxylation. Most metalloenzymes are oxidases, hydroxylases and superoxide dismutases. Physiological functions related to copper are based on the biochemical functions of one or more copper metalloenzymes. Serum copper levels are influenced by numerous humoral factors [2, 4-10].

In pregnancy, copper levels in maternal serum rise, more or less in parallel with increases in serum ceruloplasmin. At the same time, total body copper levels increase, but not in the tissues normally associated with copper homeostasis. The placental transport system changes during the latter stages of the development resulting in the transport of higher copper values towards the end of gestation than that of earlier pregnancy. Most of the copper transferred

across the placenta is found in the foetal liver, and during pregnancy serum levels in the foetus actually drop. Copper uptake is a carrier-mediated process, while intracellular transfer is mediated by proteins known as chaperones. The copper uptake is enhanced by a high affinity carrier Ctr1, which is expressed early in pregnancy, transferred to chaperones and carried to the ATPases, where it is pumped across the cell membrane. Copper is delivered to the developing foetus via specific transporters in the placenta that are regulated by the mother's estrogen and insulin levels [11].

These findings have implications for better understanding of preeclampsia, intrauterine growth retardation, the development of babies born to mothers with gestational diabetes and some genetic disorders. Lipid peroxides in serum and placental tissue, and iron, copper and ceruloplasmin levels in serum were significantly increased in pregnant women with severe eclampsia [3].

During pregnancy, the metabolism of copper and iron is tightly interlinked and the deficiency of one has marked effects on the metabolism of the other metal. In the mother, iron deficiency results in the increase of liver copper levels. This is associated with an increase of serum copper levels in the mother and in the activity of maternal serum ceruloplasmin. Given the high incidence of maternal anaemia during pregnancy, and that many of those who are prescribed iron supplements show no significant improvement, it is tempting to conclude that at least some of the cases are the consequence of low copper when considering iron supplement administration, copper status must be also taken into account [3].

Adequate maternal copper supply is essential for normal embryogenesis. Studies in laboratory animals as well as in domestic animals under field conditions have shown that maternal copper deficiency produces effects ranging from intrauterine growth retardation and teratogenesis to embryonic or foetal death. Persistent postnatal complica-

tions of prenatal copper deficiency can also occur. Current data suggest that changes in free radical defence mechanisms, connective tissue metabolism and energy production can all contribute to the dysmorphogenesis associated with developmental copper deficiency.

Increased number of complications in pregnancy requires a simple, cheap and practical test which could quickly determine the functional condition of the placenta and foetus. Some authors [2, 9-16] suggest that serum copper levels can be used as a very sensitive indicator of condition and further possible course of pregnancy and placental functions.

Out of the total of all risk pregnancies (20-30% of all pregnancies), 10-20% are spontaneous abortions, though some authors claim the percentage is even higher (31%).

Almost  $\frac{3}{4}$  of spontaneous abortions occur between the 11<sup>th</sup> and 12<sup>th</sup> gestational week. Imminent abortion (abortus imminens) is most frequent (about 40%) of all clinically manifested forms. About 4% of all spontaneous abortions belong to habitual abortion (abortus habitualis). Habitual abortions are most complicated regarding cause, treatment and prognosis. The risk of repeated spontaneous abortions with the next pregnancy is 22%, and after three spontaneous abortions, it rises up to 47%. The causes of spontaneous abortion and stillbirth are numerous and yet not completely explained (missed abortion, missed labour). Aetiology of premature rupture of membranes is a complex issue. The literature data [2, 10, 12] suggest that serum copper decrease leads to a reduction of elastin and collagen resulting in premature rupture of membranes.

Through the scope of literature [1-19] data, we have come to a conclusion that prior to this study, there were

no relevant standard values of normal copper serum levels established concerning normal pregnancy, delivery and postpartum period as well as some pathological pregnancies. On the basis of the results achieved in this study, we suggest that the lower levels of serum copper in pregnancy could be predictors of some pathological pregnancies (habitual abortion, imminent abortion, missed abortion, missed labour, spontaneous abortion, premature rupture of membranes) and should be introduced into the protocol of routine prenatal diagnostics.

## CONCLUSION

This study reveals serum copper values in healthy non-pregnant women which range from 11.6-25.8  $\mu\text{mol/L}$ . A constant trend of increase of mean serum copper values during normal pregnancy is detected compared to mean serum copper values in healthy non-pregnant women. The mean serum copper values in investigated patients with some pathological pregnancies: habitual abortion, imminent abortion, abortion in progress, missed abortion, missed labour and premature membrane rupture were found to be statistically significantly lower than in the normal course of pregnancy. On the basis of these results, a graph of normal values for serum copper in pregnancy is established together with values for some pathological pregnancies. We conclude that these serum copper values can be used as an indicator of the condition of pregnancy and foetoplacental unit, and could be introduced into the protocol of routine prenatal diagnostics as a simple, cheap and accurate method.

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## Промене вредности бакра у серуму током трудноће

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### КРАТАК САДРЖАЈ

**Увод** Бакар је есенцијални олигоелемент и има важну улогу у људском телу. Вредност бакра у серуму се повећава током трудноће и у термину је двоструко већа. Ниже вредности повезане су с неким патолошким стањима у трудноћи.

**Циљ рада** Циљ рада био је да се одреде промене нивоа бакра у серуму током нормалне и патолошке трудноће, а затим ове вредности упореде с купремијом негравидних жена и утврди да ли је у неким патолошким трудноћама ниво бакра био нижи, односно има ли ово неког значаја.

**Методe рада** Урађено је 2.170 анализа вредности бакра у серуму: код здравих негравидних жена, здравих гравидних жена по недељама гестације (од 5. до 40. недеље), током првог порођајног доба и прве три постпарталне недеље, код жена са честим побачајима, претећим побачајем, побачајем

у току, изосталим (тзв. *missed*) побачајем (од 9. до 24. недеље трудноће), код интраутерусне смрти плода и превременог прснућа водењака (од 29. до 40. недеље трудноће). Нивои бакра су одређивани колориметријском техником батокупроина са дисулфатом као хромогеном.

**Резултати** Вредности бакра у серуму негравидних жена биле су 11,6–25,8  $\mu\text{mol/l}$ . Код здравих трудница уочено је стално повећање купремије током трудноће, са три врхунца – у 22, 27. и 35. недељи гестације; највише вредности биле су између 38. и 40. недеље. Нивои бакра у серуму жена са патолошким трудноћом били су значајно нижи.

**Закључак** Вредности бакра у серуму могу се користити као индикатор неких патолошких трудноћа.

**Кључне речи:** бакар у серуму; трудноћа; спонтани побачај; интраутерусна смрт; превремено прснуће водењака

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