



Original Research Article

Do copper levels alter in different phases of pregnancy: A hospital based cross sectional comparative study

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ABSTRACT

Introduction: Pregnant women undergo various hormonal and metabolic adaptations. The focus of the present study was to assess various biochemical parameters including serum copper in the second or third trimester pregnant women. It is a cross sectional study carried out at a tertiary care center i.e. SMIMER, Surat, India.

Material and Methods: 2nd trimester and 3rd trimester pregnant women were included in this study and compared with age matched apparently healthy women. Women with history of smoking, alcohol/tobacco addiction, liver disease, chronic renal failure, diabetes mellitus, hypertension and endocrine disorders were excluded from the study. After informed consent, blood samples were collected. Analysis of various biochemical parameters including copper were analyzed and data was analyzed.

Results: Significantly lower level of urea, creatinine, albumin, total protein, total bilirubin, alanine aminotransferase & aspartate aminotransferase activity in pregnant subjects compared to control was observed. Significantly increased dyslipidemia was observed in pregnant women compared to controls. Significantly higher levels of serum copper were observed in 3 trimester followed by 2 trimester compared to controls. This happened irrespective of age and gravida status.

Conclusion: As expected lower levels of various biochemical parameters were found in pregnant women compared to controls due to hemodilution. Important finding of this study is the dyslipidemia observed in pregnant women which may be attributed to hormonal and metabolic changes. There was an increasing pattern in the levels of serum copper as the pregnancy progresses but pattern exists in a population needs to be explored.

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1. Introduction

Like any machine tool which requires constant supply of essential elements for proper maintenance, human body also needs to be supplied nutrients in a balanced way to keep it under normal physiological milieu. Both major and minor nutrients play a crucial role in the maintenance of health. Such nutrients include vitamins and trace elements in addition to other nutrients.¹ Irrespective of gender age group, in the absence/deficiency of any of these elements may lead to detrimental effects and this is more so in case of women with pregnancy wherein the emphasis of maintaining the physiological levels is more as it affects

both mother and the child to be born. Another important and pertinent aspect in the women with pregnancy is the change in internal milieu and the onus of maintaining proper balance lies on the pregnant woman for maintaining of not only her health but also taking care of supply of nutrients to fetus. Our experience in dealing with the analysis of microelements is that a major section of population have low levels, especially vitamin D and B₁₂, hence we can expect similar trend in the levels of trace elements also. In general, copper level in blood increases in pregnancy due to increased absorption, mobilization from liver and decreased biliary copper excretion. Fetus is fully dependent on maternal copper supply.^{2,3} The demand for trace elements in normal pregnancy, especially in 3rd trimester and at parturition impose considerable systemic

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oxidative, metabolic, and inflammatory stresses that play important role in many adverse pregnancy outcomes such as miscarriage, preeclampsia, gestational diabetes mellitus, and uterine growth restriction.² Many enzymes like catalase, superoxide dismutase and cytochrome oxidase are dependent on copper. Copper is also essential for embryonic development as it is involved in metabolic reactions, angiogenesis, oxygen transport and antioxidation.⁴ Embryonic requirement for copper is fulfilled by placenta as high affinity copper transporters (CTR1) transport copper from maternal to fetal circulation.⁵ Ceruloplasmin is a protein with ferroxidase activity which strongly binds to the major part (96%) of serum copper.^{6,7} Copper deficiency during embryonic and fetal development can result in numerous gross structural and biochemical abnormalities. It is estimated that more than 50% of human conceptions fail to implant, and of those implanting, approximately 30% fail to reach term.⁸ Looking into the importance of copper in pregnant women and lacunae of literature regarding the study of copper levels in these women of this area, we have taken up this study to analyze serum copper in the pregnant women who were on second and third trimester and compared with non-pregnant controls.

2. Materials and Methods

The present study was carried out in the Biochemistry department of Surat Municipal Institute of Medical Education and Research, Surat, India. A total of 160 pregnant women (80 subjects of 2nd trimester and 80 subjects of 3rd trimester) between 20 to 40 years of age but without any history of smoking, tobacco/alcohol addiction, liver disease, chronic renal failure, diabetes mellitus, hypertension and endocrine disorders were selected from Obstetrics and Gynecology department and included in the study. 80 apparently healthy age matched subjects were randomly selected for the purpose of control subject. Ethical clearance was obtained from the institutional ethical committee. After informed and written consent, venous blood samples were collected for biochemical analysis.

2.1. Sample collection

About 5 ml of blood was collected using sterile technique. Serum was separated by centrifugation process at 3000 rpm for 10 minutes and separated serum was divided equally in two aliquots. One aliquot was used for routine biochemical parameters and the other for Copper estimation and they were stored at 2-4 C and -20 C till analysis respectively.

2.2. Biochemical analysis

Serum samples were analyzed for the estimation of creatinine by modified Jaffe's reaction,⁹ urea by Berthelot method,¹⁰ total protein by Biuret method,¹¹ albumin

by BCG method,¹² bilirubin by modified Jendrassik and Groff's method,¹³ alkaline phosphatase by IFCC kinetic method,¹⁴ alanine aminotransferase & aspartate aminotransferase by modified IFCC kinetic method,¹⁴ total cholesterol by CHOD-POD method, Triacylglycerol by GPO-POD method, HDL-cholesterol by precipitation method and LDL by direct method¹⁵ on fully automated biochemistry analyzer Erba-XL-640 after calibration with Randox multi calibrator. Serum copper concentration was estimated by Graphite furnace atomic absorption spectrometry on fully automatic AAS instrument by Thermofisher. Sample preparation was carried out as mentioned by Guler et al (1991)¹⁶ after standardization with NIST certified calibrator.

2.3. Statistical analysis

Statistical analysis of obtained results was carried out using open-epi software and libre office package. Data were represented by mean and standard deviation and p value less than 0.05 was considered significant.

3. Results

Table 1 gives details of age wise distribution of non-pregnant, 2nd trimester pregnant and 3rd trimester pregnant subjects

Table 2 shows concentration of various biochemical parameters in non-pregnant control subjects, 2nd trimester pregnant and 3rd trimester pregnant subjects. Blood urea and serum creatinine concentrations were significantly lower in pregnant subjects as compared to control subjects. Same trend was also observed with serum total protein and albumin concentration. In case of serum albumin, a significantly lower concentration was found in 3rd trimester pregnant subjects compared to 2nd trimester subjects and such trend however was not observed with total protein concentration. Serum total bilirubin concentration was significantly lower in all pregnant women as compared to control subjects. Serum alanine aminotransferase & aspartate aminotransferase activity was significantly lower in 3rd trimester pregnant cases as compared to control subjects. A significant difference in serum alkaline phosphatase activity was observed among controls, 2nd and 3rd trimester pregnant subjects with significantly higher concentrations in 2nd trimester subjects compared to non-pregnant women and significantly higher levels in 3rd trimester subjects compared to 2nd trimester. Serum total cholesterol concentration and LDL-cholesterol was significantly higher in 2nd and 3rd trimester pregnant women as compared to control subjects. Serum HDL levels were significantly lower in second trimester compared to controls. However, all these biochemical parameters were within normal range. Serum copper concentration in non-pregnant women, 2nd trimester pregnant and 3rd trimester pregnant

Table 1: Age wise distribution of pregnant and non-pregnant controls

Age (years)	Non-pregnant control	Pregnant subjects Second trimester	Third trimester	Total
20-26	37	55	48	140
27-33	27	21	29	77
34-40	16	04	03	23
Total	80	80	80	240

Table 2: Concentrations of routine biochemical parameters and copper in non-pregnant, 2nd trimester and 3rd trimester pregnant subjects

Parameters	units	Control (N=80)	2nd trimester (N=80)	3rd trimester (N=80)	All pregnant women (N=160)
Urea		17.03 ± 5.5	11.81 ± 4.2*	10.2 ± 3.9*	11.2 ± 4.1*
Creatinine		0.77 ± 0.16	0.54 ± 0.18*	0.56 ± 0.25*	0.55 ± 0.22*
Total Bilirubin		0.54 ± 0.30	0.34 ± 0.14	0.42 ± 0.20	0.39 ± 0.18*
Total Cholesterol	mg/dl	143 ± 37	159 ± 70*	176 ± 70*	166 ± 70*
Triglyceride		117 ± 50	123 ± 65	170 ± 81*	147 ± 77*
HDL		44 ± 10	38 ± 17*	42 ± 13	39 ± 15*
LDL		78 ± 25	103 ± 54*	108 ± 44*	105 ± 49*
Total Protein		5.75 ± 1.15	4.89 ± 1.52	4.92 ± 1.35	4.95 ± 1.43*
Albumin	g/dl	3.59 ± 0.78	3.02 ± 0.70*	2.88 ± 0.64*	2.95 ± 0.67*
Alanine aminotransferase	U/L	22.2 ± 16.2	20.3 ± 22.6	14.3 ± 7*	17.2 ± 17
Aspartate aminotransferase		29.5 ± 13.8	26 ± 23.1	20 ± 9.7*	22.1 ± 17.9*
Alkaline phosphatase		58 ± 35	60 ± 53*	102 ± 52*	77 ± 56*
Copper	ug/dl	45 ± 27	115.2 ± 50.9*	145 ± 48*	130 ± 51*

subjects was $45 \pm 27 \mu\text{g/dL}$, $115.2 \pm 50.9 \mu\text{g/dL}$, $145 \pm 48 \mu\text{g/dL}$ respectively. Serum copper concentration was significantly higher in 2nd and 3rd trimester subjects as compared to control subjects. When the levels of serum copper were compared between two trimester, higher levels were found in third trimester.

Table 3 shows serum copper concentration in non-pregnant controls, 2nd t and third trimester pregnant subjects distributed according to age groups of 20-26 years, 27-33 years and 34-40 years. Serum copper concentration was higher in pregnant subjects as compared to non-pregnant control subjects of corresponding age groups. However, in each category of subjects, no significant difference among various age groups was observed.

Table 4 shows the serum copper concentration according to gravida status of pregnant subjects. It was found that serum copper concentration was significantly higher in 3rd trimester as compared to 2nd trimester pregnant subjects in both, primi-gravida and multi gravida. However, no significant difference between primi-gravida and multigravida in the subjects who were in 2nd and 3rd trimester.

4. Discussion

In the present study, we have examined the pattern of various biochemical parameters and serum copper

concentration in the second and third trimester of pregnant women and compared it with the non-pregnant age matched control subjects. A total of 240 women were included in the study. Out of these 80 were in second trimester, 80 were in third trimester and 80 were age matched non-pregnant control subjects.

Among the various biochemical parameters, blood urea and serum creatinine levels were significantly lower in second and third trimester pregnant women as compared to control subjects. This may be due to changes in the vascular and interstitial tissue, which results in increased cardiac output, renal plasma flow and glomerular filtration rate.^{17,18} Our results are in correlation with the earlier findings of other workers.¹⁹

One important physiological change in pregnancy is hemodilution which leads to decrease in many biochemical parameters. Considering this aspect, we have studied many biochemical parameters to find out change of pattern of these parameters pertaining to functional assessment of liver such as total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Many studies have been carried out to find out pattern but so far, no clear pattern has been established in different trimesters.²⁰⁻²²

Serum albumin concentration was significantly lower in second and third trimester pregnant women, however serum

Table 3: Serum copper levels in different age groups of non-pregnant and pregnant women in different trimesters

Age group (years)	Non-pregnant	2 nd trimester	3 rd trimester	P value
20-26	44 ± 28 (N=37)	115 ± 51 (N=55)	144 ± 47 (N=56)	p<0.05
27-33	46 ± 24 (N=27)	114 ± 44 (N=21)	143 ± 49 (N=21)	p<0.05
34-40	49 ± 27 (N=16)	127 ± 89 (N=04)	185 ± 57 (N=03)	p<0.05
P value	p=0.8	p=0.9	p=0.3	

Table 4: Details of serum copper levels according to gravida status

	Primigravida	Multigravida	p value
2nd Trimester	105 ± 50 (N=17)	118 ± 51 (N=63)	p=0.4
3rd trimester	149 ± 44 (N=18)	144 ± 49 (N=62)	p=0.7
Total	127 ± 52 (N=35)	131 ± 52 (N=125)	p=0.7
p value	p<0.05	p<0.05	

total protein concentration didn't show such difference, but when the pregnant women of this study were compared against control subjects for total protein concentration, a significantly lower concentration than control subjects was observed. There may be negative feedback effect of alpha-fetoprotein of fetal origin on the maternal production of albumin during pregnancy.²³ Our results are correlation with the findings of other workers.^{24–26}

Among the liver function tests, total bilirubin level was significantly lower in all the groups of pregnant women as compared to control subjects. Serum alanine aminotransferase & aspartate aminotransferase activity were significantly lower in 3rd trimester pregnant women as compared to control subjects. In few studies a marginally lower alanine aminotransferase and/or aspartate aminotransferase activity has been found in third trimester however in majority of published data serum alanine aminotransferase & aspartate aminotransferase activity level did not find to be changed during pregnancy.^{27–31} Serum alkaline phosphatase activity was significantly higher in second and third trimester pregnant women as compared to control subjects with highest level in third trimester. Our findings are in correlation with Bacq et al (2013).³² The rise in 3rd trimester can be explained by the increased production of bone isoenzyme.^{32–35} The changes in various liver parameters indicate that these changes are transient as any other physiological change a woman undergoes during pregnancy.

Dyslipidemia was found in the pregnant women by looking at the levels of various serum lipid parameters as compared to non-pregnant subjects. Serum total cholesterol and LDL were significantly higher in second and third trimester pregnant women, serum triacylglycerol levels were significantly higher in 3rd trimester pregnant women, and serum HDL level was significantly lower in second trimester pregnant women. As Insulin resistance is commonly observed in pregnant women^{36–38} increased insulin resistance might be associated with development of dyslipidemia as the above-mentioned changes pertaining to

various lipid profile observed in the present study. Our findings are in correlation with other workers.^{19,36,37}

Like in any other individual, balanced supply of trace elements is a crucial aspect in pregnant women to maintain proper health. In fact, it is more important in pregnancy as the needs of mother and fetus has to be taken care. Different trace elements have different roles and most of the trace elements work in tandem. In pregnancy it is essential to maintain normal iron levels in serum and to maintain these levels the daily requirement of iron is more than what a non-pregnant woman consumes. It is not only sufficient to supply the iron but also a proper absorption has to take place, for that a different trace element i.e. copper is required as the copper containing ceruloplasmin play a crucial role in the absorption of iron. Further lower level of copper in pregnant woman is associated with pathological pregnancies i.e. habitual abortion, imminent abortion, missed abortion, missed labor, spontaneous abortion, premature rupture of membrane.³⁹ Considering this aspect, we have analyzed serum copper in the present study. Serum copper was analyzed using atomic absorption spectrometer in non-pregnant control, second trimester and third trimester pregnant women. Serum copper concentration levels were 45 ± 27, 115.2 ± 50.9, 145 ± 48 µg/dl in non-pregnant control, second and third trimester pregnant women respectively. The levels of second and third trimester were significantly higher than that of control subjects. Further the level of third trimester were significantly higher than that of second trimester. One important aspect that has to be taken into consideration the serum copper levels increased inspite of existing hemodilution. The findings of the present study are in concurrence with the results reported by previous workers.^{40–42} The reference range of serum copper concentration is 70-140 µg/dl in normal healthy population.⁴³ Non-pregnant women in our study had lower serum copper levels than that of reported reference values suggesting a general trend of low serum concentration of copper in women, as most of the subjects of our study

belonged to middle and lower middle-income group in whom dietary intake may not be sufficient to maintain adequate levels of essential nutrients like trace elements. Second trimester copper level were within reference range whereas third trimester level were higher than that of reference range. Such increase in copper level with progression of pregnancy could be partly due to increased synthesis of ceruloplasmin as a result of increased level of maternal estrogen. In addition to this, altered hormonal milieu also decreases the biliary copper excretion.^{44,45} Other pertinent point behind the observation of increased serum copper levels in second and third trimester compared to non-pregnant women is that the study subjects were those who were visiting a tertiary care hospital and aware of maintain proper balance of nutrients during pregnancy either by dietary intake or through supplementation. However, one cannot be sure of the observing similar trend if it is carried out in population of middle and lower middle-class society outside the purview of hospital visits i.e population based studies. To come to a definitive conclusion regarding the trend of serum copper in different trimesters, it is advisable to carry out both hospitalized and population-based studies in a large number of population. Such studies are necessary as copper plays very important role in the maintenance of serum iron levels which in turn required for adequate synthesis of hemoglobin.

We have further examined serum copper concentration in the different age groups of non-pregnant control subjects, second trimester and third trimester pregnant subjects. Serum copper concentration level was found to be significantly elevated as gestation period advances but no significant differences in the concentration of serum copper in the different age group women who were in same trimester. This shows that serum copper concentration is not dependent on age but solely dependent on gestational period. Similar findings were reported by other workers.⁴⁶ We have also studied serum copper levels in primigravida and multigravida but did not find any significant difference.

5. Conclusion

Biochemical parameters including copper were analyzed in serum in controls and pregnant women. Important findings of this study are:

1. Significantly lower level of urea, creatinine, albumin, total protein, bilirubin, alanine aminotransferase & aspartate aminotransferase and increased dyslipidemia was observed in pregnant subjects as compared to controls as higher levels of lipid parameters except HDL were found compared to controls.
2. Serum copper levels were significantly high in 3rd trimester followed by 2nd trimester compared to controls irrespective of age and gravida status.
3. The existence of less than normal levels of serum copper in healthy controls is need to be looked into.

6. Source of funding

None.

7. Conflict of interest

None

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