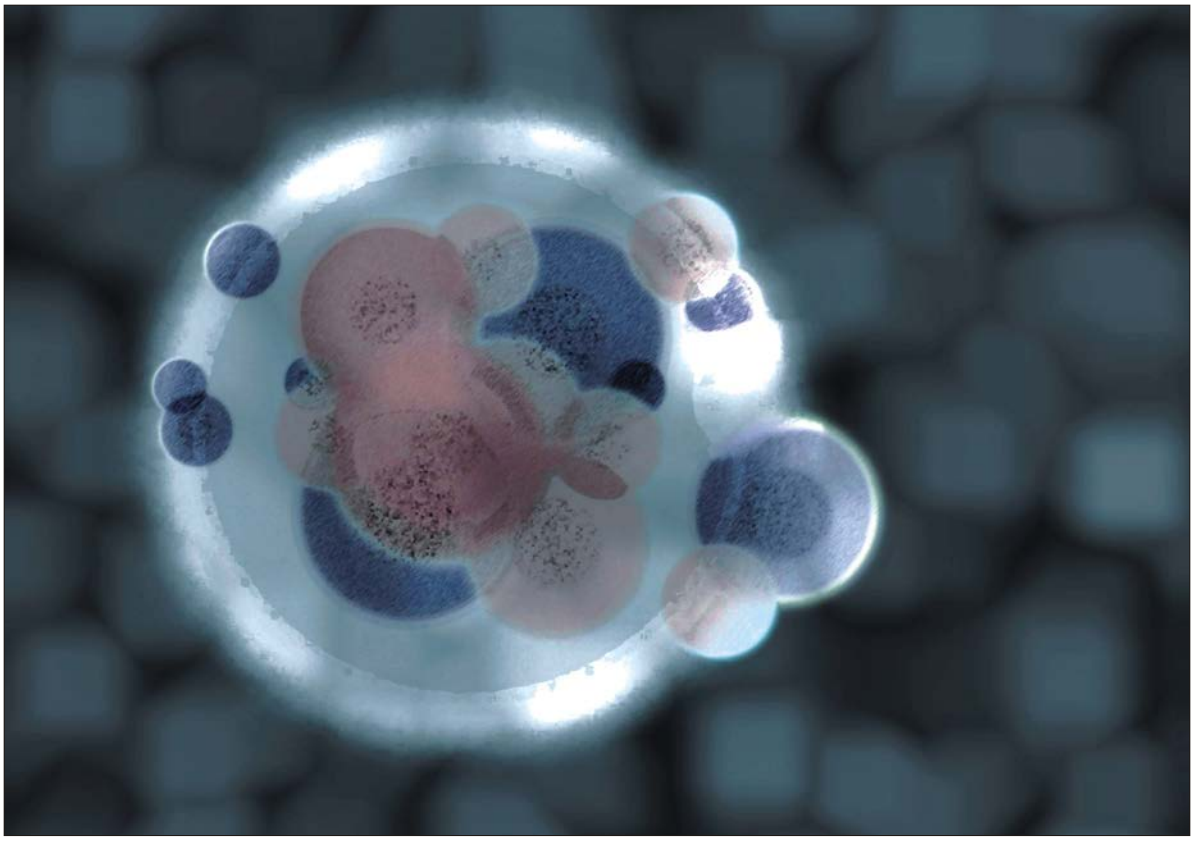

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Maternal Serum Copper Concentration in Premature Rupture of Membrane: A Case-Control Study

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Abstract: Copper is an integrated parts of metal-protein required far varieties of oxide-reductive metabolic pathways in human. Copper deficiency is considered as risk factors in some pregnancies. Premature rupture of membrane is a pregnancy complication with major adverse effects and is believed maternal Copper deficiency can also be considered as interventional factors. This study was done to evaluate if there is a correlation between maternal serum Copper concentration and premature rupture of membrane in pregnancy. In this case-control study 60 pregnant women with Premature Rupture of Membrane (PROM) were selected as case group including term and pre term the control group consist of 60 pregnant women with normal delivery of term and pre term states. Both group were matched for maternal and pregnancy age. In case and control group the pregnancy at term and pre-term were grouped independently as well. In general the maternal mean serum Copper concentration were 192.4±78.2 and 201.08±82.06 in case and control groups, respectively but this differences statistically was not significant. Data in this study revealed that the absolute value of maternal serum Copper concentration of term or pre term in case groups was slightly lower than related controls. Drop in maternal Copper concentration in some disturbed pregnancies such as premature rupture of membrane is previously demonstrated and based on our data the absolute Copper serum concentration of women with premature rupture of membrane was also slightly lower compared to healthy pregnancy but it was not statistically significant.

Key words: Copper, healthy pregnancy, premature rupture of membrane

INTRODUCTION

Copper is an essential element required for normal human metabolism. Studies indicated that serum Copper deficiency in pregnant women can be accompanied with some adverse effects such as Premature Rupture of Membrane (PROM) in growing fetus leading to either abortion or fetus weight reduction and even fetus growth retardation there are some studies which can find a clear cut role for Copper in pregnancy outcome (Yasodhara *et al*., 1994; Olivares and Uauy, 1996; Ebb *et al*., 1991; Czeizel, 1995; Fu, 1989).

The metabolic pathways in human comprised of many biochemical reactions which mainly catalyzed by enzymes. The enzyme which are protein in nature predominantly require non-protein substances for their biological activity. The non-protein substances can be either an organic or some elements such as Copper, Iron and Zinc which are considered as vital factor for the activity of vast majority of enzymes responsible for oxido-reduction biochemical routs which are crucial in metabolic pathways (Yasodhara *et al*., 1994; Olivares and Uauy, 1996; Ebb *et al*., 1991; Czeizel, 1995).

It is reported that many metabolic disorders are originated as result of Copper deficiency which are considered as essential part of any adequate daily regimen. The Copper is not only a vital factor also crucially required prenatally and fetus growth and development are impaired as result of reduced serum Copper level. Copper is an element with direct involvement in pregnancy outcome and this period of prenatal life is accompanied with alteration in Copper metabolism in fetus and pregnant mother (Alvarez *et al*., 2007; Bro *et al*., 1988; McMichael *et al*., 1994).

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There are some reports indicating the reduction of serum Copper concentration can be adversely affect the pregnancy leading to abortion in the first trimester with no side-effect in the second trimester. Other findings in this area of research elaborate that the third trimester of pregnancy accompanied with higher serum Copper concentration in pregnant women (Alebic-Juretic and Frkovic, 2005).

The growing fetus receives the Copper required for its growth and development through placenta and any change of Copper level in pregnant women directly affect the state of fetus prenatally. Some metabolic disorders in pregnancy interfere with proper supplying of Copper through placenta a matter which should be taken into consideration when dealing with Copper status during pregnancy (Serdar *et al*., 2006).

MATERIALS AND METHODS

In this case-control study 60 pregnant women with premature rupture of membrane were selected as case group the control group consist of 60 pregnant women with normal delivery pain selected as control group. Both group were matched for maternal and pregnancy age. In case and control groups the pregnancy at term and pre-term were grouped independently. The tool for collected data was based on questionnaire contains demographic information. The questionnaire were filled for each pregnant woman face-to-face when arrived at the women hospital in Dezyani teaching center at Gorgan, Iran, a hospital located at south-east Caspian Sea. The control group further divided into those with term and pre term deliver. Two milliliter of blood was taken from each women and the serum was separated subsequently. The serum Copper was determined using Randox-Standards laboratory kit and spectrophotometer techniques.

The findings of this study were analyzed using kolmogorov-smironov and Mann-whitney statistical methods and were presented in table.

RESULTS

The reference range for female Serum copper concentration is 118-302 mic dL^{-1} but this can be increased in the course of pregnancy up to the late stage of pregnancy.

Data analyzes of maternal serum copper concentration in this research project indicated the following results: The copper mean concentration were 201±86 and 207.4±88.5 in case and control groups in term pregnancies, respectively but this differences was not significant. The maternal serum concentration for case and control groups in pre-term pregnancies were 193±74.3 and 195.1±77.7. The normal maternal serum copper concentration pattern in case group was not been followed by kolmogorove-smirov statistical methods and therefore Mann-whitney statistical method was used instead to get a meaningful calculation, but based on either methods of analysis the mean differences was not significant for both case and control group as well ($p>0.05$). Although, it is appeared there is a slight decrease in the mean of maternal serum copper concentration among case group but statistically it was not significant.

Table 1: Mean serum copper concentration of term and pre term pregnancy in normal and pre-mature rupture of membrane (PROM). Serum copper concentration (μg dL^{-1})

Pregnancy status	Healthy	PROM
Term pregnancy	207.4±88.5	201±86.0
Pre-term pregnancy	195.1±77.7	193±74.3

The mean serum copper concentration in pregnant women leading to PROM in term and pre-term pregnancy were 201.4±86 and 193.1+74.3, respectively indicative of lower copper concentration in pre-term pregnancy in pre term case group compared to case with term pregnancy but again this differences was not significant ($p>0.05$).

Other findings in this study indicate that in general the mean serum concentration at term and pre-term in non-PROM pregnancy were 193.8+84.7 and 190.8±71.5 indicating slight decrease in maternal serum copper concentration in pre-term pregnancy. In addition the general the mean copper for all in pre-term pregnancies in case group was 195.1+77.7. The data analysis in this research project indicate that term pregnancy in both case and control groups showing an slightly higher mean concentration when compared internally among themselves which an indicative of importance maternal serum copper concentration for the outcome of pregnancy (Table 1).

DISCUSSION

Human metabolism crucially dependent on micronutrients such as Copper which play a vital role in metabolic pathways. The many biochemical reaction and particularly those with oxido-reduction capacities entirely associated with the presence of enough micronutrient including Copper, Zinc, Iron and many others such as vitamins. Copper within human bodies strongly attached to a protein called ceruloplasmin and Copper is not freely present in the blood circulation but is bounded with ceruloplasmin. The enzymes which utilize copper as their cofactors can consume oxygen as in oxido-reduction pathways, example in this area of metabolic pathways are

verified, but chemical energy production in human within inner mitochondrial membrane and detoxification of many drugs and toxin within the liver entirely dependent on those enzyme and metaloprotein comprising copper as the core subsequent (Alebic-Juretic and Frkovic, 2005; Merker *et al*., 2005; Knutson, 2007; Uriu-Adams and Keen, 2005; Maia *et al*., 2007; Zhang *et al*., 2004; Pathak and Kapil, 2004).

Studies indicate that the micronutrients elements such as copper, zinc are crucial in reproduction cycle in human and copper deficiency during pregnancy might be correlated with some metabolic disorders such as congenital malformations, abortion and PROM premature rupture of membrane due to Copper involvement of such metabolic pathways leading to formation of proper and integrated membrane. In absence of such biochemical pathways the protein required for membrane biosynthesis is diminished leading to rupture and initiating PROM (Yasodhara *et al*., 1994). In general it seems the copper content of female is increased during pregnancy which can be considered as normal routine metabolic pathways as required by the new physiological conditions in female and the extra copper needed for the formation and the growth of new fetus. Many studies elaborate on the role which played by copper on healthy fetus and its deficiency in the premature rupture of membrane (Bro *et al*., 1988; McMichael *et al*., 1994; Fu, 1989).

Serum copper in pregnant female is transported through a tiny regulated system via placenta and the fetus receive the copper from pregnant mother, any metabolic disorder interfering with copper translocation into fetus most probably accompanied with fetus growth disorders and growth retardation, due to copper vital requirement for some metaloproteins urgently needed for divers metabolic function as part of energy production, growth and drug detoxifications (McArdle *et al*., 2008).

Copper metabolism closely correlated with other micronutrient particularly Iron and anemia due to Iron deficiency cannot be overcome unless serum copper value and some other metabolic disorders such diabetes corrected as well to avoid the effect of copper depletion on growing fetus (Serdar *et al*., 2006).

Abortion in pregnancy is a symptom with consequences and the reasons behind it which is not clearly elaborated in details, but the premature rupture of membrane due the malfunction in the biosynthesis of proteins due to copper deficiency requiring Copper as cofactor which leading to rupture of membrane prematurely. Based on such findings the role of copper as essential elements in the integrity of health pregnancy is well documented (Fu, 1989; Olivares and Uauy, 1996).

Although, data from many studies did not established a correlation between serum copper concentration during a routine and impaired pregnancies, but contrary to those reports maternal serum copper concentration can be used as prognostic value in predicting the out-come of pregnancy and growing fetus (Alvarez *et al*., 2007; Alebic-Juretic and Frkovic, 2005; Serdar *et al*., 2006; Merker *et al*., 2005; Knutson, 2007; Uriu-Adams and Keen, 2005; Zhang *et al*., 2004; Pathak and Kapil, 2004; McArdle *et al*., 2008; Gambling and McArdle, 2004; Schulpis *et al*., 2004; Meram *et al*., 2003; Baig *et al*., 2003; Frendo *et al*., 2000; Friel *et al*., 2005; Kantola *et al*., 2000).

CONCLUSION

There are some reports suggesting that drop in copper concentration can be seen in some disturbed pregnancies such as premature rupture of membrane, based on our data this conclusion can also been derived but even the absolute maternal copper serum concentration of women with premature rupture of membrane is lower in about 5-10% compared to healthy and routine pregnancy but it was not statistically significant. Whether this lower amount concentration of maternal copper among premature rupture of membrane pregnancies is a trigger factor in initiating the disruption of pregnancy it needs further comprehensive investigation.

Mean while the maternal serum concentration might be considered as clinical diagnostic index in pregnancy follow-up. If the assumption of intervening maternal copper concentration in initiating PROM is correct the serum copper concentration can be considered as medical diagnostic venue which can be played as important tool clinically when dealing with disturbed pregnancies.

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