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Study of Zinc and Copper Levels in Maternal Serum and Fetal Umbilical Cord in Preterm Labours

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Abstract

Current study designed to assess the status of zinc and copper in women with preterm labour compared to women with term labour. 100 pregnant (50 in preterm labor and 50 in term labour) included in this study. Both study & control group age and parity are matched. Micronutrients Cu & Zn levels (both in maternal serum & fetal umbilical cord) are studied in both groups along with other measures. Normal serum copper level range in pregnancy is taken as 85-170 µg/dl. And umbilical cord copper range as 60-90 µg/dl. Maternal serum copper levels are high in study group (preterm group-114.9) compared to control group (term mothers-108.5) the with an insignificant p value of 0.540. Whereas, umbilical cord copper levels are less in study group (57.7) compared to control group (73.6) (p=0.0001). This implies that 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. Another finding observed was, umbilical cord copper is less than the maternal copper irrespective of period of gestation. Serum zinc values in term pregnancy is taken as 78-132 µg/dl. Maternal serum zinc levels are high in control group (103.7) than in study group (91.8) (p=0.0001). In the same way umbilical cord zinc levels are more in control group (121.6) than in study group (101.2) (p=0.0001. Another finding was umbilical cord zinc levels are less than the maternal zinc levels irrespective of period of gestation. In present study, relationship of birth weight with maternal and umbilical cord copper was observed. Umbilical cord copper levels had a positive correlation with birth weight (p=0.001). In the same way, relationship of birth weight with maternal and umbilical cord zinc was observed. The study showed that maternal serum zinc levels had positive correlation with birth weight (p=0.0001). Umbilical cord zinc levels also had a positive correlation with birth weight, with a significant (p=0.0001). In the present study maternal/neonatal complications vs. Preterm and term was studied, which showed that higher neonatal complications occurred in preterm neonates (26%) compared to term neonates (10%) with a significant (p=0.03). In the same way, higher maternal complications occurred in preterm mothers (18%) compared to term mothers (6%) with a significant (p=0.03). No studies were available in literature regarding copper, zinc deficiency in relation to development of neonatal complications. Neonatal complications in relation to maternal serum and umbilical cord blood levels of copper and

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zinc were studied. The mean values of maternal serum and umbilical cord blood levels of both copper and zinc were found to be less in cases with fetal complications (p=0.0001).

Keywords: Micronutrients; fetal growth; maternal outcome.

Introduction

Micronutrients are vitamins and minerals required in minute amounts for normal functioning, growth and development [1]. Adequate maternal micronutrient status is especially vital during pregnancy and lactation. Micronutrient deficiencies are exacerbated in pregnancy, leading to potential adverse effects not only on the mother but also on fetus. Therefore, micronutrient status plays an important role in pregnancy and birth outcomes. Preterm birth is leading risk factor of neonatal morbidity and mortality. Preterm delivery occurs after 26 weeks but before 37 weeks of gestation [2]. Inspite of increasing antenatal care the rates of preterm delivery and low birth weight have increased in recent years [3]. Nutrition is believed to play a role in the pathogenesis of adverse pregnancy outcomes including preterm birth [4]. Micronutrients deficiencies are usually found in pregnant woman [5]. They regulate the balance between free radicals and anti oxidants [6]. Minerals and trace elements such as zinc, copper, iron, selenium, calcium, magnesium and other micro nutrients have significant influence on the health of pregnant woman and growing fetus [7]. Trace elements like copper and zinc are essential and contribute in the onset of preterm labour. Severe maternal zinc deficiency has been associated with spontaneous abortion and congenital malformation, whereas milder forms of zinc deficiency have been associated with low birth weight, intrauterine growth retardation, preterm delivery [8,9]. Additionally low plasma zinc has also been reported to correlate with pregnancy complications such as prolonged labour, hypertension, and postpartum haemorrhage [10]. Because pregnant woman, especially in developing countries, are considered as a high risk group for zinc deficiency, and maternal zinc supplementation has been suggested by several groups as one possible nutritional intervention during pregnancy to improve pregnancy outcome [11].

The importance of copper for prenatal development was demonstrated by studies of diseases in lambs and other animals called enzootic ataxia, which is characterised by various neurological, skeletal, and connective tissue abnormalities [12]. In human adults, severe copper deficiency is relatively rare, whereas signs of moderate copper deficiency were observed in human infants and a variety of conditions [13]. Copper deficiency caused by inadequate maternal dietary intake is very rare, whereas moderate copper deficiency attributed to secondary causes, such as disease states, drug interactions and nutritional genetic factors, are more common and may result in pregnancy complications.

The knowledge that zinc and copper are essential for growth and development of rapidly growing tissue like the fetus has lead to the investigation of zinc and the copper status in the pregnant mother as well as the new born by many workers. Some attempts have been made to correlate these levels with various complications of pregnancy like preterm delivery as well as the indicators of health in the newborn. Present designed to prove copper and Zinc deficiencies as contributory factors for the onset of preterm labour and their deficiency affects neonatal outcome.

Materials & Methods

This is a prospective Case control study done in the Department of Obstetrics and Gynaecology, Narayana Medical College & Hospital, Nellore for a period of 2 years (October 2015 – October 2018). All pregnant women in labour undergoing preterm and term delivery attending labour room for delivery in obstetrics department.

50 pregnant women undergoing preterm delivery were recruited in the study group. A similar number (50) healthy pregnant woman undergoing term delivery are recruited in control group.

Pregnant women are recruited into the study after obtaining the fully informed and written consent. The criteria (Inclusion/ Exclusion) for getting recruited being:

Inclusion Criteria: Pregnant women in labor; Age of patients between 18-39 yrs; Gestational period >26 to < 37 weeks in study group and Gestational period > 37 weeks in control group.

*Exclusion Criteria***:** Pregnant women with co morbidities like diabetes mellitus or gestational diabetes, chronic hypertension, renal, cardiovascular, liver, endocrine diseases and any other chronic illnesses, hydatidiform mole & malignancy, intake of vitamins, antioxidants during the current pregnancy, urinary tract infections are excluded.

Apart from routine antenatal investigations specific investigations were sent related to the present study. Serum copper, Umbilical cord copper, Serum zinc, and Umbilical cord zinc were analysed.

Procedure: Blood samples were collected preferably from the antecubital vein of the mother at the time of delivery. For the new born, cord blood was taken from maternal end of umbilical cord to coincide precisely with the newborn's venous blood level. 2 ml Sample was collected in to plan tube. Serum was separated by centrifugation and stored at -120°C to measure the analytes. Serum zinc and serum copper are measured by calorimetric method.

Statistics: Frequency and percentage of each parameter was calculated and analysed. The data obtained was analysed using SPSS software Version 17.0.

Results

The above figure shows an age groups of 18-39 yrs. Maximum no. of women were between 20-24 yrs of age among preterm mothers and 20-29 yrs of age among term mothers.

The above table 1 shows that the maximum no. of patients belong to low SES among preterm mothers and term mothers 44% & 36% respectively (Table 1).

The Table 2 shows that maximum no. of women belong to the BMI range of < 24.9 kg/m^2 among both preterm and term mothers – 74%-62% respectively in this BMI range of < 24.9. It shows that the maximum no. of women (76%) are unbooked among preterm mothers, whereas maximum no. of women (56%) are booked among term mothers.

The maximum no. of women are second Para

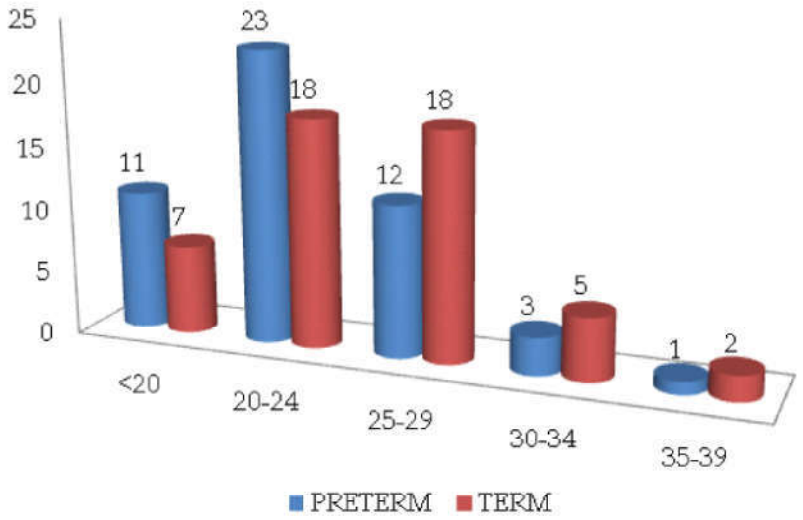

Fig. 1: Age distribution – Preterm v/s Term.

Table 1: Socio economic status (SES) – preterm vs. term

SES	Preterm mothers		Term mothers	
	Frequency (n/t)	Percentage	Frequency (n/t)	Percentage
Low	22/50	44.0	18/50	36.0
Middle	18/50	36.0	15/50	30.0
Upper middle	10/50	20.0	17/50	34.0
Total	50	100.0	50	100.0

Table 2: Body mass index (BMI) – preterm vs. term

BMI (Kg/m2)	Preterm mothers		Term mothers	
	Frequency (n/t)	Percentage	Frequency (n/t)	Percentage
<24.9	37/50	74.0	31/50	62.0
25 – 29.9	10/50	20.0	15/50	30.0
>30	3/50	6.0	4/50	8.0
Total	50	100.0	50	100.0

(36%) among preterm mothers and Primigravidae among term mothers(40%). The maternal copper levels are more among preterm mothers (114.9) than in term mothers (108.5)(p=0.54) which is not significant. The umbilical cord copper levels are more in term neonates (73.6) than in preterm neonates (57.7) (p=0.0001). The maternal serum zinc levels are more among term mothers (103.7) than in preterm mothers (91.8) (p=0.0001).

The umbilical cord zinc levels are more in term neonates (121.6) than in preterm neonates (101.2) (p= 0.0001).

Total no 3. of cases- 50 each. Total no. of controls-50 each.

It was shows that compared to maternal serum copper levels, umbilical cord copper levels are less irrespective of preterm or term deliveries. Whereas, compared to maternal zinc levels, umbilical cord zinc levels are high. It shows that maternal copper levels are more in mothers with baby birth weights <2.5 kgs whereas the umbilical cord copper levels are more in mothers with baby birth weight >2.5 kgs, with p value 0.8 which is not significant and 0.001 which is significant respectively. It was shows that the maternal zinc levels and umbilical cord zinc levels are more if the babies birth weight is >2.5 kgs compared to the babies of birth weight <2.5 kgs with significant p value 0.0001 & 0.0001 respectively.

It shows that spontaneous vaginal delivery rate is more among terms compared to preterm mothers 78% & 58% respectively. Forceps delivery is more among preterms than terms 12% & 2% respectively. Ventouse delivery rate in terms is 4%. Ventouse application is contraindicated in preterm babies due to immature fetal skull. LSCS rate is more among preterms than terms 30% and 16% respectively. It shows that the maternal complications are more among women with preterm deliveries (18%) than with term deliveries (6%). PPH is more among preterm deliveries than term 12% & 4% respectively. Wound infection is more among preterm deliveries than term 4% & 1% respectively.

Puerperal sepsis is seen in one case among preterm mothers and not found in term mothers. Higher fetal complications occurred (26%) in preterm babies compared to term babies (10%) with a significant p value <0.05.

It shows that among the babies with complications their respective maternal and umbilical cord copper levels are less when compared to babies with no complications with a significant p value <0.05.

Table 3: Maternal serum and Umbilical cord Cu & Zn – Preterm vs. Term deliveries

	Copper		Zinc	
	Maternal	**Umbilical cord**	**Maternal**	**Umbilical cord**
Preterm	114.97±22.5	57.71±10.87	91.84±18.94	101.20±16.35
Term	108.5±28.8	73.63±14.26	103.76±15.14	121.62±18.70
p value	0.540	0.0001	0.0001	0.0001

Table 4: Fetal complications vs. Maternal serum and umbilical cord zinc levels

	Fetal complications		
	Present	**Absent**	**p value**
	Mean (µg/dl)	**Mean (µg/dl)**	
Maternal Zinc	78.94±15.26	101.94±15.95	< 0.0001
Umbilical cord Zinc	89.89±21.30	116.13±16.77	<0.0001

Table 5: Cumulative Correlations

		Maternal Copper	**Maternal Zinc**	**Umbilical Copper**	**Umbilical Zinc**	**Birth weight**	**APGAR 5 min**
Maternal Copper	Pearson Correlation	1	-.038	.465**	.033	.025	-.059
	p value		.709	.000	.742	.808	.563
	N	100	100	100	100	100	100
Maternal Zinc	Pearson Correlation	-.038	1	.174	.788**	.419**	.278**
	p value	.709		.083	.000	.000	.005
	N	100	100	100	100	100	100
Umbilical Copper	Pearson Correlation	.465**	.174	1	.259**	.332**	.195
	p value	.000	.083		.009	.001	.052
	N	100	100	100	100	100	100

Umbilical Zinc	Pearson Correlation	.033	.788**	.259**	1	.491**	.279**
	p value	.742	.000	.009		.000	.005
	N	100	100	100	100	100	100
Birth weight	Pearson Correlation	.025	.419**	.332**	.491**	1	.451**
	p value	.808	.000	.001	.000		.000
	N	100	100	100	100	100	100
APGAR 5 min	Pearson Correlation	-.059	.278**	.195	.279**	.451**	1
	p value	.563	.005	.052	.005	.000	
	N	100	100	100	100	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

Discussion

For healthy intrauterine development, the fetus requires adequate amounts of macro, micronutrients and trace elements, which are only obtained from the maternal blood via placenta [14-16]. Micronutrients have an important influence on the health of both mother and fetus. Deficiency of micronutrients during pregnancy may give rise to various complications like anaemia, preeclampsia, preterm labour and fetal growth restriction. Periconceptional multivitamin use was associated with 16% reduced risk of preterm births, but studies regarding micronutrient deficiency during the pregnancy leading to preterm labour and neonatal complications are sparse.

The high maternal copper level in normal pregnancy is a reflection of estrogen level [17]. About 90-95% of circulating copper of circulating copper remains as ceruloplasmin and a small fraction is diffusible, which maintains copper level of neonates. Amongst various factors affecting copper level, elevated level of oestrogen during pregnancy also increase the synthesis of ceruloplasmin by making copper available through mobilization from maternal tissues especially liver. The serum copper levels may be lower in preterm infants because of immaturity of the liver to synthesize ceruloplasmin. The smaller hepatic stores of zinc and copper in preterm infants also may be refelected in serum concentrations of these elements.

Studies like Bro et al., [18] (preterm-797.1±142.8, term- 772.2±126.2 µg/dl) and Wasowicz et al., [19] (preterm- 226±50, term- 182±36 µg/dl) had maternal copper levels more among preterm than in term mothers.

Whereas few other studies like Islam et al., [20] (preterm- 245±17, term- 269±19 µg/dl), Sulthana et al., [21](preterm- 115.9±22.03, term- 186.0± 50.45µg/dl).

The present study correlates with Bro et al. and wasowicz et al. studies. Which shows that maternal copper levels among preterm and term mothers has a mean of 114.9±22.5 µg/dl and 108.55±28.87 µg/dl respectively, which suggests that the maternal copper levels are more among preterms than in terms.

The present study values also found to be in par with those studies 91 vs. 103 respectively.

Studies like Bro et al. (preterm- 118±28.9, term- 138.7±28.9 µg/dl) and had umbilical cord copper levels more among term than in preterm neonates.

Whereas few other studies like Wasowicz et al. (preterm- 61±23, term- 48±19 µg/dl) and sulthana et al. (preterm- 38.2±8, term- 56.5±22 µg/dl) had umbilical cord copper levels more among preterm than in term neonates.

The present study correlates with Bro et al. studies. which shows that the umbilical cord copper levels among preterm and term mothers has a mean of 57.71±10.8 µg/dl and 73.63±14.2 µg/dl respectively, which suggests that the umbilical cord copper levels are more among terms than in preterms.

Finally, The present study shows that irrespective of term or preterm, umbilical cord copper levels (65.67±12.5 µg/dl) are less compared to maternal copper levels (111.7±25.65 µg/dl)

Islam et al., sulthana et al., Kiilholma et al., Bro et al., showed in their studies that umbilical cord copper levels were less compared to maternal copper levels irrespective of term or preterm.

Zinc is passively transferred from mother to fetus across the placenta. Possible mechanism of higher level of zinc in the cord blood could be to allow efficient transfer of zinc from mother to fetus, there is decreased zinc binding capacity of maternal blood during pregnancy. This in turn allows the fetus to capture the zinc for its high enzymatic and other functions related to growth. However, other

workers attributed this fall of zinc in the maternal blood to physiological adjustment in response to expanded maternal blood volume.

The present study values found to be in par with those studies 91 vs. 103 respectively.

Studies of Kiilholma et al., [22] (preterm- 54±12, term-63±9 µg/dl) and Bro et al. (preterm- 211±33, term-215±31 µg/dl) had maternal zinc levels more among term than in preterm mothers.

The present study correlates with Kiilholma et al. and Bro et al. studies, which shows that the maternal zinc levels among preterm and term mothers has a mean of 91.8±18.9 µg/dl and 103.7±15.1 µg/dl respectively, which suggests that the maternal zinc levels are more among terms than in preterms

The present study values found to be in par with those studies 101 vs. 121 respectively.

Studies like Islam et al. (preterm-137±16, term- 118±5 µg/dl) Kiilholma et al. (preterm-93±9, term- 82±10 µg/dl) Bro et al., (preterm-100.5±16.7, term- 95.5±16.7 µg/dl) had umbilical cord zinc levels less among term than in preterm mothers.

Whereas other study Jewani and vani (preterm-94±17, term-128±14 µg/dl) had maternal zinc levels more among preterm than in term mothers [23].

The present study correlates with Jewani and vani, which shows that the umbilical cord zinc levels among preterm and term neonates has a mean of 101.2±16.3 µg/dl and 121.6±18.7 µg/dl respectively, which suggests that the umbilical cord zinc levels are more among terms than in preterms.

Finally, the present study shows that irrespective of term or preterm, umbilical cord zinc levels (111.4±17.5 µg/dl) are more, compared to maternal zinc levels (97.7±17 µg/dl). Islam et al., Kiilholma et al. and Wasowicz et al showed in their studies that umbilical cord zinc levels were more than maternal zinc levels irrespective of term or preterm.

Another study i.e Maamouri et al showed that maternal copper levels in women with babies of birth weight <2.5 kgs is less when compared to women with babies of birthweight >2.5 kgs [24]. In the present study, that maternal copper levels in women with babies of birth weight <2.5 kgs (110.8±20.5 µg/dl) is more when compared to women with babies of birthweight >2.5 kgs (109.6±20.5 µg/dl) with no significant correlation (p=0.8).

The present study correlates with Maamouri et al. Which shows that umbilical cord copper levels in neonates with birth weight <2.5 kgs (62.9 ±14.57 µg/dl) is less when compared to neonates of birth weight >2.5 kgs (70.6± 14.09 µg/dl) with significant correlation (p-0.001). The present study correlates with Wasowicz et al., Maamouri et al., Suman et al. which shows that the maternal zinc levels are more in women with babies of birth weight more than 2.5 kgs (102±18 µg/dl) than in women with babies of birth weight less than 2.5 kgs (93.2±24 µg/dl) With significant p value 0.0001.

The present study shows that the umbilical cord zinc levels are more in women with babies of birth weight more than 2.5 kgs (121.08±17.17 µg/dl) than in women with babies of birth weight less than 2.5 kgs (108.01±26.36 µg/dl) with significant p value 0.0001, thus proving that active transport of Zn from mother to fetus transplacentaly directly or indirectly influencing the birth weight.

The present study noted the development of various maternal complications during the time of labour and until the time of discharge, Correlation between term vs. Preterm deliveries and their relation to maternal and umbilical cord levels of copper and zinc were also observed. 12 out of 100 mothers developed maternal complications like Post partum haemorrhage (PPH), Wound infection, puerperal sepsis.

Maternal complications were more among preterms than terms, 18% & 6% respectively. PPH is more among preterms than term deliveries 12% & 2% respectively, also Caesarean deliveries rate is more in preterms than terms 30% & 16% respectively. The indications of caesarean section in preterms is mainly uterine inertia & fetal distress. Uterine inertia is due improper development of gap junctions in lower uterine segment and less number of oxytocin receptors in preterm uterus. PPH is also more in preterms because of the same reason. Liu et al., observed that maternal morbidity increases following preterm caesarean delivery. The most common causes are haemorrhage and infectious morbidity [25]. Wound infection was more in preterm mothers than in term 4% & 2% respectively. Puerperial sepsis was noted only in one mother belonging to study group. This might be because of poor nutrition and poor hygienic practices.

The present study observed the neonates until their time of discharge, in order to look for development of any neonatal complications and their relation to maternal and umbilical cord levels of copper and zinc. 18 out of 100 babies developed neonatal complications like respiratory distress syndrome, neonatal jaundice, interventricular haemorrhages, NEC, hypoglycaemia and

hypothermia. There were no other studies found who compared the relation between development of neontal complications with maternal and umbilical cord levels of copper and zinc, hence it is not possible to compare the present study with any other study.

The present study shows that the mean maternal copper value of the neonates who developed neonatal complications (82.5±23.3 µg/dl) is less compared to the mean maternal copper value of the neonates who did not develop neonatal complications (112.1±18.05 µg/dl) with a significant p value (<0.0001).

The mean umbilical cord copper value of the neonates who developed neonatal complications (53.71±10.8 µg/dl) is less compared to the mean umbilical cord copper value of the neonates who did not develop neonatal complications (68.3±14.46 µg/dl) with a significant p value (<0.0001). The mean maternal zinc value of the neonates who developed neonatal complications (78.94±15.26 µg/dl) is less compared to the mean maternal zinc value of the neonates who did not develop neonatal complications (101.94±15.95 µg/dl) with a significant p value (<0.0001).

The mean umbilical cord zinc value of the neonates who developed neonatal complications (89.89±21.3 µg/dl) is less compared to the mean umbilical cord zinc value of the neonates who did not develop neonatal complications (116.13±16.77 µg/dl) with a significant p value (<0.0001).

Conclusion

Increased knowledge about the importance of these specific antioxidant micronutrients crucial part that they play in maintaining successful pregnancy and long/short-term health of both mother and baby made a key focus for future health strategies in improving pregnancy outcomes. This is particularly important with regards to preterm labour, where oxidative stress/loss of tensile strength of membranes contributing an essential component to its etiology. Copper and zinc supplementation either alone or in combination with a general multi-nutrient supplement may have a significant effect not only on the incidence of preterm labour, but may also reduce the development of neonatal complications which are more in preterms. The best way to prevent preterm labour in an effective manner is the establishment of an adequate prenatal control system, whose procedures should contain an adequate micronutrient supplementation.

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