

An Observational Study to Correlate Maternal Serum and Cord Blood Zinc with Fetal Growth Restriction

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Abstract

Objectives: To study maternal serum and cord blood zinc as causal factor in fetal growth restriction and to find out correlation, if any, between birth weight and maternal serum and cord blood zinc levels.

Material and methods: This prospective observational study was carried out on 120 term pregnant women who attended the Department of Obstetrics and Gynaecology, Pt. B. D. Sharma PGIMS, Rohtak, of which, 60 had FGR babies and 60 had normal growth babies. Serum zinc levels were studied in these women and cord blood zinc levels in their neonates.

Results: After adjusting for other variables in the multivariable model we found that the mean serum zinc level in study group women was $115.65 \pm 6.36 \mu\text{g/dL}$ at term and $116.91 \pm 6.39 \mu\text{g/dL}$ in late preterm neonates. Also, we found that the mean cord blood zinc levels were $136.03 \pm 9.25 \mu\text{g/dL}$ in study group and $135.24 \pm 4.72 \mu\text{g/dL}$ in control group in term neonates while in late preterm neonates, it was $135.06 \pm 9.52 \mu\text{g/dL}$ in study group and $133.18 \pm 6.58 \mu\text{g/dL}$ in control group. A statistically significant positive correlation was found between birth weight of FGR babies with the maternal serum zinc levels at term and between cord blood zinc levels and birth weight in both preterm and term neonates.

Conclusion: Zinc is an essential micronutrient during pregnancy and is needed for fetal development and placental functions. Its role in fetal growth and development, need of supplementation in pregnant women needs to be studied further to demonstrate better clinical outcomes in women with growth retarded fetus.

Keywords: Cord blood zinc, Fetal growth restriction, late preterm neonates, maternal zinc, micronutrients, term neonates.

Introduction

Fetal growth restriction (FGR) has been defined as the rate of fetal growth that is below the growth potential of a specific fetus as per the race and gender of fetus. FGR is a clinical definition and applies to neonates born with clinical features of malnutrition and in-utero growth retardation,

irrespective of their birth weight percentile. FGR can be a diagnosis at term and even in babies born prematurely. The incidence of FGR is approximately 5-10% of all pregnancies.¹ Fetal growth is regulated at multiple levels starting from maternal components to placenta,

environmental factors and even fetal components. The maternal- placental- fetal unit act in harmony to provide needs of fetus while supporting the physiological functions of the mother. The maternal causes of FGR include malnutrition, substance abuse and smoking, high blood pressure, chronic kidney disease, chronic anemia, advanced diabetes mellitus, hematological disease, cardiovascular disease, respiratory disease and infections. These factors hamper nutrition delivery to the fetus leading to FGR. The placental factors comprise of factors leading to chronic placental insufficiency as in placental infarcts, circumvallate placenta, chorioangioma or velamentous cord insertion.²

Idiopathic FGR counts for around 40% of all FGR cases.³ One of the investigated causes behind the reduced birth weight is nutritional deficiency in the mother. Micronutrients like zinc comprise a small yet significant part to this nutrition. It is needed in general metabolism pathways and so is an important type 2 nutrient. Zinc is one of the most abundant trace element in humans and interacts with proteins by promoting enzymatic processes where it has either catalytic or coactive or a structural role. Thus, its role becomes particularly important in period of increased metabolism as in fetal growth.

Birth weight is significant indicator of the normal growth milestones during fetal life and in determining neonatal prognosis apart from being a reflection of maternal health. FGR has important implications not just for the fetus, child and adult, but also for the parents and the society. Multiple studies have been conducted to study causes of FGR⁴⁻⁸ but studies on micronutrients as causal factor in FGR are rare. Keeping that in mind, the present study was undertaken to study maternal serum zinc and cord blood zinc as causal factor in fetal growth restriction.

Material and Methods

This prospective observational study was carried out on pregnant women who attended the Department of Obstetrics and Gynaecology, Pt.

B. D. Sharma PGIMS, Rohtak after obtaining their informed and written consent. 120 women were included in the study, 60 cases and 60 controls. Women at term with clinical or sonographic diagnosis of FGR were considered as cases. Controls were taken from normal healthy women at term similar to cases but carrying normal growth babies. Women with PIH and chronic hypertension, had history of alcohol use or smoking or use of any supplements apart from iron, calcium and folic acid, women with antepartum infections, with APH, PROM, prolonged labour, history of blood transfusions in current pregnancy, uterine malformation and with any systemic disease were excluded from the study. Study was approved by Institutional Ethics Committee.

Gestational age was calculated from first day of last menstrual period and was confirmed by first trimester scan, if available. Women with difference of 2cm or more between period of gestation and symphysio-fundal height were clinically diagnosed as Fetal Growth Restriction or women diagnosed with FGR babies on color Doppler velocimetry even in absence of any clinical difference in SFH, were included as cases in the study. 6ml venous blood samples of study subjects were collected in red vacutainers and labelled by name and Hospital Registration Number of patient. 6ml cord blood samples from placental end of umbilical cord of neonates of study subjects were also collected in red vacutainers at the time of delivery and labelled by name and Hospital Registration Number of patient. Serum was separated by centrifugation and stored at -20°C till analysis. Samples were analyzed for zinc levels using colorimetric kit.⁹

Statistical Analysis

At the end of the study, all the data was compiled and analysed by using Student t-test for quantitative variables and Chi-square test for qualitative variables. A p value of <0.05 was considered statistically significant. Statistical package for Social Sciences (SPSS) version 21.0

was used for statistical analysis. Correlation Coefficient was calculated to deduce correlation between the variables.

Result

Majority of women belonged to 21-25years age group i.e 50% in both study and control group.

Majority women belonged to upper lower socioeconomic status in both groups. It was found that majority patients were nulliparous in both the groups. The educational levels between study and control population was similar.

The mean pre-pregnancy weight was similar in both groups.

Table 1: Demographic parameters

	Study group	Control group	P value
Mean age	23.85±4.45yrs	23.48±3.64yrs	0.664
Mean caloric intake (kcal)	2359.83±76.74	2336.67±55.13	0.325
Mean BMI (kg/m ²)	21.35±0.82	21.5±0.79	0.304

The mean abdominal girth was found to be more in control group. The difference between the two groups was statistically significant (p value <0.0001)

Majority of the women in study group (57.14%) had difference of 2-4cm between gestation age and symphysio-fundal height in the study group.

Of these, 4.76% women had SFH difference more than 4cm and 21.43% women had a difference of less than 2cm while in control group, 41.18% women had less than 2cm difference between SFH and gestational age (p<0.0001).

Table 2: Comparative birth weight between the two groups

Birth weight(kg)	Term		Late preterm	
	Study Group (n=42)	Control Group (n=51)	Study group (n=18)	Control group (n=9)
<1.8	2 (4.76%)	0 (0%)	3 (16.67%)	0 (0%)
1.8-1.99	2 (4.76%)	0 (0%)	4 (22.22%)	0(0%)
2-2.499	38 (90.48%)	0 (0%)	11 (61.11%)	2 (22.22%)
>=2.5	0 (0%)	51 (100%)	0 (0%)	7 (77.78%)
Mean ± SD	2.18 ± 0.21	2± 0.27	1.95±0.21	2.58±0.23
P value	<0.0001		0.0002	

Of the study group subjects, only 5% underwent cesarean section, all due to fetal distress.

Table 3: Mode of delivery

Mode of delivery	Study group (n=60)	Control group (n=60)	P value
LSCS	3 (5%)	0 (0%)	0.244
Vaginal delivery	57 (95%)	60 (100%)	

NICU admissions were significantly more in study group while there were no NICU admissions in control group and 25% of admitted neonates expired in NICU

Table 4: NICU admission and outcome

NICU admission	Study Group (n=42)	Control Group (n=51)	P value
No	38 (90.48%)	51 (100%)	0.038
Yes	4 (9.52%)	0 (0%)	
OUTCOME			
Discharged	3 (75%)	0 (0%)	
Expired	1 (25%)	0 (0%)	

The difference between the serum zinc values in study group and control group was found to be statistically non-significant at both late preterm and term gestation. (Reference range for serum zinc at biochemistry lab PGIMS Rohtak was 60-120µg/dl). Also, the difference between cord blood level of zinc in both the groups at late preterm and term gestation was not statistically significant.

Table 5: Zinc levels (µg/dL)

	>37weeks		34-37weeks	
Serum zinc levels (µg/dL) (Maternal)	Study Group (n=42)	Control Group (n=51)	Study group (n=18)	Control group (n=9)
60-120	35 (83.33%)	45 (88.24%)	13 (72.22%)	8 (88.89%)
>120	7 (16.67%)	6 (11.76%)	5 (27.78%)	1 (11.11%)
Mean ± SD	115.65 ± 6.36	2 6.16	116.91±6.39	114.6±6.52
P value	0.497		0.628	
Cord blood Zinc				
>120	42 (100%)	51 (100%)	18 (100%)	9 (100%)
Mean±SD	136.03±9.25	135.24±4.72	135.06±9.52	133.18±6.58
P value	0.616		0.602	

It was observed that, in the study group, there was statistically significant correlation between maternal serum zinc levels and birth weight at term, such that increase in birth weight was observed with increase in maternal serum zinc levels but birth weight decreased with increasing serum zinc levels in control group. However, this correlation between them was statistically non-

significant. No statistically significant correlation was demonstrated between maternal serum zinc levels and birth weight in the control group. Statistically significant correlation of cord blood zinc with the birth weight was demonstrated in the late preterm study group and the term study group.

Table 6: Correlation of Zinc with birth weight

	Maternal		Cord blood	
	Study group	Control group	Study group	Control group
34-37 weeks				
Correlation coefficient	0.394	0.306	0.611	0.096
P value	0.107	0.437	0.008*	0.843
>37 weeks				
Correlation coefficient	0.350	-0.271	0.361	0.048
P value	0.024*	0.055	0.019*	0.739

Spearman rank correlation coefficient (*) indicates significant

Correlation of serum zinc levels ($\mu\text{g/dL}$) (Maternal) with birth weight(kg) in study group at term

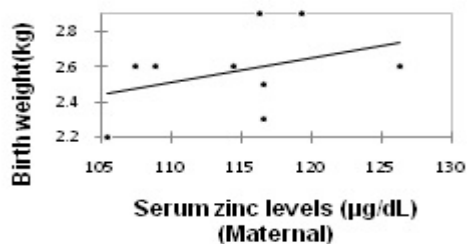


Fig 6.1

Correlation of serum zinc levels ($\mu\text{g/dL}$) (Maternal) with birth weight(kg) in control group at term

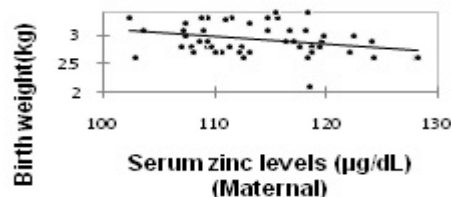


Fig 6.2

Correlation of serum zinc levels ($\mu\text{g/dL}$) (Maternal) with birth weight(kg) in 34-37weeks in study group

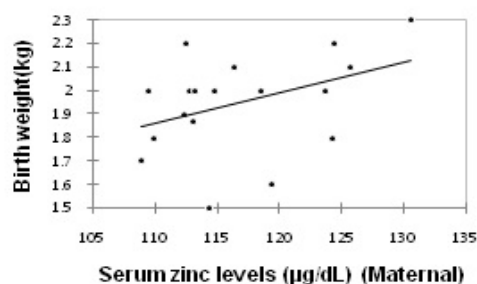


Fig 6.3

Correlation of serum zinc levels ($\mu\text{g/dL}$) (Cord blood) with birth weight(kg) in 34-37weeks in study group

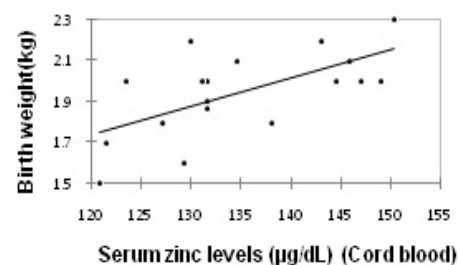


Fig 6.4

Correlation of serum zinc levels ($\mu\text{g/dL}$) (Cord blood) with birth weight(kg) at term in study group

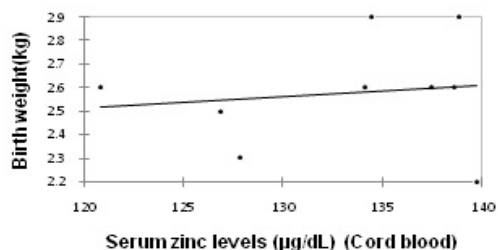


Fig 6.5

Correlation of serum zinc levels ($\mu\text{g/dL}$) (Maternal) with birth weight(kg) in 34-37weeks in control group

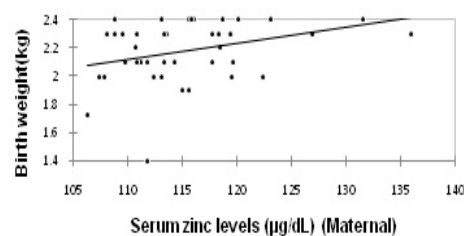


Fig 6.6

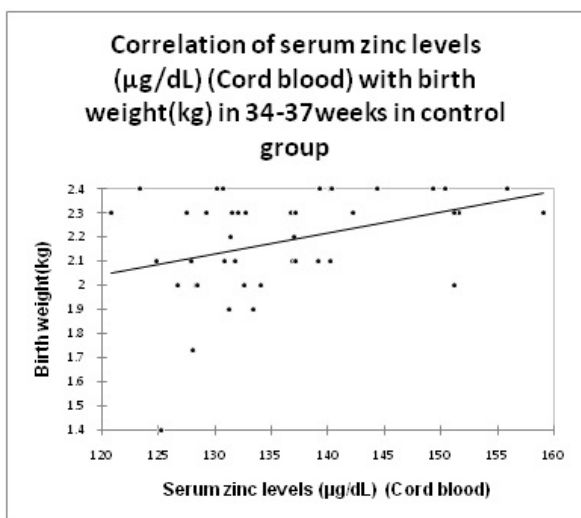


Fig 6.7

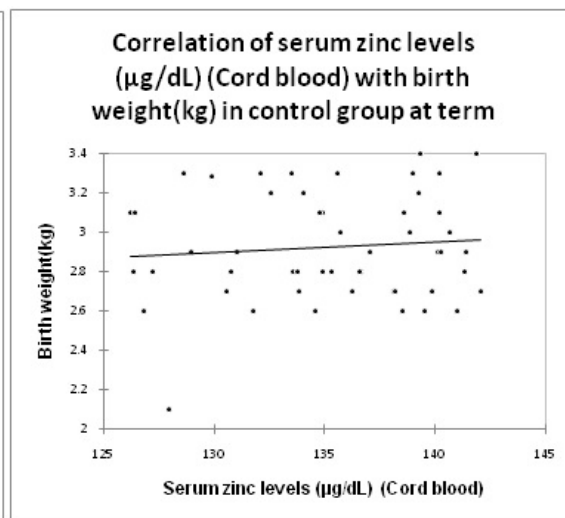


Fig 6.8

Discussion

Micronutrients play a small yet pivot role in cellular growth and differentiation. The present study was conducted to study maternal serum zinc level as causal factor in fetal growth restriction and to find out correlation, if any, between birth weight and maternal serum levels of zinc so as to influence prevention and treatment through micronutrient supplementation or avoiding these micronutrients during antenatal period.

FGR is more prevalent in teenage pregnancy as well as in elderly gravida but in the present study majority of women (50%) in the study group were in age group 21-25years. This was similar to the findings by Roberfroid *et al.*¹⁰ and Ab-Bakari-Rwebembra *et al.*¹¹ However, the mean age was higher in studies by Melda Amalia *et al.*¹² and Tsuzuki *et al.*¹³ this can be accounted to cultural differences in age of marriage around the world.

Fetal growth restriction is more commonly seen in nulliparous women. The majority of the

women (55%) in the present study were nulliparous. This was in concordance with study conducted by Bermudez *et al.*¹⁴ in which 54.5% women were nulliparous.

Lower socioeconomic status is considered a risk factor for FGR. Majority of the women (76.66%) in present study belonged to lower socioeconomic status based on Modified Kuppuswamy Scale. The findings were similar as in study by Manandhar T Prasad *et al.*¹⁵ where 63.3% women belonged to lower socioeconomic class and Muhammad T *et al.*¹⁶

Symphysio-Fundal height is considered a simple, safe, cheap and reasonable clinical parameter for timely diagnosis of FGR babies. The difference between SFH (cm) and gestational age in weeks more than 2cm is considered FGR, though severe FGR is found with difference of more than 4-6cm. Here, 38.1% of women were showing no discrepancy or <2cm discrepancy in SFH but were diagnosed to have FGR fetus on Doppler studies. Table 7 shows comparative results with Manandhar T *et al.*

Table 7: Symphysio-Fundal Height

SFH difference	Present study (study group)	Manandhar T et al ¹⁵
No difference	16.67%	8.33%
<2cm	21.43%	11.66%
2-4cm	57.14%	50%
>4cm	4.76%	30%

FGR babies are more prone to intranatal hypoxia and are unable to bear stress of normal labour and so land up in cesarean sections and this is more commonly seen in severe type of FGR. However, majority of the women in present study delivered vaginally as majority of the study group women in present study had neonates with mild FGR. Table 8 shows comparative distribution between various studies.

Table 8: Mode of delivery

Mode of delivery	Present study	Manandhar T et al ¹⁵	Jaafar et al ¹⁷
LSCS	5%	61.66%	54%
NVD	95%	38.32%	46%

FGR is characterised usually by low birth weight. The mean birth weight in study group of present study was lower than in studies by Bermudez et al¹¹, Villar et al⁷ & Jaafar et al.¹⁰ The differences in mean birth weight of present study to other studies could be attributed to the fact that average birth weight in India is lower than western countries.

Table 9 shows that the mean serum zinc level in women with FGR babies was $115.65 \pm 6.36 \mu\text{g/dL}$ and in women with normal growth babies was $113.92 \pm 6.16 \mu\text{g/dL}$ and this was statistically non-significant. This was in agreement with study by Srivastava et al²⁰ where also no difference was seen between the two groups. This was discordant to studies conducted by Suman et al¹⁸ and Jyotsna S et al.¹⁹ We conclude that there might be a threshold of serum zinc level below which there can be association between occurrence of FGR and maternal serum zinc levels and in present study serum zinc in both the groups were found to be in normal range. Also, other unknown underlying factors might coexist in etiology of FGR.

The mean serum zinc level was found higher in study group ($116.91 \pm 6.39 \mu\text{g/dL}$) women between 34-37 weeks of gestation compared to study by Elizabeth et al³⁵ where it was $70.25 \pm 24.59 \mu\text{g/dL}$. This difference can be due to difference in mineral distribution and salinity depending on the geographical area.

In the present study, the mean cord blood levels of zinc were similar in study group ($136.03 \pm 9.25 \mu\text{g/dL}$) compared to the control group ($135.24 \pm 4.72 \mu\text{g/dL}$). This was in agreement in study by Srivastava et al²⁰ where no statistically significant difference was observed between cord blood zinc levels in the two comparable groups. However, a statistically significant difference was observed in the groups in study by Jyotsna S et al¹⁹ and Elizabeth et al²¹. This difference could be due to difference in geographical area where studies were conducted and difference in food habits of the population and the difference in laboratory conditions where the samples have been analysed.

Table 9: Comparison of mean serum zinc level in maternal serum and cord blood

>37weeks	Mean maternal serum zinc level in study group (µg/dL)	Control group	P value
Present study	115.65±6.36	113.92±6.16	0.497
Suman S et al ¹⁸	45.96 ±15.14	81.33±45.96	<0.001
Jyotsna S et al ¹⁹	67.02±15.99	83.59±18.46	<0.05
Srivastava et al ²⁰	6.31±5.09µg/mL	5.67±2.49µg/mL	Non significant
34-37weeks			
Present study	116.91±6.39		
Elizabeth et al ²¹	70.25±24.59		
>37 weeks	Mean Cord blood zinc in study group	Control group	P value
Present study	136.03±9.25	135.24±4.72	0.616
Jyotsna S et al ¹⁹	83.45±16.74	93.74±16.74	<0.05
Srivastava et al ²⁰	7.86±8.16µg/ml	9.46±8.35µg/ml	Non significant
Elizabeth et al ²¹	78.09±18.39	92.24±19.40	Significant
34-37 weeks			
Present study	135.06±9.52		
Tsuzuki et al ¹³	89±14.3		
Gupta et al ²²	46.26±22.54		

Conclusion

Idiopathic FGR is a rare entity. Zinc is an essential micronutrient during pregnancy and is needed for fetal development and placental functions. The present study shows a statistically significant correlation between maternal zinc levels and FGR in term neonates.

The study had a few limitations. The dietary content of zinc was not quantified. Also, serum levels of zinc do not truly define the amount of this micronutrient in the body. Therefore, further larger scale studies are needed to explore the role of these micronutrients in fetal growth and development, their need of supplementation in pregnant women and to demonstrate better clinical outcomes in women with growth retarded fetus.

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