e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(8); 812-818

Original Research Article

An Examination of the Link between Maternal Serum Zinc Levels and Fetal Congenital Malformations at a Tertiary Care Hospital in the Erode District

R. Sathya[1], A. Gayathri[2], R. Renju[3], Revathi. A[4*], Panneerselvam Periasamy[5]

[1,2,3,4]Assistant professor, Department of Obstetrics and Gynaecology, Government Erode Medical College Hospital, Perundurai, Erode, Tamilnadu, India

[5]Assistant Professor, Department of Physiology, Government Erode Medical College, Perundurai, Erode, Tamilnadu, India

Received: 28-05-2023 / Revised: 29-06-2023 / Accepted: 30-07-2023

Corresponding author: Dr. Revathi. A

Conflict of interest: Nil

Abstract:

Background: Pregnant women frequently experience zinc insufficiency, particularly during the third trimester. However, there is inadequate information on the relationship between zinc deficiency and congenital abnormalities in Indian population. Therefore, the purpose of this study was to ascertain whether serious congenital abnormalities in babies are related to maternal serum zinc insufficiency.

Methods: This descriptive, case–control study involved mothers of 50 neonates with congenital anomalies on serum zinc levels of mothers who gave birth to babies with clinically apparent congenital malformations was undertaken at Government erode medical College Hospital, Perundurai during the period 2022-2023. During the same period, serum zinc was measured in 50 mothers who had delivered normal new-borns without congenital malformations (control group).

Results: Study group and control group, majority of the patients were in the 21.25 and 26-30 yrs age groups Mothers. In the study group 60% of babies were males and 40% of babies were females. In the control group 52% of babies were males and 48% of babies were females. The mean serum zinc level in the study group was 44.95 µg/dl (SD 14.4). Mean serum zinc level in the control group was 86.43 µg/dl (SD 7.88). There is statistically significant difference in the zinc level between the two groups (P value < 0.001). In study group mean serum zinc level in primi 50.64 (SD 13.2) multi 40.46 (SD 14.84). In control group primi 85.33 (SD 7.6) multi 87.44 (SD 8.09). The lowest value of maternal serum zinc was found with hydrocephalus (20.1 µg/dl) and highest value 78.82 with polydactyl.

Conclusions: This study throws light on the fact that lower maternal serum zinc levels may be an associated factor in the pathogenesis of congenital malformations, especially of the central nervous system. Low zinc levels during conception or during early embryogenesis may operate as a cause of congenital malformations. Hence zinc supplementation may be started in early pregnancy or preconceptional period as prophylaxis.

Keywords: Serum Zinc, Congenital Malformations, Maternal, Fetal, anomalies.

Introduction

Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations. A major malformation is a structural abnormality that has serious medical, surgical or cosmetic consequence. The subject of congenital malformations is of considerable importance as it contributes significantly to perinatal mortality and morbidity. The aim of obstetric practice is achieved only when a pregnant women is blessed with a normal healthy child, congenital malformation is the unequivocal manifestation of abnormal prenatal development. The cause of most of the congenital malformations is unknown, although both hereditary and environmental factors are considered to be important Trace elements like vitamins are nutrients that help the body to perform vital cellular functions. They generally function as compounds or cofactors for many enzymes. Next to iron, zinc is the most commonly studied trace element during pregnancy. Zinc is an important metabolic substance for the mother and the fetus. Zinc deficiency appears to have a marked effect on growing and proliferating tissues. Zinc deficiency during the antenatal period leads to diverse adverse effects on the newborn including fetal mortality, fetal malformations, teratogenicity and intrauterine growth retardation. Because foetal needs for zinc

are so high, women are more likely to experience a zinc deficit during pregnancy[1-4].

Zinc has long known to be an essential element for the growth and development of living things. Prasad et al., first described zinc deficiency in man[5]. Glucose, Lactose, Soya protein, meat enhance zinc absorption. Zinc is better absorbed from human milk than from cow's milk. After absorption, albumin is the major plasma carrier, although some zinc is transported by transferring and α2 macroglobulin. Most of the zinc in the blood is localisted in RBCs and WBCs.

Zinc is required for the activity of RNA polymerase important in cell division. One of the most important nutrients for the Immune system. Zinc deficiency results in lowered glucose tolerance. It is demonstrated that addition of zinc increases and prolongs the physiological potency of steroid hormones. Reduced zinc in serum is associated with decreased motility of sperms. Essential for all phases of cell cycle

Experiment on pregnant rats with zinc deficient diet by Hurley et al in 1966 has shown that zinc deficiency appears to have a most marked effect on the growing or proliferating tissues. Even transitory periods of ingestion of the zinc deficient diet during pregnancy resulted in significant teratogenesis. The most frequent congenital anomalies found in decreasing order of occurrence were, clubbed feet, fused or missing digits (syndactyly), hydrocephalus and hydranencephalus, urogenital abnormalities, scoliosis and kyphosis, lung abnormalities, small or missing eyes, short or missing mandible, hernias and heart anomalies[6].

The malformations observed at term have their origins of course at earlier stages. In the 14 day embryo from a zinc deficient female, malformations of the face and limbs are already apparent. Even on the eleventh day of gestation, embryos from zinc deficient females show considerably less development than do normal embryos[6]. These early changes are very significant in terms of the high incidence of malformations of the central nervous system. After only 4 days of a zinc deficient diet, abnormal changes are already seen in the pre implantation blastocyst. Such abnormal eggs occur in high incidence, only 18% of eggs from zinc deficient females had formed normal blastocysts as compared with 97% of controls. Even at 3 days of gestation abnormal cleavage is apparent in the preimplantation egg. Additional findings consistent with the idea that zinc deficiency causes aberrations of nucleic acid synthesis come from cytogenetic studies. Chromosome spreads prepared from fetal liver of zinc deficient fetuses showed chromosomal aberrations, especially gaps and terminal deletions. Such chromosomal abnormalities were also seen in maternal bone marrow and occurred in significant incidence in both maternal and fetal tissues.

Lawrence et al. concluded that women receiving adequate diets have a lower incidence of fetal neural tube defects than women receiving poor diets[7]. Wynn and Wynn (1981) reported epidemics of congenital malformations particularly following wars and famines[8]. Soltan M.H. and Jenkins D.M. (1982) reported mean maternal plasma zinc levels to be significantly lower in women who gave birth to congenitally malformed infants than in controls (ie.) 4.032 ± 2.16 as compared to 10.36 ± 2.04 micromoles / litre respectively[9].

Buamah (1984) showed that serum zinc concentrations were lower in anencephalic pregnancy than in normal control subjects of similar gestational age suggesting that low zinc levels may be an associated factor in the pathogenesis of central nervous system malformation. Of the trace elements zinc is the most extensively studied[10]. The detrimental effects of trace element deficiencies on conception and fetal development have been studied extensively in animal models. Deficiency of zinc is associated with many pregnancy complications.

Swanson and king estimate that 100 mg of zinc is retained in maternal and fetal tissues during pregnancy. This is equivalent to about 5% of the whole body zinc content. During the third trimester zinc retention is at most - 1 mg daily. If approximately 25% of the dietary zinc is absorbed a woman would need to consume an additional 4 mg of zinc to meet the needs in the 3rd trimester. The corresponding increased dietary zinc needs for the 2nd and 3rd trimesters are 0.5 mg and 1.5 mg respectively. Among vegetarians, usual zinc intake may be lower. Adaptive mechanisms may alter the zinc use during pregnancy so that increased demand is met without an increase in dietary zinc[11].

More recently leucocyte zinc content has been used as an indicator of zinc deficiency. During pregnancy, the zinc content of WBCs falls and lower values have been observed with congenital anomalies. Furthermore fetuses with congenital anomalies themselves have reduced zinc content in cord blood leucocytes. Functional abnormalities of leucocyte prostaglandin metabolism were also found. PGE2, F2 ratios and PGF2α production correlated with cellular zinc content although total prostaglandin production was not altered. The clinical implication of these findings are unclear, but in zinc deprived rats, abnormally prolonged labour is normalised by treatment with PGF2α.

Zince deficiency in pregnant rats resulted in high rate of embryonic death, severe intrauterine growth

retardation, and high incidence of congenital malformations affecting every organ system[6]. Golali Pour MJ & Mansouri AR (2006), reported mean maternal serum zinc level to be significantly lower in women who gave birth to congenitally malformed infants than in controls[12].

Aim of the Study:

To establish the relationship between maternal serum zinc level and congenital malformations of fetus.

Materials and Methods:

This is the case control study. A study on serum zinc levels of mothers who gave birth to babies with clinically apparent congenital malformations was undertaken at Government Erode Medical College Hospital, Perundurai, and Erode during the period 2022 to 2023

Inclusion criteria

1. 50 women who gave birth to babies with congenital malformations
2. irrespective of gestational age formed the study group.
3. 50 women who gave birth to normal healthy term babies formed
4. the control groups. Control group population included patients of similar
5. age group without any pregnancy complications. The subjects were
6. selected randomly irrespective of socioeconomic status.

Exclusion criteria

1. History of drug intake known to cause congenital malformations
2. History of infections like rubella etc. History of exposure to
3. radiation
4. Women who gave birth to babies with obvious clinically apparent
5. chromosomal anomalies and nonchromosomal syndromes.
6. Diabetic mothers
7. History of alcoholism
8. History of seizure disorders
9. History of zinc supplementation

In all these patients, detailed history including diet, history of consanguinity, previous congenitally malformed babies, previous abortions, family history of congenital malformations was made. Complete general and obstetric examination was made. Ultrasound was done to detect congenital malformations. Babies were examined after delivery for congenital malformations.

Blood samples about 5ml in autoclaved test tubes were obtained from both study and control group patients within 24 hrs after delivery. All the glassware used were thoroughly washed with distilled water before blood was collected. Serum zinc estimation was done by using colorimetric

Statistical analyses

Data were analyzed using the SPSS software for Windows (version 13.0) (SPSS Inc., Chicago, IL). Chi-square test was used for comparing proportions. Student's unpaired t-test was applied for testing the differences between continuous variables. Cross-tabulation and multivariate analyses were used for exposing the associations between the dependent and the independent variables. A two-sided p value of <0.05 was considered significant at 95% level. Pearson's correlation test was used for seeing the correlation between continuous variables. However, the comparison between a quantitative variable and a qualitative variable was made with the help of Point biserial correlation.

Ethics

Intuitional Ethical Committee approved the protocol. Finally, informed written consent was taken from all the mothers after full explanations of the nature and purpose of the procedure used for the study. Anonymity was maintained throughout the study, and none of the names was used in the database.

Results:

Majority of patients in both study and control groups were in the 21-25 and 26-30 age groups. 4 patients in the study group were in the 31-35 age group, whereas in the control group only one patient was above 30 years of age.

Table 1: Distribution of patients according to Gravidity

			CC		Total
			Cases	Controls	
	Primi	Count	30	22	52
		% withinCC	60.0%	44.0%	52.0%
	G 2	Count	12	15	27
		% withinCC	24.0%	30.0%	27.0%
	G 3	Count	7	9	16
		% withinCC	14.0%	18.0%	16.0%
		Count	1	2	3
		% withinCC	2.0%	4.0%	3.0%

	G 4	% withinCC	0	2	2
		Count	0.0%	4.0%	2.0%
	G 5	% withinCC	50	50	100
Total			100.0%	100.0%	100.0%

Majority of patients in both the groups were multiparous (Table-1). All the patients in both study and control groups belonged to low socioeconomic status. In the study group 32 (64%) patients belonged to Class IV and 18 (36%) patients belonged to Class V. In the control group 28 (56%) patients belonged to Class IV and 22 (44%) patients belonged to Class V.

Table 2: Distribution of patients in both study and control groups according to Sex to the baby

			SC		
			Cases	**Controls**	**Total**
BabySex	Female	Count	20	24	44
		% withinSC	40.0%	48.0%	44.0%
		Count	30	26	56
	Male	% withinSC	60.0%	52.0%	56.0%
		Count	50	50	100
		% withinSC			
Total			100.0%	100.0%	100.0%

In the study group 60% of the babies were males and 40% of the babies were females (table 2). In the study group there were 21 (42%) live births and 29 (58%) still birth. In the control group, there were no still births.

Table 3: Mean serum zinc levels in the study and control groups

SC	N	Mean	Std. Deviation	Std. Error Mean
Age Cases (Yrs)	50	25	3.768	.533
Controls	50	24	4.250	.601
Baby CasesWt.	50	1.808	.6414	.0907
Controls	50	3.002	.3461	.0489
Maternal Cases Serum	50	44.95	14.49	2.04935
Controls Level Zinc	50	86.43	7.88381	1.11494

The mean serum zinc level in the study group was 44.95 µg/dl (SD 14.4). Mean serum zinc level in the control group was 86.43 µg/dl (SD 7.88). There is statistically significant difference in the zinc level between the two groups (P value < 0.001). (Table 3). There is no influence of parity on maternal serum zinc level.

Table 4: List of Congenital Malformations observed in the study

		Frequency	Percent
Valid	Anencephaly	14	28.0
	Anencephaly with	2	4.0
	Meningomyelocele		
	Cleft Lip, Cleft Palate	4	8.0
	Hydrocephalus	11	22.0
	Hydrocephalus	2	4.0
	Meningomyelocele		
	Imperforated Anus	3	6.0
	Meningomyelocele	7	14.0
	Microcephaly	1	2.0
	Micropenis	1	2.0
	Polydactyly	2	4.0
	Spina Bifida	2	4.0
	Syndactly & Polydactyly	1	2.0
	Total	50	100.0

In our study (table 4 & Fig-1) maximum babies (28%) had anencephalic and 22% of the babies were hydrocephalus. 6% syndactyly, polydactyly. 6% had defects pertaining to the genitourinary system. Live births were 42% and still births were 58% in the study group. Whereas in the control group there were not still births. The lowest value of maternal serum zinc was found with hydrocephalus. (20.1 µg/dl) and highest value 70.82 in µg/dl in polydactyly.

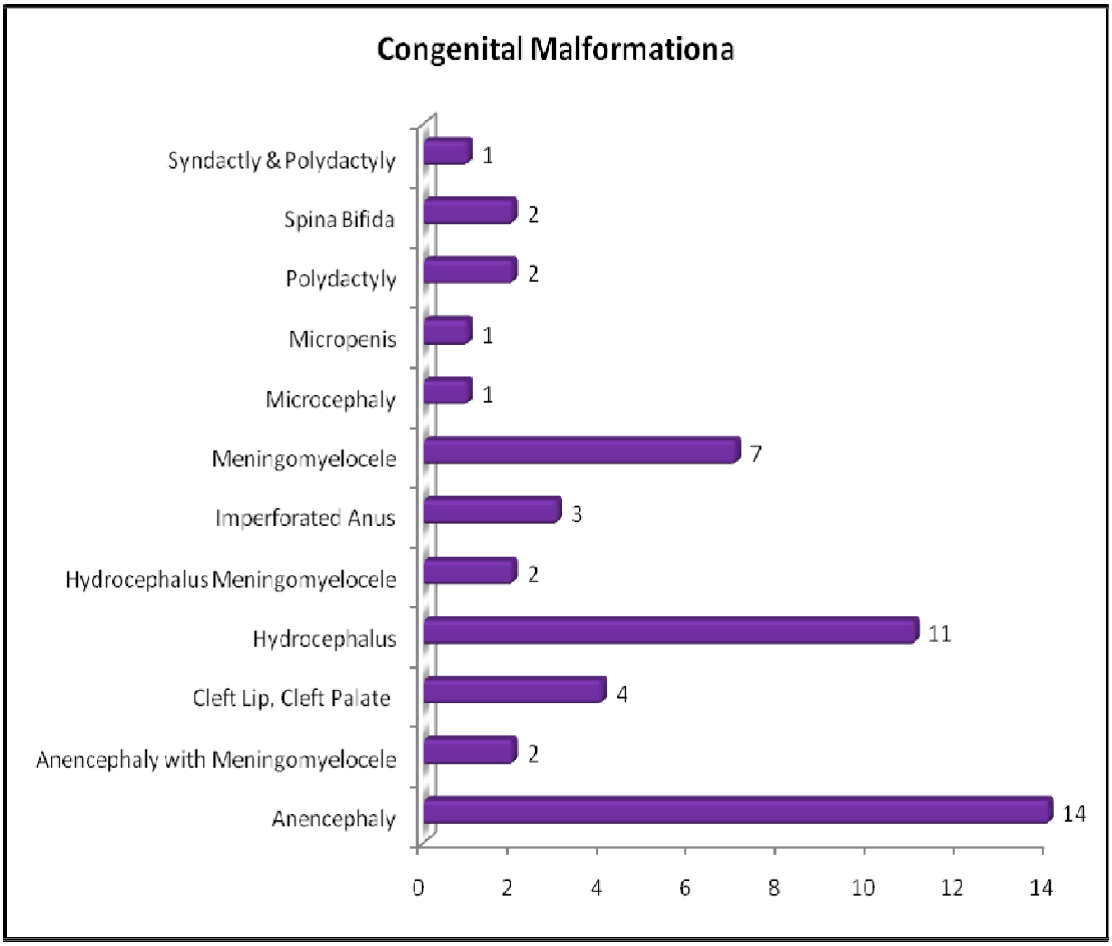

Figure1: List of Congenital Malformations observed in the study

Discussion

Maternal malnutrition is one of the main reasons of low birth weight in India. Low birth weight babies have a higher risk of morbidity. Birth weight has long-term consequences on not just the perinatal stage but also childhood and adulthood. Micronutrients other than iron are frequently overlooked while protein and energy shortages are given a lot of attention. Micronutrient deficiencies during pregnancy have been linked to LBW, according to some research.

In the current study, in experimental group 60% of babies were males and 40% of babies were females. In the control group 52% of babies were males and 48% of babies were females. The mean serum zinc level in the study group was 44.95 µg/dl (SD 14.4). Mean serum zinc level in the control group was 86.43 µg/dl (SD 7.88). There is statistically significant difference in the zinc level between the two groups (P value < 0.001). According to the research of Ismail Mohamed et al.[13], there is a statistically significant association between cord zinc and gestational age. This might be as a result of the fact that foetal zinc absorption rises with gestational age, with 60–70% of it happening in the third trimester. Additionally, a consistent progression of rising mean zinc levels with gestational age was seen, with term newborns having the highest levels and very preterm neonates having the lowest. There were substantial direct associations between cord zinc levels and gestational age, according to research by Abass R. M. et al. [14].A necessary nutrient called zinc cannot be produced by the human body. Zinc plays a key role in transcription factors and serves as a catalytic cofactor for the enzymes that control cell differentiation and maturation. In order for human growth and development to occur as optimally as possible, zinc is a crucial trace element. Zinc plays an intracellular role in cell division and the production of nucleic acids in addition to providing protection against free radicals. For growth and development, the maternal mineral status during gestation is crucial. Preterm babies are at risk for zinc and other important nutrients for brain development deficiency because they are born before the period of accelerated intrauterine foetal growth.

These substances must be transported from the maternal blood to the placenta by carrier proteins. It is unknown how much of these carrier proteins are present late in pregnancy and at birth, despite

the fact that the foetus depends on its own synthesis of them to supply minerals to all of its organs. Potential nutritional deficiencies in premature foetuses may be serious if the transfer of essential nutrients from mother to foetus has not kept up with the needs of the foetus because the absolute amount of nutrients, vitamins, and trace elements transported across the placenta increases as gestation progresses.

Such deficiencies may lead to a decreased accumulation of these substances in the fetus's storage organs. As a result, the neonatologist faces the problem of delivering adequate nutrition in the early neonatal period, particularly to the premature newborn whose potential specific mineral deficiencies at birth are not well established. Even though zinc is relatively little required, our bodies depend on it for a number of essential processes. Since the amount of zinc needed is minimal, its sufficiency must be carefully examined.

In addition, several of the trace elements interact with one another. As a result, their needs must be supplied appropriately while taking into account their interactions, safety, and toxicity. In the present study, In study group mean serum zinc level in primi 50.64 (SD 13.2) multi 40.46 (SD 14.84). In control group primi 85.33 (SD 7.6) multi 87.44 (SD 8.09). Anencephaly (28%) was the commonest malformation in our study. The lowest value of maternal serum zinc was found with hydrocephalus (20.1 µg/dl) and highest value 78.82 with polydactyl.

According to Abdellatif et al.'s study [15] full-term newborns had a mean cord serum zinc level of 88 18 g/dl, compared to 73 13 g/dl in preterms. A few studies, such as those by Iqbal, et al. and Gomeze, show no correlation between cord blood zinc and birth weight. According to a study by Nisha Gupta et al. [16], this may be because of a delay in the separation of the plasma and blood sample collection, a different sample size, or national differences in diet. Since over one-fourth of the world's low birth weight morbidity originates in poor nations like India, the impact of maternal zinc on newborn growth parameters is significant.

Conclusion

According to the study's findings, of the variables examined, low maternal serum zinc levels are substantially linked to foetal congenital deformity. Both the mother and the foetus need zinc for proper metabolism. Zinc shortage appears to have a significant impact on growing tissues, altering the metabolism of nucleic acids and leading to congenital abnormalities.

This research sheds insight on the possibility that reduced maternal serum zinc levels contribute to the aetiology of congenital abnormalities, particularly those affecting the central nervous system. With the demands of pregnancy, a slight zinc shortage at or before conception could become severe, especially if it is accompanied by anorexia and vomiting. Congenital deformities may be brought about by low zinc levels during conception or early development. Therefore, zinc supplementation may be begun as a preventative measure during early pregnancy or the pre conceptional period.

In summary, zinc deficiency plays a dynamic role in the development of congenital abnormalities in newborns, particularly anomalies of the central nervous system. Dietary counselling should be given, especially to mothers who have a history of having babies who were born with congenitally deformed conditions. Additional large-scale research on zinc supplementation will open the door to a better knowledge of zinc and show that intervention may lessen the occurrence and severity of congenital abnormalities.

Limitations:

The sample size was modest, and it only came from one Tertiary Hospital. The mother's socioeconomic situation and diet were not taken into account.

Acknowledgements:

We sincerely thank each and every one of the participants for taking part in research study. The authors thank the Government Erode Medical College and Hospital, Perundurai, Tamil Nadu, for providing the necessary facilities.

Author's contribution:

Dr. R. Sathya - conceptualization, data curation, investigation, methodology, project administration, visualization, writing—original draft, writing—review and editing; **Dr. A. Gayathri** - conceptualization, methodology, writing—original draft, writing—review and editing; **Dr. R.Renju** - conceptualization, visualization, supervision, writing—original draft; **Dr. Revathi. A** and **Panneerselvam Periasamy** - methodology, writing—original draft, writing, review and editing.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

Data Availability: All datasets generated or analyzed during this study are included in the manuscript.

Informed Consent: Written informed consent was obtained from the participants before enrolling in the study

References

1. Prasad AS: Zinc deficiency in women, infants and children. J Am Coll Nutri.1996; 15(2):113-20.
2. Etemad K, Yavari P, Mehrabi Y, Haghdoost A, Motlagh ME, Kabir MJ, et al. Inequality in utilization of in-patients health services in Iran. Int J Prev Med. 2015; 6:45.
3. Moradi-Lakeh M, Vosoogh-Moghaddam A. Health sector evolution plan in Iran; equity and sustainability concerns. Int J Health Policy Manag. 2015; 4(10):637-40.
4. Moradi-Lakeh M, Namiranian N. Increasing trend of low birth weight in rural areas of Iran: a warning. Iran J Pediatr. 2013;23(1):123-4
5. Prasad A S. Zinc deficiency has been known of for 40 years but ignored by global health organisations BMJ 2003; 326:409.
6. Hurley L.S. Zinc deficiency in prenatal and neonatal development. New York. Alan P. 1977: 47.
7. Mosley BS, Cleves MA, Siega-Riz AM, Shaw GM, Canfield MA, Waller DK, Werler MM, Hobbs CA; National Birth Defects Prevention Study. Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States. Am J Epidemiol. 2009 Jan 1; 169(1):9-17.
8. Arthur Wynn, Margaret Wynn. (1990) The Need for Nutritional Assessment in the Treatment of the Infertile Patient. Journal of Nutritional Medicine 1:4, pages 315-324.
9. Soltan MH, Jenkins DM. Maternal and fetal plasma zinc concentration and fetal abnormality. Br J Obstet Gynaecol. 1982 Jan; 89(1):56-8.
10. Buamah PK, Russell M, Bates G, Ward AM, Skillen AW. Maternal zinc status: a determination of central nervous system malformation. Br J Obstet Gynaecol. 1984 Aug; 91(8):788-90.
11. Swanson, C.A., and J.C. King. 1987. Zinc and pregnancy outcome. Am. J. Clin. Nutr. 46:763–771. [PubMed]
12. Golalipour MJ, Mansourian AR, Keshtkar A. Serum zinc levels in newborns with neural tube defects. Indian Pediatr. 2006 Sep; 43(9):809-12. PMID: 17033120.
13. Abdellatif M, Elhawary IM, Mahmoud MM, Youness ER, Abuelhamd WA. Cord levels of zinc and copper in relation to maternal serum levels in different gestational ages. Egypt Pediatr Assoc Gaz. 2021; 69(1).
14. Abass RM, Hamdan HZ, Elhassan EM, Hamdan SZ, Ali NI, Adam I. Zinc and copper levels in low birth weight deliveries in Medani Hospital, Sudan. BMC Res Notes. 2014; 7(1):1–5.
15. Abdellatif M, Elhawary IM, Mahmoud MM, Youness ER, Abuelhamd WA. Cord levels of zinc and copper in relation to maternal serum levels in different gestational ages. Egypt Pediatr Assoc Gaz. 2021; 69(1).
16. Gupta N, Bansal S, Gupta M, Nadda A. A comparative study of serum zinc levels in small for gestational age babies and appropriate for gestational age babies in a Tertiary Hospital, Punjab. J Family Med Prim Care. 2020 Feb 28; 9(2):933-937.