

Association of Low Maternal Serum Zinc with Second Trimester Induced Abortion of Fetus with Neural Tube Defect (NTD)

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Abstract

Background:

The pathogenesis of neural tube defects (NTD) is till now unknown and literatures blame some nutrient deficiency like folic acid as a risk factor. Zinc deficiency has been proposed to play a role in the pathogenesis of NTD; however, enough controversy in published articles is present to permit the conduction of the current study.

Aim: To evaluate the association between maternal zinc and occurrence of NTD.

Patients and methods: Current case control study enrolled 27 women who underwent induced second trimester abortion for diagnosed NTD and 53 women with normal pregnancies. Serum zinc was estimated and correlated with rate of NTD. The study was carried in Al-Diwanyia teaching hospital, it is conduct from January 2016 till February 2017.

Results: Low zinc was highly significantly associated with higher rate of neural tube defect in comparison with normal zinc level ($P=0.006$). The risk of low zinc in association with neural tube outcome was evaluated using odds ratio which was 3.99 and a 95% confidence interval of 1.44-11.09; the etiologic fraction of zinc in predisposing to neural tube defect was 0.424.

Conclusion: Low maternal zinc is significantly associated with higher rate of NTD.

Key words: Zinc deficiency, neural tube defects

INTRODUCTION

Neural tube defect is heterogeneous and complicated congenital abnormality of the central nervous system which includes a variety of types such as spina bifida, anencephaly and encephalocele. They represent an important cause of morbidity and mortality at perinatal period [1]. Globally, the incidence of NTD is variable and differences in incidence have been reported in different seasons, gender, socioeconomic status of parent and maternal age [2]. Several factors have led to reduction in NTD incidence and these include early prenatal diagnosis and selective termination of NTD babies, genetic counseling and folic acid, zinc and B12 supplementation during pregnancy [3]. The pathogenesis of NTD is not fully understood; however, an interaction between genetic and environmental factors has been proposed [4, 5]. A number of chromosomal and monogenic disorder have been observed to be accompanied by NTD and it is estimated that around 10% of NTD are associated with chromosomal abnormality such as trisomy 18, trisomy 13, trisomy 21 and triploidy [6, 7]. The frequency of NTD is higher among low birth weight, multiple pregnancy low gestational age and female gender [8,9] in regions with reported high incidence of NTD it is routine practice to measure serum alpha fetoprotein as a screening test to detect those abnormalities as early as possible hence a cutoff value of 2.5 multiples of the median (MoM) in singleton pregnancies when maternal serum samples taken at 15 to 20 weeks is an indication to carry out detailed US to establish the diagnosis [10]. When the biparital diameter is difficult to be viewed, the suspicion of anencephaly is high. Reduction of incidence and recurrence of NTD has been observed when folic acid is given to the mother in the preconception period [11], on the other hand, other studies showed that the use of zinc and methionine supplementation also reduced the incidence

of NTD significantly [12, 13]. The action of zinc in the human body metabolism is explained by its enzymatic affinity. In human there is a number of important zinc-containing metalloenzymes such as alkaline phosphate, carbonic anhydrase, DNA and RNA polymerase, alcohol dehydrogenase and thymidine kinase [14]. Deficiency of zinc results in growth retardation and retarded sexual maturation and supplementation of zinc is effective in promotion of growth and sexual development in zinc-deficient children. (15) On the other hand zinc is essential for spermatogenesis and stability of the chromatin structure of the sperm [16]. Profound zinc deficiency leads to impaired immune function since it is needed for the maturation and activation of T-lymphocytes [17]. In addition, zinc plays an essential role in control of appetite [18]. The concentration of maternal zinc is variable according to gestational age and it becomes lower as pregnancy advances. (19) it has been reported also that low maternal zinc is associated with pregnancy induced hypertension, prolonged rupture of membranes, abruption placenta, inefficient uterine contractions, prolonged or non-progressive labor, and maternal hemorrhage and infections [20]. So the aim of the present study was to evaluate the association between maternal zinc and occurrence of NTD.

PATIENTS AND METHOD

This study was designed as case control study, it was carried in Al-Diwanyia teaching hospital, it is conduct from January 2016 till February 2017. The case group consist of 27 women who terminated their pregnancies as result of second trimester ultrasound diagnosis of neural tube defect (anencephaly), whereas the control group was 53 selected according to demographic and obstetric characteristics and have normal ultrasound with document normal fetal outcome. All pregnant women with singleton pregnancy

who had induced abortion in their second trimester for fetal NTD diagnosed by u/s in the period of this study were included in our study. Women who had history of epilepsy with or without antiepileptic treatment, diabetics, anemic patients and those who did not receive their folic acid supplementations were excluded from this study. All fetuses aborted in this hospital during the study period were examined after abortion for NTD (anencephaly). The health of neonates in the control group was assessed clinically by an obstetrician and pediatrician. A questionnaire covering all relevant clinical and demographic factors was filled out for each case.

Determination of maternal serum zinc

Three milliliters of venous blood were obtained from each case and control women by venipuncture using disposable syringes. Blood was collected in a disposable plastic tube and left to stand at room temperature for not less than 15 minutes. Tubes were then centrifuged and sera were separated immediately using disposable pipette. The serum of each individual sample was put in sterile tube and was stored at -20°C . Determination of serum zinc was done according to instruction outlined by the providing company. The accepted reference value for zinc in serum is 80-120 $\mu\text{g/dl}$ (10.7 to 18.4 $\mu\text{mol/l}$). Values below 70 $\mu\text{g/dl}$ were used for the statistical analysis of this parameter.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS version 20). Numeric variables were presented as mean \pm SD (standard deviation), whereas categorical variables like were presented as number and percentage. Chi-square, corrected Chi-square and Fischer exact tests were used to study association between any two categorical variables according to fulfillment of individual test assumption, while independent samples t-test and Mann Whitney U test were used to study difference of mean between any two groups if variables were normally

distributed or not normally distributed, respectively. Evaluation of risk was conducted using Odds ratio and 95% confidence interval together with etiologic fraction estimation. P-value of ≤ 0.05 is considered significant, whereas P-value of ≤ 0.01 was considered highly significant.

RESULTS

Table 1 showed the demographic characteristics of the study sample. Mean age of patients was not significantly different from that of control women, 29.44 \pm 8.36 years versus 28.25 \pm 9.63 years ($P=0.584$), also mean gestational age showed no significant difference between both groups, 27.52 \pm 5.00 weeks versus 28.53 \pm 6.31 weeks ($P=0.472$), additionally, there was no significant difference in mean birth weight between the two groups, 1233.30 \pm 987.62 grams versus 1637.70 \pm 1191.07 grams ($P=0.133$). Rate of abortion was 18.52% in patients whereas it was 6.55% in control group; however, no statistical significance was found ($P=0.156$). The frequency of previous children with neural tube defect, also was not significantly different between both groups, 0% versus 1.89% ($P=1.000$), as well as the frequency of children with other congenital anomalies, 22.22% versus 7.55% ($P=0.220$). Comparison of positive drug history revealed no statistical significance,

18.52% versus 9.43% ($P=0.274$). In addition, multi-parity rate was not significantly different in both groups, 48.15% versus 45.28% ($P=0.808$).

Table 2 showed the effect of low zinc on outcome of having a child with neural tube defect. Low zinc was highly significantly associated with higher rate of neural tube defect in comparison with normal zinc level ($P=0.006$). The risk of low zinc in association with neural tube outcome was evaluated using odds ratio which was 3.99 and a 95% confidence interval of 1.44-11.09; the etiologic fraction of zinc in predisposing to neural tube defect was 0.424.

Table 1: Demographic characteristic of the study sample and control group

Characteristics	Cases (n=27)	Control (n=53)	P
Maternal age (Mean \pm SD) years	29.44 \pm 8.36	28.25 \pm 9.63	0.584 ^a
Gestational age (Mean \pm SD) weeks	27.52 \pm 5.00	28.53 \pm 6.31	0.472 ^a
Birth weight (Mean \pm SD) g	1233.30 \pm 987.62	1637.70 \pm 1191.07	0.133 ^b
Previous abortion n (%)	5 (18.52)	3 (5.66)	0.156 ^c
NTD n (%)	0 (0.00)	1 (1.89)	1.000 ^d
Anomaly n (%)	6 (22.22)	5 (9.43)	0.220 ^c
Drug n (%)	5 (18.52)	4 (7.55)	0.274 ^c
Parity (Multiparous) n (%)	13 (48.15)	24 (45.28)	0.808 ^c

a: Student t-test; b: Mann Whitney test; c: Corrected Chi square test; d: Fischer exact test; NTD: neural tube defect

Table 2: Effect of low maternal zinc on neural tube defect outcome

Zink	Cases (n=27)	Control (n=53)	P*	Odds ratio	95% CI	EF
Low	13 (48.15%)	10 (18.87%)	0.006	3.99	1.44-11.09	0.424
Normal	14 (51.85%)	43 (81.13%)				

CI: Confidence interval; EF: Etiologic fraction; *: Chi square test

DISCUSSION

In our study the results demonstrate that there was an association between low serum zinc level and conception with fetuses with NTDs. Our finding is similar to Buamah et al. (1984) who found that the serum zinc concentrations were lower in the anencephalic pregnancies than in the normal control subjects [21]. In Turkey, several authors study the association between maternal serum zinc level and NTD and they reached to results comparable to our results [22, 24]. Golalipour et al. had done two studies in Iran; 1st one in (2006) and the 2st in (2009), in both of them they found that there was a significant association between the presence of NTDs and zinc deficiency [25, 26]. Maternal age is another important risk factor for NTDs in our study, where women with age more than 35 years old have a higher risk to have fetus with NTDs than women aged less than 35 years with a *p*-value of 0.021. The results of current study are comparable to results obtained by Whitemen et al. (2000) who state that "women aged more than 35 years had a substantially increased risk of having an NTD-affected pregnancy" [27]. Another study also concluded that there is an increased risk of having an offspring with NTDs for mother 40 years of age or older and there is also evidence that mothers 19 years old or younger have a higher risk for having a child with spina bifida [28]. In contrast, the current study showed no significant relationship between serum zinc level and maternal age (*p*-value=0.101). Consumption of medications in the 1st trimester of pregnancy in a factor that is widely accepted as a cause in congenital malformations which goes with what was found by Mandiracioglu A et al. (2004), who state that "Drug intake during pregnancy was identified as a risk for NTD development (OR: 6.65, 95% CI : 2.26-20.2)", which is comparable to our results that demonstrate increased risk of NTDs by the effect of drug exposure with *p*-value=0.013. [29]. Also we found that consumption of medications associated with low serum zinc level (*p*-value=0.03) but we did not find any study to compare with it. Our explanation, we can't specify these drugs causing NTDs, this need deep investigations and assessment (i.e. it could be the deficiency may be related to the chronic illnesses to which these drugs were prescribed or may be related to the medication which need thorough investigation and study). Histories of previous NTDs and previous abortion are associated with low serum zinc level as it shown in our study (*p*-value=0.014, 0.021 respectively) which is comparable to the results of another study carried out in 2006 [30]. In our study maternal serum zinc level was found to be decreased when gestational age increased and this can be explained by the physiological changes that occur in pregnancy which includes volume

expansion, hormonal changes, and increased fetal zinc requirement for new tissue formation. This results or comparable to that of other authors who found that with each trimester there is a progressive decline in serum zinc level in normal pregnancy [31].

CONCLUSION

In this study there is an association between NTDs and low serum zinc levels, adding to the evidence about the importance of nutritional and maternal health factors in the etiology of this disease. So we recommend that zinc supplementation should be considered with folic acid supplementation in balanced formula, for three months' preconception ally, for further decrease in the occurrence and recurrence of NTDs.

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