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Paternal and maternal zinc status: Do they have effect on fetal outcomes?

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Abstract

Background: The deficiency of specific micronutrients in mothers including zinc increases the risk of pregnancy complications. Although there are many studies in literature describing the relationship between low maternal zinc levels and poor pregnancy outcomes including prematurity and low birth weight; there is not any study on paternal zinc level. In this study, we aimed to define the relationship between deficiency of maternal and paternal zinc levels and prematurity and low birth weight. **Material and Methods:** We determined the zinc levels of parents of preterm infants (102 mothers and 108 fathers) low birth weight infants (43 mothers and 42 fathers) and healthy term infants (108 mothers and 111 fathers). **Results:** We found that low maternal zinc levels increased the preterm delivery risk by 4.95 fold and each 10 mg increase in maternal zinc level resulted in 6.9 g increase in birth weight. We showed that the critical maternal cut off value of zinc level was 75UI/L. There was no effects of low paternal zinc level on preterm birth or low birth weight. **Conclusion:** It seems that zinc status of mothers is related to poor pregnancy outcomes such as prematurity and low birth weight and healthy nutrition of mothers is a simple strategy for prevention of those complications.

Keywords: Zinc level, Preterm, Low birth weight, Mothers, Fathers.

INTRODUCTION

Low birth weight and preterm infants are at high risk for respiratory, gastrointestinal, immunological, neurological, and developmental complications and majority require intensive care [1]. Pre-pregnancy weight, diet, and micronutrient levels and chronic diseases have influence on pregnancy outcomes. It is known that deficiency of specific micronutrients including iron, zinc, folate, vitamin C, and calcium increases the risk of pregnancy complications.

Zinc is the major factor of fetal growth and its deficiency is seen five times more in developing countries [1-3]. The literature has reported that zinc supplementation to mothers with low body mass index during pregnancy increased the birth weight of infants.

Although there are many studies in literature describing the relationship between low maternal zinc levels and poor pregnancy outcomes including prematurity and low birth weight; there is not any study on paternal zinc level which is the other important component of fertilization. Male genital organs have

higher zinc levels compared to other body secretions [7]. Studies have shown that zinc has an important role in many enzymatic pathways such as testicular steroidogenesis, testicular development, and stabilization of sperm chromatin, etc. and the disruption of any of them results in male infertility [7]. The fetus formed by the abnormal sperm, an outcome of zinc deficiency, could have many different morbidities [7]. Hence we hypothesized that paternal zinc levels should also be assessed in the context of potential risk for prematurity and low birth weight and aimed to define the relationship between deficiency of maternal and paternal zinc levels and prematurity and low birth weight.

MATERIALS AND METHOD

In this study we planned to use 560 serum samples which we collected and used before for the study entitled 'Prevalence of celiac disease in parents of preterm or low birth weight newborns' [8] and stored in optimal conditions. Serum samples of 287 infants' parents, which were centrifuged at 3000 rpm for 15 minutes and stored at -40 ºC were assessed.

Parents were evaluated in three groups

Group I: Mothers and fathers of infants with gestational age <37 weeks (preterm infants)

Group II: Mothers and fathers of infants with birth weight<2500g (low birth weight infants)

Group III: Mothers and fathers of healthy term infants with normal birth weight

Serum samples of seven infants' parents were excluded due to technical problems. On the second look 28 maternal and 19 paternal serum samples who belonged to different babies were excluded, too. Thus zinc level was studied in parents of 111 infants in Group 1 (102 mothers, 108 fathers), of 48 infants in Group 2 (48 mothers, 42 fathers), and of 121 infants in Group 3 (107 mothers, 111 fathers) (Fig. 1).

Serum Zn levels were measured using atomic absorption spectrometry (Perkin Elmer analyst 800-AAS, Encino, California, USA). Power analysis showed that a minimum of 462 samples ($\alpha = 0.05$ $1-\beta$ (power) = 0.80) should be included for a reliable conclusion.

Data were statistically evaluated using IBM SPSS for Windows version 22.0. Kruskal-Wallis test and Conover pairwise comparison method were used for comparisons of quantitative data. Comparison of qualitative data was performed by Pearson chi-square test. Relationship between variables was assessed by Spearman rank correlation coefficient. Odds ratio estimations made by logistic regression analysis. Also, linear regression analysis was conducted for determination of significant variables. ROC analysis was used for the prediction of best cut-off value. In all analyses, p value <0.05 was considered significant.

The study was approved by the Institutional Ethic Board of the İnonü University (2006/83).

RESULTS

Demographic findings of infants and their parents were shown in Table 1. Serum samples of 280 infants (111 preterm, 48 low birth weight, and 121 term, normal birth weight) were analyzed for maternal and paternal serum zinc levels (102 mothers and 108 fathers of preterm babies, 43 mothers and 42 fathers of low birth weight infants, 107 mothers and 111 fathers of term/healthy infants)(Fig. 1).

Table 1. Demographic characteristics of the infants and their parents.

		Group 1 N=111	Group 2 N= 48	Group 3 N=121	Total N=280	p
Gender	Male	62 (55.9%)	21 (43.8%)	64 (55.9%)	147 (100%)	0.521
	Female	49 (44.1%)	27 (56.3%)	57 (47.1%)	133 (100%)	
Mean gestational age (wk.)		31.3 ± 3	38 ± 1.1	38.5 ± 1.1	35.7 ± 3.8	0,00
Mean birth weight (g)		1524 ± 54	2082 ± 323	3267 ± 481.8	2365 ±922.6	0,00
Mean birth height (cm)		39.0 ± 3.3	41.6 ± 6.8	49.4± 2.6	42.3±5.7	0,00
Mean head circumference (cm)		29.4 ± 3.9	32.1± 3,8	34.4 ± 1.6	31.3 ± 3.3	0,00
1. min. APGAR score (mean)		4.4 ± 0.5	4.2 ± 1.4	4.7 ± 0.8	4.3 ± 0.9	0,09
5. min. APGAR score (mean)		8.2 ± 0.6	8.5 ± 0.5	8.7 ± 1	8.38 ± 0.7	0,22
Consanguinity		27 (21.4%)	7 (14.1%)	28 (46.3%)	62 (100%)	0.427
Multiple pregnancy		19 (17.1%)	5 (10.4%)	2 (1.6%)	26 (100%)	0.002
Early membrane rupture		34 (30.6%)	5 (10.4%)	3 (2.4%)	42 (100%)	0.000
Polyhydroamniosis		2 (1.8%)	1 (2.1%)	1 (0.8%)	4 (100%)	0.42
Oligohydroamniosis		6 (5.4%)	2 (4.2%)	0	8 (100%)	0.03
History of infertility		15 (13.5%)	5 (10.4%)	4 (3.3%)	24 (100%)	0.02

Smoking	7 (6.7%)	4 (8.3%)	7 (5.7%)	18 (100%)	0.596
Pre-eclampsia	19 (17.1%)	8 (16.7%)	4 (3.3%)	31 (100%)	0.000
Gestational diabetes	9 (8.1%)	1 (2.1%)	4 (3.3%)	14 (100%)	0.205
Uterine anomaly	2 (1.2%)	0	2 (1.6%)	4 (100%)	0.574
Maternal age (mean)	28.4 ± 0.4	28.1 ± 1.1,	29.1 ± 0.3	28.5 ± 0.9	
Paternal age (mean)	31.7 ± 1.3	32.6 ± 2.2	33.2 ± 1.6	32.5 ± 2.5	

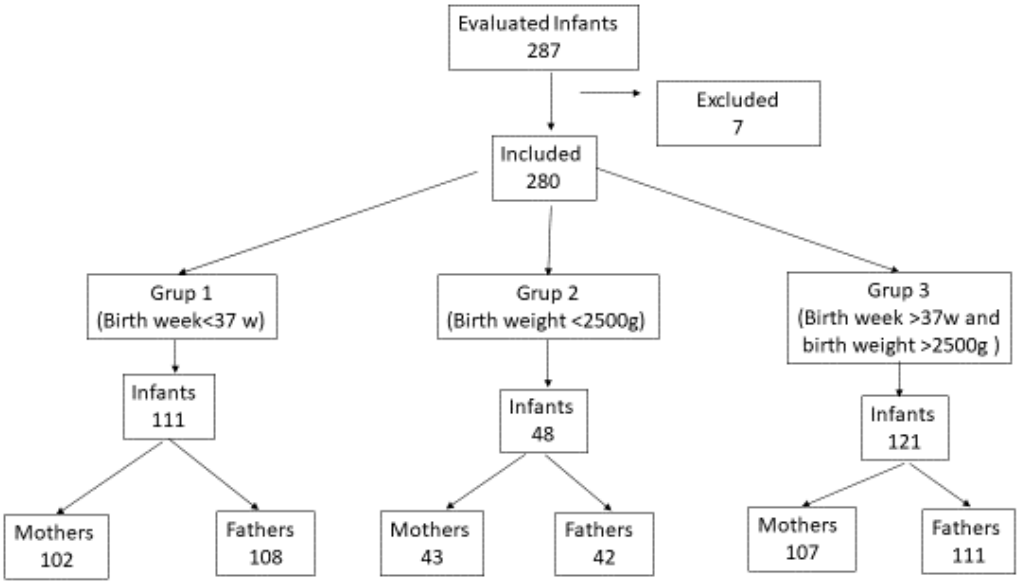

Figure 1: The algorithm of the participants' election.

Table 2 summarizes the zinc status of parents. A statistically significant difference in maternal zinc level was found among groups (p=0,004). Mean maternal zinc levels among groups were compared by Anova analysis. Individual comparisons between patient groups and controls were also performed (Table 2). Mean paternal zinc level among groups revealed no statistical significance.

Table 2. Median values of maternal and paternal zinc levels and comparisonbetween groups.

		Group 1	Group 2	Group 3	Total	p value
Number of samples	Maternal	102	43	107	252	
	Paternal	108	42	111	261	
Mean maternal zinc level (IU/L)		77.5	86.8	91.9	85.4	0.003
Mean paternal zinc level (IU/L)		95.9	97.1	111.5	101.5	0.056
Maternal zinc level	Low	37 (51.4%)	11 (15.3%)	24 (33.3%)	72 (100%)	0.004
	Normal	64(39.3%)	30(18.4%)	69(42.3%)	163 (100%)	
	High	1(5.9%)	2 (11.8%)	14 (82.4%)	17 (100%)	
Paternal zinc level	Low	18 (47.7%)	5 (13.2%)	15 (39.5%)	38 (100%)	0.057
	Normal	79 (45.1%)	30 (17.1%)	66 (37.7 %)	175 (100%)	
	High	11 (22.9%)	7 (14.6 %)	30 (62.5 %)	48 (100%)	

Logistic regression analysis revealed that each 10 mg of maternal zinc level decrement increased preterm delivery by 4.95fold. Spearman correlation coefficient test showed that there was a weak significant relationship between low birth weight and low maternal zinc level (Fig. 2).

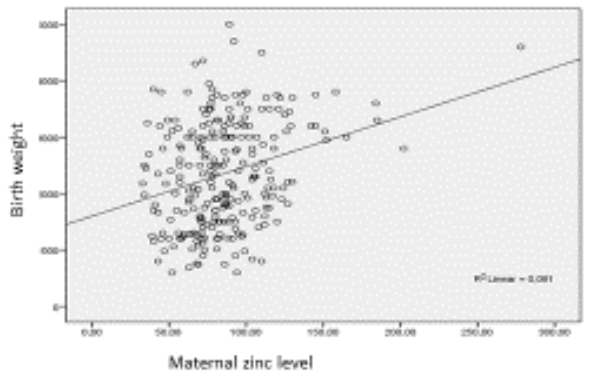

Figure 2: The relationship between birth weight and maternal Zn level according to Spearman analysis.

Multiple linear regression performed to determine the factors affecting birth weight revealed a coefficient as R^2=0.315. According to this model, significant variables were preeclampsia, early membrane rupture, multiple fetus, and low maternal zinc level. Each 10 mg increase in maternal zinc level resulted in 6.9 g increase in birth weight. ROC analysis revealed cut off value of maternal zinc level for low birth weight risk as 75 IU/L(Fig. 3).Paternal zinc levels were higher than the cut off zinc value in all three groups (Table 2). There is no statistically significant relationship between paternal zinc level and preterm and/or low birth weight.

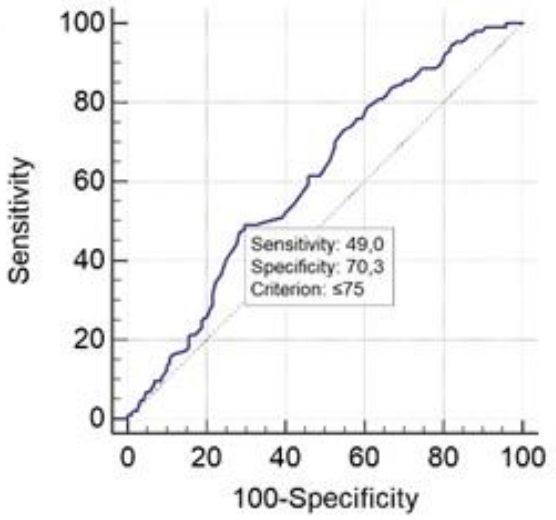

Figure 3: Maternal zinc level and birth weight relationship (Roc Analysis).

DISCUSSION

Zinc has key roles in the cell division, growth, anti-oxidation system, and gene expression [9-11]. The relationship of maternal zinc level and fetal development and pregnancy outcomes has been shown in many experimental and clinical studies [4, 6, 10, 11, 14]. It was reported that while severe zinc deficiency during the first 10 days of conception caused malformed fetus by 22%, if it occurred during the first 12 days, the ratio of abnormal fetuswas%56 [12]. Microscopic abnormalities in brain development due to zinc deficiency were observed between 10 and 12 days [12]. This teratogenic effect has been demonstrated in animal experiments, including preimplantation period, which may also occur with maternal zinc level fluctuations [12].

Maternal zinc deficiency seen in the first and third trimesters of pregnancy results in many pregnancy complications; deficiency in early pregnancy causes teratogenicity due toabnormal DNA synthesis and protein structure [13]. This effect which was further enhanced by the fluctuation in zinc level was demonstrated in animal experiments [14]. Moderate zinc deficiency increases apoptosis markedly. In a previous study, it was shown that development of pharyngeal arch, optic vesicle, forelimb root and neural tube was more affected [15]. This apoptotic effect is caused by the activation of the caspase pathway as a result of activation of the intrinsic mitochondrial cytochrome C pathway [16]. Caspase 3 activation is an indication of zinc deficiency [17]. If this deficiency occurs during the mid-gestation, the posterior dorsal midline of the neural crest cells will be affected leading to developmental as well as heart abnormalities [17]. A moderate deficiency is sufficient for the effect of zinc on growth. This effect is exerted via extracellular signal-regulating kinase (ERK1/2) [12]. Mitosis plays a critical role in the continuation of the ERK cycle, which takes place in the G1 phase. The decrease in ERK 1/2 causes a decrease in cell proliferation. Growth hormone is influenced by the zinc level; low zinc level decreases the plasma insulin-like growth hormone 1 (IGF1) level, the activator of growth hormone, disrupting growth hormone axis [12]. Although fetus attempts to protect itself from maternal zinc deficiency by active zinc transport from the mother, fetal growth pauses by multiple mechanisms and poor pregnancy outcomes such as prematurity and low birth weight occur [5].

Previous studies showed that serum zinc levels of preterm and low birth weight infants were significantly lower in preterm or low birth weights infants compared to term healthy newborns [3, 5-7, 11, 14, 17, 18, 20, 23]. In one of those studies, zinc deficiency was also defined in mothers of preterm and low birth weight infants [5].In a further large series with a total of 500 infants, it was found that maternal zinc level was significantly lower in low birth weight infants compared to normal weight term infants [18]. In another small scale study including 56 infants, no significant relationship between maternal zinc level and gestational age and birth weight was found [19]. Plasma zinc level was reported to be lower in antenatal women with severe pre-eclampsia and eclampsia but no significant relationship between zinc level and low birth weight was found [20]. According to Cochrane meta-analysis, zinc supplementation in pregnancy has reduced the risk of prematurity by 0.86 percent [8]. In a randomized controlled study, maternal zinc supplementation did not decrease the risk of prematurity or low birth weight [21].

In our study, we found that low maternal zinc levels increased the preterm labor risk in accordance with some of the above studies [1-3, 6, 9, 21-23]. We determined that each 10 mg decrease

in maternal serum zinc level increased the risk of having a preterm infant by 4.95 times. Although there are many studies for or against to our hypothesis, there is not any revealing a clear relationship with low birth weight and maternal zinc as we have shown in our study: each 10 mg increase in maternal zinc level caused a 6.9 g increase in birth weight. Thus the effect of maternal zinc on each gram of birth weight has not been reported in previous studies. Furthermore we determined the maternal threshold zinc level for low birthweight risk as 75 IU/L by Roc analysis.

Although literature focuses on the maternal side of the conception in the context of zinc deficiency, none of the studies investigated the probable relationship between parental zinc status and the pregnancy outcomes. Zinc deficiency during the conception period disrupts the homeostasis of fetal life and paternal zinc levels may also be effective during pre-implantation period. The fact that the zinc level in male reproductive organs is quite high and zinc deficiency causes male infertility with oligospermia, and affects genetic material [7], we thought that it would be reasonable to investigate the paternal side as well. However, we did not find a relationship between low paternal zinc levels and low birth weight or prematurity. However, considering the lack of further data on this subject, we believe that this relationship should be investigated both experimentally and clinically.

In conclusion, deficiency of zinc, which has a key role in chromatin structure and function, can lead to disruption during embryogenesis. This is clinically manifested by fetal mortality, malformation, neural tube defects and growth retardation. In advanced gestational weeks, this micronutrient deficiency may cause preterm birth and low birth weight infants. In this study we showed that each 10 mg of maternal zinc level decrement increased preterm delivery by 4.95 fold and each 10 mg increase in maternal zinc level resulted in 6.9 g increase in birth weight. Therefore, it seems that healthy nutrition is a simple strategy for prevention of poor pregnancy outcomes such as prematurity and low birth weight. A proposal of a cut off maternal zinc value of 75IU/L as a red flag to alert physicians for a need for zinc supplementation to avoid poor pregnancy outcomes could be studied further.

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