Maternal Iron, Copper, Magnesium and Calcium Levels in Preterm Delivery and the Effect of These Trace Elements on Birth Weight

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OBJECTIVE: To compare the maternal micronutrient levels in patients suffering from preterm delivery and women with term pregnancies and to assess the effect of maternal serum micronutrient levels on birth weight.
STUDY DESIGN: Fifty preterm laboring pregnant women and 20 term pregnant women were enrolled. Serum iron, magnesium, copper and calcium levels were measured with "flamed atomic absorption technique". Hemoglobin levels, gestational age, birth weight, Apgar scores of the first and fifth minutes, socioeconomic status and smoking habits were evaluated.
RESULTS: The mean value of serum iron levels was statistically lower in preterm group when compared with the term group. Other micronutrient levels were not differing. Birth weight, Apgar scores of the first and fifth minutes, gestational ages, hemoglobin and serum iron levels were found to be significantly lower in preterm group ($p<0.001$). Maternal serum iron levels, and hemoglobin levels were found to be correlated with gestational age and birth weight; however, with regression analysis only iron was found to be an independent factor affecting gestational age and birth weight.
CONCLUSION: Maternal serum iron level is linearly correlated with birth weight and infant birth weight, but other micronutrients seem to have no association with preterm delivery and birth weight.
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Key Words: Preterm birth, Iron, Copper, Magnesium, Calcium

Preterm birth complicates 5 to 10 percent of all births worldwide and is associated with 75% of perinatal morbidity and mortality for infants born without congenital anomalies.[1] Many nutritional factors can theoretically affect the mechanisms controlling the continuation of pregnancy or initiation of labor. Low maternal micronutrient intake or inadequate stores have been associated with premature birth and low birth weight.[2] Maternal deficiencies of iron, magnesium, copper, calcium and zinc have been reported to be associated with preterm birth and other poor pregnancy outcomes.[3-8] Recently we found that maternal serum zinc level is linearly correlated with birth weight and tends to be lower in preterm deliveries, although not an independent factor (Demirturk et al. unpublished data). Our aim in this study was to compare the maternal iron, copper, magnesium and calcium levels in patients suffering from preterm delivery and women with term pregnancies and to assess the effect of maternal serum levels of these trace elements on birth weight.

Materials and Methods

Fifty pregnant women admitted with the diagnosis of preterm labor and delivered and 20 normal term pregnant women who also delivered in the perinatology department of Dr. Zekai Tahir Burak Women's Health Training and Research Hospital between May 1999 and June 1999 and who were eligible were enrolled in this study. Women with preterm rupture of membranes, preeclampsia, abruption placentae, placenta previa, multiple gestation, excessive or inadequate amniotic fluid volume, anomalous fetus, uterine anomaly, diabetes mellitus, asthma, drug abuse and pyelonephritis were excluded. Pregnant women whom their gestational ages were between 20-37 weeks, who had at least 3 contractions in 20 minutes according to non-stress test and who had at least 2 cm of dilatation and 80% of effacement were diagnosed as preterm labor. Ultrasonography was used to confirm the gestational age. Patients who did not deliver were excluded. The serum was collected before the administration of tocolytic agents. Pregnant women in the control group had gestational ages of 37 weeks and over, had at least 2 cm of dilatation and 80% effacement.

While choosing the patients in the study and control groups, attention was paid for them to have similar feeding habits and socio-economic status. Socio-economic status was based on the monthly income of the families.

Ten cc of peripheral venous blood was collected from each case and put in plain biochemistry tubes. Then they were centrifuged with 3000 rpm for 5 minutes to separate the serum. The serum was kept in deep freeze of -25ºC until the analysis time.

Samples were analyzed in "Gulhane Military Medical Academy, Faculty of Pharmacology, Toxicology Department". Measurements were performed with double-beam atomic absorption spectrophotometer system and serum zinc-

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Table 1. Comparison of Control and Preterm Delivery Groups

	Control (n=20) X±SD	Preterm (n= 50) X±SD	p
Age (year)	26.40±4.98	23.92±5.17	0.052
Birth weight (g)	3269.50±211.12	1940.00±593.60	p<0.001*
Apgar (first minute)	7.00±0.00	5.26±1.55	0.002*
Apgar (fifth minute)	9.00±0.00	7.26±1.75	0.007*
Gestational age (weeks)	38.20±1.11	31.61±3.35	p<0.001*
Gravidity	1.65±0.67	1.8±1.12	0.580
Parity	0.65±0.67	0.56±0.81	0.662
Iron level (µg/ml, mean±SD)	1.85±0.43	0.74±0.38	p<0.001*
Copper level (µg/ml, mean±SD)	1.79±0.25	1.79±0.34	0.990
Magnesium level (µg/ml, mean±SD)	21.34±2.91	20.98±2.32	0.589
Calcium level (µg/ml, mean±SD)	97.17±5.01	97.13±4.89	0.975
Hemoglobin (g/dl)	12.72±0.91	9.12±1.66	<0.0001*

*: statistically significant

Table 2. Comparison of mean iron, copper, magnesium and calcium levels between extremely preterm, very preterm, preterm and term labors.

	<28 weeks of gestation	28-32 weeks of gestation	32-37 weeks of gestation	>37 weeks of gestation	p
	(n: 9)	(n: 15)	(n: 26)	(n: 20)	
Iron level (µg/ml, mean±SD)	0.78±0.41a	0.58±0.21b	0.80±0.43c	1.85±0.43d	<0.0001*
Copper level (µg/ml, mean±SD)	2.02±0.42	1.72±0.29	1.77±0.30	1.79±0.25	0.113
Magnesium (µg/ml, mean±SD)	22.37±4.23	21.07±1.29	20.44±1.71	21.34±2.91	0.230
Calcium (µg/ml, mean±SD)	97.88±4.09	97.53±5.52	96.63±4.90	97.17±5.01	0.9

*: for a and b: p=0.638, for a and c: p=0.999, for a and d: p<0.0001, for b and d: p=0.328, for b and d: p<0.0001, for c and d: p<0.0001

levels were measured by "flame atomic absorption techniqu-e." 213.9 nanometers of wave length was used. Serum was diluted with 1% of nitric acid in appropriate conditions and each sample was measured two times with straight calibration. Air-acetylene was used for the gas medium. Every dilution was done with bidistilled deionized water. Every chemicalthat was used had analytic purity. Polypropylene tubes wereoriginal and used only once. The laboratory cut-off value for serum iron, copper, magnesium and calcium levels were 1.2 µg/ml, 1.18 µg/ml, 18 µg/ml and 80 µg/ml respectively. The study was approved by the institution's ethical committee and all patients gave informed consent to the study.

Statistical Analysis

SPSS for Windows Release 11.01 Program was used for statistical analysis of the data. Student's t-test and Man Whitney U tests were used to compare the parameters between the groups. Pearson's correlation analysis and regression analysis were applied in order to determine the correlation of micronutrients with other parameters and to determine the factors that were independently affecting the birth weight and duration of pregnancy respectively. A p value less than 0.05 was assumed to be significant. To compare micronutrient levels in extremely preterm, very preterm, preterm and term groups Kruskal-Wallis and Man Whitney U tests were used. For this analysis level of significance was set at 0.0167.

Results

When the ages, gravidity and parity of the control and preterm groups were compared, no significant differences were found (p=0.145). Comparison with regard to smoking and socioeconomic status also yielded no significant difference between groups with p values of 0.381 and 0.327 respectively. Birth weight, Apgar scores of first and fifth minutes, gestational age, hemoglobin and maternal serum iron levels were found significantly lower in the preterm group. Groups were similar with regard to serum copper, magnesium and calcium levels (Table 1).

Comparison of mean iron, copper, magnesium and calcium levels between extremely preterm, very preterm, preterm and term labors were depicted in Table 2. The extremely preterm, very preterm and preterm groups did not differ with regard to iron; however, all these three groups were found to have significantly lower serum iron levels when compared with the term pregnancies. No statistically significant differences were found between these 4 groups with respect to maternal serum copper, magnesium and calcium levels (Table 2).

Table 3 shows the correlation of gestational week and birth weight with assessed parameters. In correlation analysis serum iron level was found to be positively associated with gestational age and birth weight. In order to determine the exact effect of iron on these parameters, regression analysis was applied. In regression analysis, iron was found to be an independent factor for gestational age and birth weight (beta=0.660, p=<0.0001, beta=728, p=<0.0001 respectively); however, other trace elements that were assessed were found to have no effect on gestational age and birth weight. Hemoglobin level did not come out to be an independent factor affecting the gestational age or birth weight (beta=-0.191, p=0.480 and beta=-0.427, p=0.090 respectively)

Table 3. Correlation of gestational week and birth weight with assessed parameters

	Gestational week		Birth weight	
	r	p	r	p
Birth weight	0.934	<0.0001*	1	-
Apgar 1st minute	0.648	<0.0001*	0.617	<0.0001*
Apgar 5th minute	0.636	<0.0001*	0.603	<0.0001*
Gestational week	1	-	0.934	<0.0001*
Maternal age	-0.045	0.712	0.010	0.933
Smoking	0.008	0.947	0.013	0.916
Socioeconomic status	0.02	0.871	0.01	0.999
Gravidity	-0.086	0.480	-0.077	0.527
Parity	0.41	0.739	0.043	0.725
Hemoglobin	0.571	<0.0001*	0.623	<0.0001*
Iron	0.610	<0.0001*	0.686	<0.0001*
Copper	0.060	0.960	0.025	0.960
Magnesium	-0.005	0.966	0.017	0.886
Calcium	-0.033	0.785	-0.032	0.790

*: Statistically significant

Discussion

Micronutrient adequacy at the time of conception and during gestation is clearly important for a number of pregnancy outcomes. Trace elements have important roles in fetal development and growth[9,10] and their deficiencies may be associated with poor pregnancy outcomes. Maternal deficiencies of iron, magnesium, copper, and calcium have been reported to be associated with preterm birth and other poor pregnancy outcomes[3-8]

Low iron status had been associated with increased risk of preterm and low birth weight.[2] In the present study iron, but not hemoglobin, was found to be an independent factor for gestational age and birth weight. Iron deficiency is suggested to lead changes in stress hormones such as norepinephrine,[11] cortisol and corticotrophin-releasing hormone concentrations,[12] and indexes of oxidative stress that may adversely affect gestation, fetal growth or both.[12] There are many studies on iron supplementation. The results of one large trial conducted in Finland in which routine iron supplementation was compared with selective supplementation, indicate a tendency toward a protective effect of iron supplementation on preterm birth rates.[13] However, this population was a well-nourished population. The effect of iron supplementation in developing countries may be more pronounced.

Magnesium is critical for bone formation, cellular integrity, multiple enzyme functions[14] and its deficiency has been suggested to be associated with pre-eclampsia, and preterm delivery,[3] and possibly with low birth weight. In the present study, however, maternal serum magnesium levels were not found to be associated with preterm birth and low birth weight. Although some supplementation studies reported a statistically significant reduction in preterm birth rates with supplementation, most of these trials had methodological weaknesses,[15] and the trial with the highest methodological quality showed no effect on reducing preterm birth.[16]

Many authors have emphasized the importance of an adequate copper intake during pregnancy.[17] Copper plays an important role in the maturation of collagen and elastin and thereby contributes to the maintenance and integrity of many vital structures.[18] It has been suggested that low maternal micronutrient intake of copper possibly is associated with preterm birth and low birth weight.[2] However, in this study no association was found between maternal serum copper levels and preterm birth and low birth weight.

Maternal serum calcium level did not differ between preterm and term groups in the present study. In some studies maternal calcium levels were found to be lower in the preterm groups[19] and this was explained by a decrease in maternal serum calcium concentration to a nadir at 32-36 weeks and then a rise to term,[20] so calcium deficiency was not thought to be an etiologic factor for preterm delivery. In a meta-analysis no protective effect of calcium supplementation on preterm delivery could be demonstrated.[21]

In summary maternal serum iron level seems to be an independent factor for preterm birth and low birth weight possibly by interfering with the stress hormones. Other assessed micronutrients-magnesium, copper and calcium-seem to have no association with preterm delivery and low birth weight. If this is the case then maternal serum iron levels may be used to detect a special subgroup of patients that is under risk of preterm birth.

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