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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Effects of maternal intake of n-3 fatty acids on lipid profile and leptin concentration in cord blood

Anne tarafından alınan n-3 yağ asitlerinin kordon kanı lipid profiline ve leptin konsantrasyonuna etkisi

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ABSTRACT

Objectives: Maternal intake of n-3 long chain polyunsaturated fatty acids (LC-PUFAs) has positive effects on fetal development and pregnancy outcomes. Leptin plays an important role in placental transportion of LC-PUFAs. In this study, we aimed to evaluate the effects of maternal n-3 LC-PUFAs intake on anthropometric parameters of mother and newborn, the levels of fatty acids (FAs) and leptin in cord blood.

Material and Methods: Thirty-one pregnant women were included. Eighteen were assigned to the control group and 13 received a supplement containing n-3 LC-PUFAs during last trimester of gestation (supplemented group). Physical examinations of the participants were performed and additional data were collected with a questionnaire. FAs and leptin concentrations in cord blood samples were analyzed using gas chromatography-mass spectrometry (GC-MS) and enzyme-linked immunosorbent assay (ELISA) kit respectively.

Results: A total amount of n-3 PUFAs significantly increased after treatment. n-6/n-3 PUFAs ratios and the leptin levels were lower in the supplemented group (P=0.052, P=0.140 respectively). There were positive correlations between leptin levels and the z scores for birth weight, height and head circumference of the newborns in the control group. The supplementation affected leptin concentration to be positively correlated with n-6/n-3 PUFA ratios.

Conclusion: Daily supplementation with n-3 LC-PUFAs might be effective to improve mother and newborn health.

Keywords: Leptin, Fatty acids, Cord blood, Newborn, Pregnancy

ÖZ

Amaç: Anne tarafından, n-3 uzun zincirli çoklu doymamış yağ asit (UZ-ÇDYA)'lerinin alımı, fetal gelişim ve hamilelik sonuçları üzerine pozitif etkilidir. Leptin, UZ-ÇDYA'larının plasentadan geçişinde önemli bir rol alır. Bu çalışmada, anne tarafından alınan UZ-ÇDYA'larının, anne ve yenidoğanın antropometrik ölçümlerine, kordon kanındaki yağ asitlerine ve leptin düzeylerine olan etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya 31 hamile kadın dahil edildi. Bunların 18'i kontrol grubuna alınırken 13'ü hamileliklerinin son trimesteri boyunca, n-3 UZ-ÇDYA içeren bir ilaç aldı (ilaçlı grup). Katılımcıların fizik muayeneleri yapıldı ve bir anket yardımıyla ek veriler elde edildi. Kordon kanındaki yağ asitleri ve leptin konsantrasyonları, sırasıyla gaz kromatograf kütle spektrometri (GC-MS) ve enzim bağlantılı immunosorbent test (ELISA) kiti kullanılarak analiz edildi.

Bulgular: Toplam n-3 ÇDYA'ların miktarı ilaç kullanımıyla anlamlı olarak arttı. İlaçlı grupta n-6/n-3 ÇDYA'larının oranı ve leptin düzeyleri daha düşüktü (P=0,052, P=0,140 sırasıyla). Kontrol grubunda, leptin düzeyleri ile yeni doğanların doğum kilosu, boyu ve baş çevresi arasında pozitif ilişki vardı. İlaç kullanımı, leptin konsantrasyonlarını, n-6/n-3 ÇDYA oranları ile pozitif ilişkili hale getirdi.

Sonuç: Günlük n-3 UZ-ÇDYA'larının alımı, anne ve yeni doğan sağlığının iyileşmesinde etkili olabilir.

Anahtar kelimeler : Leptin, Yağ asitleri, Kordon kanı, Yenidoğan, Hamilelik

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Introduction

Since it is well known that intake of n-3 long chain polyunsaturated fatty acids (LC-PUFAs) in pregnancy improve gestation outcomes and newborn health, higher intake of n-3 LC-PUFAs during pregnancy is recommended [1]. Placenta has a significant impact on the transport of fatty acids from the maternal to the fetal circulation. Fatty acid composition of cord blood is changed by maternal diet and it reflects how much fatty acid can be taken by the fetus [2].

Leptin takes a role on placental transport of nutrients such as fatty acids from mother to fetus [3]. Leptin levels in plasma are higher in pregnant mothers than that in non-pregnant mothers [4]. It is expressed from adipose tissue of mother and fetus and also placenta in utero [5]. Maternal leptin levels in the plasma increase in the second trimester of pregnancy [6]. This might be caused by increased adipose depots and increased synthesis by the placenta. It is observed that umbilical leptin concentration is correlated with pregnancy outcomes and play a key role in fetal development [7-8].

Even if, it is well known that the level of fatty acids influence the expression and the level of leptin in non-pregnant women [9], there is a lack of data about the impact of maternal n-3 LC-PUFAs intake on leptin levels during perinatal period [10].

For this reason, the aim of the present study was to evaluate the influence of n-3 LC-PUFAs supplementation taken by mothers during the last trimester of gestation on anthropometric parameters of mother and newborn and fatty acid composition of cord blood. As a secondary outcome, we also aimed to analyze the correlations of leptin levels in cord blood with these parameters.

Material and Methods

Participants

This study was a longitudinal study and conducted at Medipol University Hospital in Istanbul, Turkey between September 2015 and December 2016. Thirty-one expecting women at 22nd – 24th weeks of gestation were invited to participate in the study during their routine prenatal care visits in the hospital. The study was approved by Istanbul Medipol University Ethics and Research Committee. All women provided written informed consent to participate in the study and all procedures were in accordance with the Declaration of Helsinki. The pregnant women who gave preterm birth and had a history of chronic diseases and/or consumed omega-3 fatty acid supplements were excluded.

Supplementation

Thirteen pregnant women of 31, who accepted to take the supplement, were in the supplemented group and 18 pregnant women were in the control group. The mothers in the supplemented group received daily a softgel (Martek Biosciences Corporation, Solgar, Leonia, NJ, USA) containing 504 mg eicosapentaenoic acid (EPA) + 378 mg docosahexaenoic acid (DHA) from last trimester of gestation until delivery. The mothers in the control group did not take any supplement or placebo. Both groups did not take a dietary instruction.

Anthropometric parameters

The body weight of the mothers was measured with a portable scale to the the nearest 0.1 kg which was conducted with subjects in minimal clothes, while the height of them was measured using a portable measuring device to an accuracy of ± 0.5 cm which was fixed on the wall, with subjects standing straight with back, buttock, heals, and head against the wall. Body mass index (BMI) was calculated as body weight in kilograms, divided by the square of the body height in meters. We collected additional information data from the mothers by using a questionnaire.

Physical examination of the newborns was performed following birth. We calculated age- and sex-specific z scores for weight, height and head circumference of the newborns according to the World Health Organization (WHO) growth standards.

Laboratory Methods

Blood samples were collected from the umbilical cord after delivery. Plasma was separated in 1 hour and frozen immediately at -80 C^0 until analysis. The samples were thawed on ice and vortexed vigorously before performing the assays.

In order to evaluate the effects of the supplementation on fatty acid status, we quantified the fatty acid composition in the cord blood samples using a gas chromatography-mass spectrometry (GC-MS). Briefly, the lipids in serum were extracted according to Bligh and Dyer method. Fatty acid composition of extracted lipids was determined by conversion into fatty acid methyl esters (FAME). The FAME were separated and analyzed by a gas chromatography-mass spectrometry (GC-MS) (Shimadzu QP-2010, Kyoto, Japan). Standardization was performed using a standard mixture involving 37 fatty acids. Chromatograms were analysed in terms of % by weight of total fatty acids.

Plasma leptin levels were measured by an enzyme-linked immunosorbent assay (ELISA) kit (Millipore, MA, USA), according to the manufacturers' instructions with a sensitivity of 0.78 ng/mL – 100 ng/mL. None of the samples was under the detection limit of the ELISA kit.

Statistical analysis

Statistical analyses were performed using Statistical SPSS software (version 13.0; SPSS Inc., IL, USA). According to the distribution of data whether normally distributed or not, the differences between the means/medians belonging to two groups were analyzed by the appropriate statistical tests such as Unpaired t test/Mann Whitney U test. The data were presented as mean ± standard deviation (SD) or median, range. Nonparametric Spearman's correlation coefficient was used to find any correlation between leptin level in cord blood and the other parameters. A *P* value of <0.05 was considered statistically significant.

Results

Anthropometric parameters

The anthropometric parameters of the mothers and babies are shown in Table I. There were no statistical differences between both groups according to mother age, number of previous pregnancies, BMIs of the mothers before pregnancy, maternal body weight gain during pregnancy and gestational age at delivery.

Medians of z scores for weight, height and head circumference of the newborns in the supplemented group were lower then the levels in the control group. But, these were not statistically significant.

Fatty acid compositions of cord blood

In Table II, we depicted the mean ± SD for fatty acid concentrations in umbilical cord plasma. The supplementation induced some significant changes in fatty acid levels of cord bloods.

As expected before, the supplementation significantly increased EPA and DHA levels in the cord bloods of the supplemented group. Simultaneously, total amount of n-3 PUFAs was significantly higher after treatment.

On the other hand, we observed that the amounts of the members of n-6 PUFAs family were decreased with the supplementation except linoleic acid (LA, C18:2-n6). LA increased in the cord bloods of the supplemented group when compared to the levels in the control group. In addition, n-6/n-3 PUFAs ratios in cord bloods were lower in mothers who received the supplement than the ratios in the control group (*P*=0.052).

Moreover, the mean levels of total saturated fatty acids (SFAs) and total monounsaturated fatty acids (MUFAs) remained unchanged, while total PUFAs were slightly, but not considerably, higher in mothers who took the supplement than those in mothers of the control group.

Leptin levels and correlations with other parameters

The mean leptin levels in cord bloods were 8.5 ± 5.8 ng/mL in the control group and 5.7 ± 3.9 ng/mL in the supplemented

Table I. Effects of the EPA/DHA supplementation on anthropometric parameters of the mothers and newborns

	CONTROL GROUP (mean ± SD)	**SUPPLEMENTED GROUP** (mean ± SD)	* ***P*** **value**
n	18	13	
Maternal Age (years)	30.2 ± 3.8	32.3 ± 4.3	0.174
Number of previous pregnancies	1.5 ± 0.5	1.7 ± 0,6	0.289
BMIs of the mothers before pregnancy	22.8 ± 2.2	22.2 ± 2.5	0.479
Body weight gain of the mothers during pregnancy (kg)	15.1 ± 6.6	15.4 ± 4.7	0.865
Gestational age at delivery (days)	271.8 ± 7.7	272.1 ± 7.9	0.917
	CONTROL GROUP (median, range)	**SUPPLEMENTED GROUP** (median, range)	** ***P*** **value**
n	13	11	
z score for weight of newborn	0.57 ± 4.06	0.04 ± 1.74	0.999
z score for height of newborn	0.59 ± 4.12	0.46 ± 2.12	0.240
z score for head circumference of newborn	0.52 ± 4.58	0.42 ± 2.11	0.999

* Parametric test: Unpaired t test. ** Nonparametric test: Mann Withney U test. Significantly different from control, ***P* < 0.001, **P*< 0.05. (BMI: body mass index; EPA: eicosapentanoic acid; DHA: docosahexaenoic acid; SD: standard deviation)

Table II. Comparison of fatty acid composition (percentage by weight of total identified fatty acids; wt %) of cord bloods in the control and supplemented group.

FATTY ACID	CONTROL GROUP (mean ± SD)	SUPPLEMENTED GROUP (mean ± SD)	*P* value
n	**18**	**13**	
C 14:0	0.78 ± 0.35	0.77 ± 0.32	0.938
C 15:0	0.19 ± 0.05	0.20 ± 0.04	0.651
C 16:0	32.74 ± 1.18	33.00 ± 1.27	0.563
C 17:0	0.25 ± 0.05	0.27 ± 0.07	0.421
C 18:0	12.29 ± 1.21	11.59 ± 1.27	0.127
C 20:0	0.28 ± 0.11	0.23 ± 0.11	0.211
C 22:0	0.22 ± 0.08	0.19 ± 0.08	0.260
Total SFAs	46.77 ± 1.96	46.30 ± 1.29	0.451
C 16:1	3.34 ± 0.67	3.31 ± 1.10	0.912
C 17:1	0.16 ± 0.05	0.11 ± 0.04	**0.005**
C 18:1	17.81 ± 1.87	17.59 ± 1.68	0.729
C 20:1n9	0.07 ± 0.02	0.1 ± 0.06	0.434
C 24:1	0.25 ± 0.13	0.20 ± 0.30	0.577
Total MUFAs	21.57 ± 2.38	21.22 ± 2.13	0.668
C 18:2n6 (LA)	10.83 ± 2.04	12.76 ± 3.37	0.056
C 18:3n6	0.30 ± 0.09	0.20 ± 0.11	**0.009**
C 18:3n3	0.13 ± 0.15	0.16 ± 0.09	0.641
C 18:4n3	0.07 ± 0.04	0.10 ± 0.03	0.226
C 20:2n6	0.66 ± 0.20	0.50 ± 0.31	0.090
C 20:3n6	3.11 ± 0.77	2.26 ± 0.93	**0.009**
C 20:4n6	12.98 ± 1.39	12.65 ± 2.10	0.608
C 20:5n3 (EPA)	0.08 ± 0.03	0.15 ± 0.08	**0.021**
C 22:4n6	0.37 ± 0.10	0.26 ± 0.08	**0.003**
C 22:5n6	0.58 ± 0.21	0.36 ± 0.17	**0.004**
C 22:5n3	0.09 ± 0.05	0.15 ± 0.07	**0.026**
C 22:6n3 (DHA)	2.57 ± 0.66	3.17 ± 0.91	**0.043**
Total PUFAs	31.66 ± 1.75	32.50 ± 2.26	0.255
Total n-3 PUFAs	2.85 ± 0.68	3.52 ± 0.98	**0.032**
Total n-6 PUFAs	28.82 ± 1.99	28.99 ± 2.36	0.830
n-6/n-3 PUFAs ratio	10.68 ± 2.65	8.82 ± 2.34	0.052

(SFAs: saturated fatty acids; MUFAs: monounsaturated fatty acids; PUFAs: polyunsaturated fatty acids; LA: linoleic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; SD: standard deviation)

group. It was decreased in the supplemented group without any statistical differences ($P = 0.140$).

As shown in Table III, with non-parametric Spearman correlation analysis of the data, we found no significant correlation between leptin concentrations and mother ages, number of previous pregnancies and maternal body weight gain during pregnancy in both groups.

There were nonsignificant negative correlation between leptin concentrations and BMIs of the mothers before pregnancy and nonsignificant positive correlation between leptin concentrations and gestational ages at delivery in both groups

An interesting finding was the positive correlation between leptin levels and the z scores for birth weight, height and head circumference of the newborns in the control group. But, the associations with z scores for birth height and head circumference changed to the nonsignificant negative correlations in the supplemented group (Table III).

There was a nonsignificant negative correlation between leptin concentrations and SFAs levels in both groups but this correlation was stronger in the supplemented group. Furthermore, we observed that the supplementation resulted in a nonsignificant negative correlation between leptin concentrations and the total n-3 PUFAs concentrations. But there were no correlations between leptin concentrations and the total n-6 PUFAs concentrations in both groups. On the other hand, the supplementation made leptin concentrations in the cord blood positively correlated with n-6/n-3 PUFA ratio. But, these correlations failed to be statistically significant (Table IV).

Table III. Association of leptin concentrations in cord bloods with anthropometric parameters of the mothers and newborns in the control and supplemented group.

	LEPTIN CONCENTRATIONS IN CORD BLOOD			
	CONTROL MOTHERS		SUPPLEMENTED MOTHERS	
	Spearman's correlation coefficient	*P* value	Spearman's correlation coefficient	*P* value
Maternal Age (years)	-0.423	0.071	0.476	0.118
Number of previous pregnancies	-0.212	0.384	0.420	0.153
BMIs of the mothers before pregnancy	-0.253	0.311	-0.406	0.191
Body weight gain of the mother during pregnancy	0.110	0.664	0.213	0.485
Gestational age at delivery (days)	0.252	0.312	0.523	0.067
z score for weight of newborn	0.523	0.067	0.245	0.467
z score for height of newborn	0.581	**0.037**	-0.240	0.478
z score for head circumference of newborn	0.590	**0.034**	-0.410	0.273

Table IV. The correlation between each fatty acid concentration (percentage by weight of total identified fatty acids; wt %) and leptin concentration in the cord bloods of both groups.

	LEPTIN CONCENTRATIONS IN CORD BLOOD			
	CONTROL MOTHERS		SUPPLEMENTED MOTHERS	
FATTY ACID	Spearman's correlation coefficient	*P* value	Spearman's correlation coefficient	*P* value
C 14:0	-0.034	0.893	-0.410	0.164
C 15:0	0.098	0.700	-0.490	0.089
C 16:0	0.053	0.836	-0.363	0.223
C 17:0	-0.082	0.746	-0.055	0.858
C 18:0	-0.395	0.104	-0.159	0.603
C 20:0	0.093	0.713	-0.096	0.754
C 22:0	-0.176	0.484	-0.259	0.393
Total SFAs	-0.200	0.425	-0.522	0.067
C 16:1	0.474	0.047	0.451	0.122
C 17:1	0.039	0.876	-0.400	0.176
C 18:1	0.176	0.484	0.401	0.174
C 24:1	-0.056	0.826	-0.047	0.880
Total MUFAs	0.267	0.284	0.522	0.067
C 18:2n6 (LA)	-0.199	0.428	-0.236	0.437
C 18:3n6	0.041	0.869	0.039	0.900
C 18:3n3	0.019	0.950	0.107	0.819
C 18:4n3	0.289	0.487	0.308	0.614
C 20:2n6	0.377	0.123	0.198	0.517
C 20:3n6	0.311	0.210	0.099	0.748
C 20:4	-0.174	0.489	0.154	0.616
C 20:5n3 (EPA)	0.296	0.248	-0.489	0.107
C 22:4n6	0.075	0.769	0.168	0.583
C 22:5n6	0.025	0.922	0.287	0.343
C 22:5n3	0.308	0.264	0.228	0.588
C 22:6n3 (DHA)	-0.137	0.587	-0.308	0.306
Total PUFAs	-0.174	0.489	-0.132	0.668
Total n-3 PUFAs	0.082	0.748	-0.385	0.194
Total n-6 PUFAs	-0.183	0.468	-0.088	0.775
n-6 / n-3 PUFAs ratio	-0.080	0.754	0.379	0.201

(SFAs: saturated fatty acids; MUFAs: monounsaturated fatty acids; PUFAs: polyunsaturated fatty acids; LA: linoleic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid)

Discussion

The nutritional factors, which affect the baby health during pregnancy, determine the risk for diseases or prevention from diseases in postnatal life [11]. n-3 LC-PUFAs have positive impact on fetal development. Several studies showed beneficial effects of higher intake of n-3 FAs, particulary DHA and EPA, on neuronal, retinal, and immune function of infants [12]. On the other hand, some studies failed to show same effects [13]. Intake of n-3 LC-PUFAs during pregnancy also plays an important role on pregnancy outcomes in a good way. It was shown that n-3 LC PUFAs consumption during pregnancy resulted in longer gestation time, increase in head circumference of newborn, higher birthweight and lower risk of early preterm birth [1, 14-15]. However, there are some studies, which could not demonstrate these correlations [14, 16-17]. We believe that, these differences might depend on different concentrations of n-3 LC-PUFAs used in these studies. Especially, the last trimester of pregnancy is a critical period for requirement of n-3 PUFAs for the fetus [18]. In the current study, we observed a tendency for a reduction in the medians of z scores for weight, height and head circumference of the newborns whose mothers daily took a supplementation of n-3 LC-PUFAs during last trimester of their gestation, however, the results were not statistically significant. In the meantime, there were no changes in gestational age at delivery between the supplemented and the control groups.

Because fetus is limited in their ability to make n-3 LC-PUFAs, n-3 LC-PUFAs in mother's diet are the main source for fetus and the transportation of them through placenta is essential [1]. It was observed that enhanced maternal dietary intake of DHA+EPA increased DHA concentrations in cord blood [19]. In our study, we found that intake of n-3 LC-PUFAs during last trimester affected fatty acid composition in cord blood and resulted in rising total n-3 PUFAs and LA.

It is known that high n-6/n-3 PUFAs ratio in maternal diet is negatively associated with development of infants [20]. Because both n-3 and n-6 PUFAs are substrates for the same enzymes, they show an inhibitory effect on the synthesis of each other. So, n-6/n-3 PUFA ratio is more important than the levels of n-3 or n-6 PUFAs individually. Even if the ideal n-6/n-3 PUFAs ratio in diet is 5:1, it increases to 10:1 -20:1 in industrialized countries [21]. In the current study, we observed that intake of EPA and DHA in last trimester resulted in a decrease n-6 /n-3 ratio in the cord blood.

Leptin, as a potent stimulator of lipolysis, is one of the key factors, which regulates mobilization of PUFAs from maternal adipose tissue into placenta. It is mainly produced by maternal and fetus adipose tissues and also placenta in prenatal life [5]. Placenta-derived leptin modulates transportation of PUFAs via placenta in response to the fetal demand [3]. Placenta has leptin receptors and through these receptors, maternal leptin is taken by placenta and fetus [22]. The binding of leptin to its receptors on placenta is regulated by maternal fatty acids. It was observed that increase n-3 PUFA intake by mother rats decreased leptin levels in suckling pups' serum [23]. In the meanwhile, it was shown that EPA and DHA decreased uptake of leptin by human placental choriocarcinoma cells while arachidonic acid stimulated it invitro [24]. In our study, we showed that intake of n-3 PUFAs during last trimester of pregnancy seemed to cause a decrease in leptin concentration of cord blood but it was not statistically significant. Furthermore, higher total n-3 PUFAs levels were associated with lower leptin concentrations in cord plasma in the supplemented group but *P* value was found statistically nonsignificant. On the other hand, there was no correlation at all in the control group.

It is belived that the ratio of n-6/n-3 PUFA in the maternal diet is more important for affecting serum leptin levels than individual levels of n-6 or n-3 LC-PUFAs. It was shown that higher n-6/n-3 PUFAs ratio in maternal diet increased serum leptin levels of rat pups [23]. Consistent with this data we observed a nonsignificant positive correlation between n-6/n-3 PUFAs ratio and leptin levels in cord bloods of the supplemented group. On the other hand, it was found in an other study that reduced n-6/n-3 PUFA ratio in maternal diet did not affect leptin levels in maternal or cord blood [10].

Beside the roles of leptin in many physiological processes, its roles in perinatal period have been studied in a few studies. Leptin might be involved in the process of placentation. It was observed that leptin levels in maternal plasma and leptin protein levels in placenta were higher in pre-eclamptic pregnants than in controls at delivery [25]. Additionally, leptin was significantly lower in mothers who delivered preterm vs term babies [26]. Some studies showed that cord blood leptin levels were positively correlated with maternal BMI, neonatal adiposity, fetal growth indeces and placental weight [7,27,28]. In this study, we observed a positive correlation between leptin levels in cord blood and newborn health outcomes (weight, height and head circumference z scores) in the control group. But interestingly this correlation was turned into negative and nonsignificant correlation in the supplemented group. We

argue that the results until today are not enough to conclude leptin is a determinant of fetal growth.

These studies prove that ideal level of leptin in maternal circulation and cord blood is important for baby and mother health. The mean cord blood leptin concentration in this study were ~ 8.5 ng/mL in the control group which was in agreement with levels in other studies [29,30]. One of the factors that affect the leptin levels in prenatal life is neonatal and mother fat mass [8]. This may explain our data that leptin levels in cord blood were positively but nonsignificantly correlated with maternal body weight gain during pregnancy.

The main limitation of this study is the relatively small sample size. Low statistical power of the results and the correlations are most likely related with this limitation.

In conclusion, our findings suggest that maternal intake of n-3 LC-PUFAs during pregnancy might play a role in lipid profile and leptin signal during prenatal development. Our data can help researchers to shape new prospective studies with larger populations and for longer periods.

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