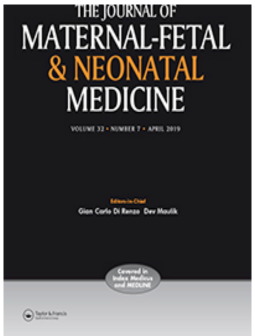

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The Mediterranean diet adherence by pregnant women delivering prematurely: association with size at birth and complications of prematurity

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ORIGINAL ARTICLE

The Mediterranean diet adherence by pregnant women delivering prematurely: association with size at birth and complications of prematurity

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ABSTRACT

Background: The Mediterranean diet (MD) is associated with decreased risk of metabolic syndrome and gestational diabetes due to the anti-inflammatory and antioxidative properties of its components. The aim was to investigate the potential association of MD adherence (MDA) during pregnancy by mothers delivering prematurely, with intrauterine growth as expressed by neonates' anthropometry at birth and complications of prematurity.

Participants and methods: This is a single-center, prospective, observational cohort study of 82 women who delivered preterm singletons at post conceptional age (PCA) $\leq$ 34 weeks and their live-born neonates. Maternal and neonatal demographic and clinical data were recorded. All mothers filled in a food frequency questionnaire, and the MDA score was calculated. Based on 50th centile of MD score, participants were classified into high-MDA and low-MDA groups.

Results: The low-MDA mothers had significantly higher pregestational BMI and rates of overweight/obesity (odd ratios (OR) 3.5) and gestational hypertension/preeclampsia (OR 3.8). Neonates in the low-MDA group had significantly higher incidence of intrauterine growth restriction (IUGR) (OR 3.3) and lower z-scores of birth weight and BMI. Regarding prematurity-related complications, the low MDA-group was more likely to develop necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity (OR 3.2, 1.3, and 1.6, respectively), while they were less likely to develop respiratory distress syndrome (OR 0.49), although the differences were not statistically significant. However, adjustment for confounders revealed MDA as a significant independent predictor of hypertension/preeclampsia, IUGR, birth weight z-score, necrotizing enterocolitis, and bronchopulmonary dysplasia.

Conclusions: High MDA during pregnancy may favorably affect intrauterine growth and certain acute and chronic complications of prematurity as well as maternal hypertension/preeclampsia.

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Bronchopulmonary dysplasia; necrotizing enterocolitis; respiratory distress syndrome; retinopathy of prematurity

Introduction

The Mediterranean diet (MD) pattern is characterized by increased consumption of unprocessed and plant foods, olive oil, and fish, whereas consumption of red meat, animal fats, sugars and salt is minimal [1]. The MD is rich in mono-unsaturated fatty acids and antioxidant polyphenols from olive oil and provides increased amounts of vitamins E and C that exert antioxidant effects. In addition, MD is rich in omega-3 long-chain polyunsaturated fatty acids (LCPUFA), which exert anti-inflammatory effects [2,3]. The benefits of the MD on adult morbidity associated with inflammation and oxidative stress, like the metabolic syndrome and cardiovascular diseases, have been well recognized [1,4,5].

Inflammation and oxidative stress are involved in the pathogenesis of gestational diabetes and hypertension/preeclampsia [6,7]. Several studies in pregnant women associated MD adherence (MDA) with lower incidence of gestational diabetes, whereas results on the effect of antioxidants on hypertension/preeclampsia are conflicting [8–10]. Moreover, MDA during pregnancy has been associated with decreased risk of intrauterine growth restriction (IUGR) and prematurity

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and higher birth weight (BW) and later adiposity in the offspring [11–14].

Preterm neonates are subjected to intrauterine inflammation and oxidative stress, which are involved in the pathogenesis of preterm labor [15–18]. Furthermore, the diminished capability of the preterm neonates to establish a steady balance between oxidant and antioxidant factors further augments their exposure to oxidative stress [19,20]. Relevant studies demonstrated that both the pre/perinatal inflammation, with and without infection, and the oxidative stress are involved in the pathogenesis of acute and chronic complications of prematurity including respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC) with and without sepsis, peri-intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD) [15,16,21–27]. Available data suggest that anti-inflammatory and antioxidant treatment during pregnancy could prevent the related neonatal morbidity in low birth weight infants. The dietary intake of omega-3 LCPUFAs by the pregnant women has been found to efficiently improve maternal and fetal status of omega-3 LCPUFAs [28]. In addition, an *in vitro* model of preeclampsia-oxidative stress indicated that antioxidant therapy with vitamin C, vitamin E, and N-acetylcysteine supplementation could counteract the adverse effects of reactive oxygen species on placenta [29]. In this context, maternal adherence to the MD during pregnancy could have a beneficial effect on complications of prematurity. However, thus far there have been no published data on the potential effect of MDA during pregnancy on complications of prematurity.

The primary aim of this study was to investigate the association of mother's adherence to the MD during pregnancy with intrauterine growth as expressed by anthropometry at birth and development of prematurity-associated complications. The secondary outcome measures were the association of MDA with pregnancy complications in women giving birth to preterm infants.

Materials and methods

Study design and population

This is a single-center, prospective, observational study of 82 pregnant women consecutively recruited among those who delivered live, preterm singletons at post conceptional age of 34 weeks or less and their newborns. Pregnant women were recruited during their hospitalization in the obstetric department for imminent preterm delivery or immediately after preterm delivery. Exclusion criteria were assisted reproduction, prepregnancy diabetes mellitus and hypertension, maternal heart and renal problems, stillbirth, evidence of congenital infections, and metabolic/genetic syndromes, death before the 40th week of postconceptional age (PCA), and refusal of parental consent.

Ethics

The study was approved by the Bioethics Committee of the Faculty of Medicine of Aristotle University of Thessaloniki and the Scientific Committee of the Hospital. Written informed consent was obtained from all mothers before recruitment.

Parental data collection and maternal MD score calculation

Information regarding parents' demographic data, educational status, and smoking attitudes were obtained through personal interview by one of the researchers. Data considering previous maternal pregnancies, current pregnancy, medications (including prenatal steroids), nutritional supplements, and delivery method were also recorded. Maternal MDA was assessed using an MD score developed and validated in the Greek population [1,30]. To this aim a nutritionist gathered information about maternal body weight before pregnancy and weight change during pregnancy (recall data), and the pregestational body mass index (BMI) was calculated. In addition, mothers were classified according to their nutrition status into normal (BMI <25) and overweight/obese (BMI ≥ 25). Then, the mothers, in cooperation with the same nutritionist, were requested to fill in a validated food frequency questionnaire about their nutritional habits during pregnancy. Participants who stated inability to recall their eating habits with accepted precision or reported changes in them during pregnancy were excluded. The MD score was calculated in accordance with the food-frequency questionnaire responses [30]. The centiles of the MD score in the study population were calculated and the 50th centile was used as a cut-off point to classify the mothers into two MD score-related groups; the high-MDA and the low-MDA groups.

Neonatal data

Neonatal data were collected prospectively and included sex, anthropometry, blood glucose, and hematocrit at birth, complications of prematurity (RDS, air leaks, patent ductus arteriosus [PDA], IVH, NEC, sepsis, BPD, and ROP), ways and duration of respiratory support, intravenous/intra-arterial line placement, rate and duration of Total Parenteral Nutrition (TPN), and duration of hospitalization. Assessment of birth weight (BW), length, and head circumference (HC) was performed using standard procedures. The BMI at birth was calculated. Anthropometry parameters were transformed into z-scores using the Fenton 2013 research bulk calculator (available at ucalgary.ca/fenton/2013chart). For definitions see Supplementary Material.

Statistical analysis

Continuous variables are presented as means and SDs or medians and range depending on value distribution (Kolmogorov–Smirnov test). Dichotomous variables are presented as counts and proportions, odd ratios (OR), and 95% confident intervals (CI). Comparisons between groups were performed using the *t*-test, Mann-Whitney test, or Fisher's exact test, as appropriate. For assessing the independent association of maternal adherence to the MD with complications of pregnancy and prematurity, and size at birth after adjustment for potential confounders, we built separate multivariable regression models with each outcome variable as dependent; logistic regression models (method stepwise forward conditional) for the dichotomous dependent variables (i.e. complications of pregnancy and prematurity) and Generalised Linear Models (Scale Response: linear) for continuous dependent variables (i.e. z-scores of anthropometry at birth). In all models, the MD-related group was included as an independent variable, while variables with established or potential association with each dependent variable were included as confounders. Continuous variables not following Gaussian distribution were transformed using natural logarithm before their use in regression analysis. The logistic regression analysis results are presented as Exp(B), 95%CI for Exp(B), and *p*, whereas Generalised Linear Models (linear response) results are expressed as B, Wald's 95%CI, and *p*. The statistical significance level was set at $p < .05$. Analyses were performed using the SPSS software, version 23 (IBM SPSS Statistics Corporation, Chicago, IL).

Results

Bivariate comparisons

The two groups were comparable as regards the parents' age and educational status as well as the mother's weight gain during pregnancy, parity, and the rate of prenatal steroid administrations, nutritional supplement use during pregnancy, caesarean section, and premature ruptures of membranes (Table 1, Table 3 in Supplementary Material). The maternal BMI before pregnancy and the rate of overweight/obesity (OR, 3.5) and hypertension/preeclampsia (OR, 3.8) were significantly higher in the low-MDA group (Table 1, Table 3 in Supplementary Material).

Regarding size at birth, neonates in the high-MDA group were less likely to be IUGR (OR = 3.3) and had significantly higher z-scores of BW and BMI at birth (Table 1).

Table 1. Maternal and neonatal data in the two Mediterranean diet adherence (MDA) – related groups.

	MDA score – related groups			
	Low-MDA ($n = 37$)	High-MDA ($n = 45$)	OR (95%CI)	p*
MDA score [m (min; max)]	21 (13; 23)	27 (24; 36)	–	<.001
Pregestational BMI [m (min; max)]	27.3 (16.3; 41.2)	23.8 (16.7; 41.4)	–	.021
Overweight/obese mothers [n (%)]	23 (62.2)	14 (31.8)	3.5 (1.4; 8.8)	.008
Weight gain during pregnancy [med (min; max)]	10.7 (1; 23)	10.0 (3; 17)	–	.208
Hypertension/preeclampsia [n (%)]	14 (38)	6 (13)	3.8 (1.3; 11.4)	.019
Gestational diabetes [n (%)]	5 (13)	5 (11)	1.22 (0.32–4.58)	.749
PCA at birth [wks, m (min; max)]	30 (24; 34)	30 (25; 33)	–	.060
Birth weight [g, m (min; max)]	1280 (650; 1580)	1200 (700; 1580)	–	.185
IUGR [n (%)]	17 (46)	9 (20)	3.3 (1.24; 8.78)	.018
Male gender [n (%)]	11 (28)	20 (44)	0.97 (0.78; 4.95)	.252
Birth weight z-score [x (SD)]	−0.83 (0.91)	−0.31 (0.90)	–	.012
Neonatal BMI z-score [x (SD)]	−0.48 (1.19)	0.04 (1.07)	–	.042
Respiratory distress syndrome [n (%)]	21 (57)	33 (73)	0.49 (0.19; 1.25)	.160
Respiratory support [n (%)]	17 (46)	26 (58)	0.62 (0.25; 1.55)	.375
Necrotizing enterocolitis [n (%)]	7 (19)	3 (7)	3.19 (0.76; 13.35)	.173
Sepsis/Necrotizing enterocolitis [n (%)]	8 (22)	6 (13)	1.75 (0.55; 5.59)	.384
Bronchopulmonary dysplasia any grade [n (%)]	10 (27)	10 (22)	1.26 (0.46; 3.46)	.797
Retinopathy of prematurity stage II-V [n (%)]	5 (13)	4 (9)	1.56 (0.39; 6.30)	.725
Days in Hospital [m, (min; max)]	50 (10; 157)	56 (1; 130)	–	.365

*Student's *t*-test, Mann–Whitney U test, Fisher's exact test.
m: median; x: mean; SD: standard deviation; CI: confidence intervals.

Table 2. Results of regression analysis models with dependent variables the pregnancy- and prematurity-related complications and size at birth.

Dependent variables	Significant independent variables	B	Exp(B)	5%; 95%CI of Exp(B)	*p*	Nonsignificant independent variables included in the model
Logistic regression (method: stepwise backward conditional)						
Pregnancy Hypertension/ preeclampsia	MDA-related groups	1.69	5.42	1.31; 22.4	.019	PCA, maternal age, parity, gender
	weight gain during pregnancy	−2.91	0.05	0.006; 0.45	.007	
Gestational diabetes	mother's age	−8.14	–	–	.022	MDA group, PCA, weight gain during pregnancy, parity, gender
	gender	2.66	14.29	1.30; 156.9	.030	
IUGR	MDA-related groups	1.31	3.70	1.14; 12.0	.029	MDA group, weight gain during pregnancy, smoking during pregnancy
	PCA	−9.58	–	–	.018	
	Gender	1.23	3.41	1.05; 11.09	.041	
Necrotizing enterocolitis	MDA-related groups	1.81	6.09	1.15; 32.2	.033	PCA, PROM, intravessel catheters, PDA, IPPV
	Gender	2.20	9.02	1.73; 46.9	.009	
Bronchopulmonary dysplasia	MDA-related groups	2.6	12.9	1.3; 124	.027	RDS, PDA, sepsis/NEC, IPPV
	PCA	44.98	–	–	.001	
	Gender	4.40	81.8	4.29; 1559	.003	
Dependent variables	**Significant independent variables**	**B**	**Exp(B)**	**Wald 5%; 95% CI**	***p***	**Nonsignificant independent variables included in the models**
Generalized Linear Model analysis (Scale Response: linear)						
Birth weight z-score	PCA	−6.78	–	−8.56; −4.99	<.001	MDA-related group, gestational diabetes, hypertension/preeclampsia, weight gain during pregnancy, smoking during pregnancy
	gender	0.60	–	0.30; 0.91	<.001	
BMI z-score	PCA	−5.2	–	−8.0; −2.40	<.001	
	Gender	−0.81	–	−1.27; 0.34	.001	

CI: confidence intervals; IPPV: intermittent positive pressure ventilation; IUGR: intrauterine growth restriction; MDA: Mediterranean diet adherence; NEC: necrotizing enterocolitis; PCA: postconceptional age at birth; PDA: patent ductus arteriosus; PROM: premature rupture of membranes; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity.

The incidence of complications of prematurity did not differ significantly between the two groups. However, there was a trend towards a higher incidence of NEC, combined sepsis/NEC, BPD, and ROP in the low-MDA group (OR 3.2, 1.7, 1.3, and 1.6, respectively), compared to the high-MDA group. On the other hand, neonates in the low-MDA group were less likely to develop RDS and require respiratory support (OR 0.49 and 0.62, respectively, Table 1). One (1) infant developed ROP of stage 3 plus and eight ROP of stage 2 or 2 plus, but none required surgical intervention. Two (2) neonates in the high MDA group developed IVH of grade III and IV, respectively. The rate of intravenous/intra-arterial catheter placement, the need of total parenteral nutrition, and the duration of hospitalization was comparable between the two study groups (Table 1, Table 4 in Supplementary Material).

Regression analysis

The multivariable regression models showed that the MDA-related group was a significant independent predictor for the development of hypertension/preeclampsia but not gestational diabetes after adjustment for confounders (Table 2). Regarding the size at birth, the MDA-related group was a significant independent predictor of IUGR rate and BW z-score, but not the BMI z-score, after adjustment for confounders (Table 2). Moreover, the MDA-related groups were independently associated with BPD and NEC after adjustment for confounders (Table 2), whereas it was not significantly independently associated with adjusted RDS and ROP.

Discussion

Results of this study confirmed that high MDA by pregnant women delivering preterm infants is associated with significantly decreased risk of IUGR and increased z-scores of BW and BMI at birth. Moreover, preterm neonates born to high-MDA mothers were less likely to develop NEC, ROP, and BPD, albeit the differences were not significant. However, adjustment for confounders revealed that maternal MDA was a significant independent predictor of the occurrence of BPD and NEC.

As regards the association of MDA during pregnancy with size at birth, published data are controversial. Studies in term neonates showed that maternal adherence to the MD-pattern had no effect on intrauterine growth [13] or was associated with lower risk of IUGR/SGA and higher BW [31,32]. In agreement with the latter reports, the current study on preterm neonates showed that high adherence to the MDA during pregnancy was associated with decreased rate of IUGR and increased weight z-score at birth that remained after controlling for factors related to the intrauterine growth.

Experimental and clinical studies outlined the role of intrauterine inflammation on the development of NEC. Animal studies showed that the foetal systemic inflammatory response is associated with loss of intestinal epithelial cell integrity and impaired epithelial differentiation, which are characteristic findings of NEC [27]. In addition, clinical studies and a meta-analysis confirmed the important role of intrauterine inflammation/chorioamnionitis on NEC development [22,33–35]. In addition, oxidative stress is a significant contributing factor to the development of NEC [36]. Nevertheless, the prophylactic administration of omega-3 LCPUFA to pregnant women with history of recurrent preterm deliveries did not prevent preterm labor and neonatal morbidity, including NEC [37]. Results of the current study showed that the risk of NEC was 180% higher in the low-MDA group and that the MDA was a significant independent factor for NEC development after adjustment for confounders. These data suggest that maternal MDA may attenuate the risk of NEC in preterm neonates.

Several studies associated intrauterine inflammation with lower incidence of RDS, which was attributed to inflammation-induced corticosteroid production [38], whereas recent studies associated the intrauterine inflammation with increased risk of RDS [16,39]. These data support a potential role of MDA in RDS development. However, our results did not show any association of MDA with RDS.

BPD is another complication of prematurity in the pathogenesis of which the intrauterine inflammation is involved [23,39]. Therefore, experimental and clinical studies have explored the role of omega-3 LCPUFA supplementation in BPD prevention. Published data suggests that omega-3-LCPUFA supplementation prenatally and postnatally may protect the newborn lung from the hyperoxia-induced lung injury and the occurrence of BPD [40,41]. These data combined with the reported elevated fetal omega-3 LCPUFA status following increased dietary intake of omega-three LCPUFA by the mother [28] indicate that high MDA during pregnancy could possibly contribute to decreased risk of BPD. Our study revealed the MDA as a significant independent predictor of BPD, after adjustment for factors potentially predisposing to BPD, supporting a beneficial effect of high MDA during pregnancy on BPD development.

Regarding ROP, the oxygen toxicity, pre- and postnatal infection/inflammation, and oxidative stress have been recognized as significant pathogenetic factors for development of this complication [25,26]. Although the association between chorioamnionitis and ROP has been questioned by a meta-analysis [24], the potential involvement of prenatal inflammation in ROP development cannot be totally disputed but should be further investigated. In the context of their anti-inflammatory effects, omega-3 LCPUFAs have been tested for ROP prevention. Relevant studies showed that increased intake of omega-3 LCPUFAs improved retinal vascularization in an experimental model of oxygen-induced retinopathy [42] and decreased the incidence of severe ROP, necessitating laser treatment in preterm infants [43]. These data suggest that the high content of MDA in omega-3 fatty acids and antioxidant factors could have a favorable effect on ROP. Our results showed that the MDA was not a statistically significant independent predictor of unadjusted and adjusted ROP, despite the fact that the neonates in the high-MDA group had 50% lower risk of developing ROP of stage 2–3. The failure of our study to demonstrate a significant effect of MDA during pregnancy on ROP could be attributed to the low incidence of severe ROP in our study population (only one infant developed ROP higher than stage 2 plus, which did not require surgical treatment).

The secondary objective of our study was to explore the association of MDA during pregnancy on gestational diabetes and hypertension/preeclampsia. *In vitro* and experimental studies indicated a preventative effect of antioxidant treatment on preeclampsia [44,45] that has been confirmed by clinical studies [46]. However, additional clinical studies and a meta-analysis could not demonstrate a beneficial effect of antioxidant treatment on preeclampsia [10,47]. The current study showed that high-MDA by women delivering prematurely was significantly associated with decreased rate of hypertension/preeclampsia before and after adjustment for potential confounders, confirming results of previous studies. The beneficial effect of MDA on hypertension/preeclampsia of pregnancy shown in our study may be attributed to the synergistic effect of the various anti-inflammatory and antioxidant components of the MD.

Regarding gestational diabetes, clinical studies reported a lower incidence of gestational diabetes in pregnant women with high adherence to the MD during pregnancy [48,49]. The current observational study in a selected high-risk population did not show any independent association between MDA and gestational diabetes. The different findings of relevant studies could be attributed to differences in the study design and population, which in our study consisted of exclusively high-risk pregnant women giving birth to preterm infants. Additionally, differences in the MD pattern and lifestyle between populations of different origin and culture may contribute to the different results among studies.

Limitations and strengths of the study

The main limitation of the current study is the low number of mother-neonate pairs studied due to the single -center design, which resulted in statistically insignificant differences between MDA-related groups, especially regarding the NEC and BPD incidence. However, adjustment for confounders, revealed the significant independent association of MDA with the above complications of prematurity. Another potential limitation is the fact that the information regarding the dietary habits during pregnancy were gathered at the end of gestation. However, information was obtained via personal interview by a trained dietician who guided mothers to recall the most representative diet habits during pregnancy. Finally, histologic examination of the placenta and assessment of oxidative stress indicators and inflammation mediators in maternal and cord blood that could add important information were not routinely performed.

The strength of our study is that it is the first to report on the effect of MDA during pregnancy on the complications of prematurity. Moreover, the prospective design of the study offers considerable reliability to our clinical data.

In conclusion, the findings of this study provide evidence that high adherence to the MD during pregnancy may have a favorable impact on intrauterine growth, as well as on NEC and BPD development in neonates born prematurely. Confirmation of our results by larger studies would have important implications for the dietary suggestions during pregnancy, especially for women at high risk for recurrent preterm delivery. Future studies should focus on the potential synergistic effect of MDA and lifestyle modifications during pregnancy on complications of prematurity.

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Disclosure statement

None of the authors declare any conflict of interest or financial disclosure.

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