Original Article

Relationship between dietary inflammatory index, hs-CRP level in the second trimester and neonatal birth weight: a cohort study

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The aim of this study was to investigate whether diet plays a role in the effect of inflammation on birth weight. The normal pre-pregnancy body mass index and healthy single pregnant women without classical inflammatory were recruited at 16–20 weeks of pregnancy and provided blood sample to measure plasma high sensitive C-reactive protein (hs-CRP) level. The Dietary Inflammatory Index (DII) score was calculated by a three-day 24 h recall method, and a cohort of 307 eligible pregnant women was established. According to birth weight, the subjects were divided into three groups: normal birth weight (NBW) group, low birth weight (LBW) group, and high birth weight (HBW) group. The hs-CRP level and DII score were significantly different between NBW and LBW groups. The risk of higher hs-CRP in the pro-inflammatory dietary group was 1.89 times than the control group (95% CI: 1.05, 3.42). The risk of LBW with higher hs-CRP was 3.81 times than normal hs-CRP (95% CI: 1.26, 11.56). The risk of LBW in the pro-inflammatory dietary group was 10.44 times than in the anti-inflammatory dietary group (95%CI: 1.29, 84.61). The pro-inflammatory dietary in the second trimester affects the hs-CRP level, showing a positive correlation. And both of two factors increase the risk of LBW.

***Key Words*: cohort study, pregnancy, dietary inflammatory index, high sensitive C-reactive protein, birth weight**

Maternal nutrition during pregnancy had an important impact on the health of offspring.[1] The inappropriate maternal nutritional increased the birth probability of high birth weight (HBW; birth weight greater than 4,000 g) or low birth weight (LBW; birth weight less than 2,500 g).[2,3] HBW was closely related to childhood and adolescent obesity, which eventually leaded to the development of metabolic diseases in adulthood.[4,5] LBW may be a risk factor of chronic diseases, such as type 2 diabetes, osteoporosis, coronary heart disease, hypertension, and kidney disease in adulthood.[6]

Low-grade inflammation during pregnancy was associated with premature birth, pre-eclampsia, gestational diabetes and LBW.[7] Low-grade inflammation was characterized by a 2–4 fold increase in serum inflammatory markers such as high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and plasminogen activator inhibitor-1 (PAI-1), without classical symptoms of redness, swelling, heat, and pain.[8,9] Animal experiments found that the injection of TNF-α in the third trimester of the rat can reduce the ability of the placenta to transport essential amino acids to the fetal circulation.[10] Maternal exposure to inflammation during pregnancy inhibited placental synthetic growth factors, which played an important role in fetal development.[11,12] In addition, birth weight and hs-CRP had been found to associate inversely.[13]

Diet plays a role in regulating inflammation. The increasing intake of β-carotene, vitamin C and vitamin E had been shown to be associated with decreasing levels of hs-CRP, IL-6 and TNF-α.[14] The intake of polyunsaturated fatty acids, especially omega-3 polyunsaturated fatty acids, was negatively correlated with levels of IL-6, IL-1ra, TNF-α, and hs-CRP.[15] The intake of nutrients such as iron, zinc, magnesium, monounsaturated fatty acids and linolenic acid was negatively correlated with level of hs-CRP.[16,17] Moreover, it had been proven that green vegetables and fruits with rich folate, flavonoids and antioxidants can significantly reduce the concentrations of serum inflammatory markers, such as TNF-α, IL-6 and hs-CRP.[18–22] Conversely, certain dietary nutrients such as saturated fatty acids and trans fatty acids can increase the levels of inflammatory marker.[23–25] Different dietary components or nutrients have different inflammatory tendencies and varying degrees.

Current research has not shown whether dietary inflammatory tendency plays a role in the effect of inflammation on neonatal birth weight and the specific effect of dietary inflammatory tendency on birth weight. Therefore, the aim of this study was to investigate whether diet plays a role in the effect of inflammation on neonatal birth weight.

As a result, we hypothesized that pro-inflammatory diets are positively correlated with hs-CRP levels and may affect neonatal birth weight. The Dietary Inflammatory Index (DII) was an indicator of the overall inflammatory tendency of diet.[26] In this study, we used the DII score to investigate the effects of dietary inflammatory tendencies on systemic inflammation and neonatal birth weight in normal pre-BMI and healthy pregnant women without classical inflammatory symptoms. Our research may provide a reasonable and scientific basis for clinically reducing the birth rate of LBW and HBW.

Methods

Study design and subjects. Singleton pregnant women in the Department of Obstetrics and Gynecology, Anhui Medical University were recruited, and a cohort of pregnant women was established. The subjects were healthy singleton pregnant women without classical inflammatory symptoms at 16–20 weeks of pregnancy and normal body mass index (BMI: 18.5–25 kg/m^2). All subjects were followed up until the end of delivery, and 40 pregnant women with complications such as gestational hypertension, gestational diabetes, preterm birth, Connective tissue

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disease, and classical inflammatory symptoms were excluded. A total of 307 pregnant women collected complete data. Informed written consent was obtained from the subjects. Ethical approval for the study was obtained from the ethics committee of Anhui Medical University.

A general information questionnaire was required while the subjects were recruited, including pre-pregnancy weight, height, income, education level, and smoking history. Subjects were asked to report all foods consumed each time from the date of recruitment for three consecutive days and were interrogated and recorded by the same researcher. The same group of doctors perform antenatal examinations and record relevant information. The fasting serum samples were collected during the second trimester. The newborn birth weight was recorded within 5 min after the end of childbirth.

The development and score of DII. In 2009, Cavicchia, a scholar in the school of public health at the university of south Carolina, and others searched extensively the English literature from 1950 to 2007 on the effect of specific dietary ingredients or nutrients on inflammatory markers (IL-1, IL-4, and IL-6), and the concept of dietary inflammatory index was first introduced.[27] Briefly, the DII is a population-based score calculated from an extensive review of the literature published from 1950 to 2010, including 1,943 articles to a total of 45 food parameters comprising various macronutrients, flavonoids and individual food items. It was developed to describe the inflammatory tendency of diet, considering the effect of each parameter in six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and CRP). In this regard, the greater the DII score, the more pro-inflammatory the diet. More negative values represent more anti-inflammatory diets.

At 16–20 weeks, the subjects were asked to recall daily dietary intake of the 3 days, and the DII formula developed by the university of south Carolina is used to calculate the DII of each dietary component/nutrient separately, and then the total number of DII points is summarized. Inflammatory effect scores were derived by first assigning "+1" to anti-inflammatory nutrients and "–1" to pro-inflammatory nutrients and then adjusting the score based on the total number of articles citing its pro-inflammatory or anti-inflammatory effects. According to the formula, the DII score were calculated for each food, and then the DII scores of all foods were summarized as the total scores of DII.

Serum specimen collection and hs-CRP detection. After completing the general information and dietary data, the pregnant women who entered the study were enrolled in the hospital's laboratory for 5 ml of fasting venous blood, placed in a test tube without anticoagulant, centrifuged to extract the upper serum and stored at low temperature for analysis. Serum hs-CRP levels were measured by turbidimetric inhibition immunoassay (Dimension RXL MAX, Westlake, OH).

Data analysis. Data analysis was conducted using the Statistical Package for the Social Sciences software ver. 21.0. The mid-pregnancy DII levels were divided into tertiles for analysis. For continuous variables, ANOVA and Least-significant Difference was used to determine the differences among different groups. For categorical variables, differences were examined by using the chi-square test. Using the multinomial logistic regression model, we took the birth weight of NBW (control group), LBW and HBW as the dependent variable, hinger serum hs-CRP level (≥3 mg/L) at the second trimester, and the tertiles of DII level as the factor, and the age of pregnant women and pre-pregnancy BMI as the co-variable, and analyzed the relationship between DII, hs-CRP level in the second trimester and neonatal birth weight.

Results

Baseline data. A total of 307 pregnant women were included in the study Pregnant women were divided into groups according to neonatal birth weight: 277 (90.2%) in the normal birth weight (NBW) group, 15 (4.9%) in the low birth weight (LBW) group, and 15 (4.9%) in the high birth weight (HBW) group (Table 1).

Dietary intakes in subjects. This study suggests that the total dietary energy intake of the subjects basically meets the individual needs. The results showed that, except for the intake of fat, vitamin A, vitamin B2 and vitamin C, the remaining energy and nutrient intake did not differ between the three groups.

Associations with DII and serum hs-CRP levels in the second trimester. The levels of serum hs-CRP of NBW, LBW and HBW were 1.60 (0.72, 3.30), 4.37 (1.50, 6.68), 2.90 (0.89, 10.22) mg/L ($p = 0.005$), and the DII levels in the second trimester were -3.47 ± 2.24, -1.44 ± 2.39, and -2.53 ± 2.90, respectively ($p = 0.002$). Serum hs-CRP levels and the DII in the second trimester were significantly different between the NBW and LBW groups. ($p<0.05$) (Table 2). This study suggested that differences in dietary intake may affect serum hs-CRP levels.

To further investigate the relationship between dietary inflammatory index and serum hs-CRP levels, this study found that 96 (31.3%) of the subjects had high serum hs-CRP levels (≥3 mg/L) in the second trimester. According to the DII as a categorical variable by tertiles, we divided 307 subjects into 3 groups, and the 1st tertiles (anti-inflammatory dietary group) was used as the control group. The results showed that the risk of excessive hs-CRP in the 3rd tertiles (pro-inflammatory dietary group) was 1.89 times that of the control group (95% CI: 1.05, 3.42). Serum hs-CRP levels were significantly positively correlated with the DII in the second trimester (Table 3).

Table 1. General characteristics and three groups according to birth weight

Variable	NBW	LBW	HBW	F/χ^2	*p*
n	277	15	15		
Age (y, means ± SD)	28.34 ± 3.12	28.33 ± 3.87	28.73 ± 3.22	0.111	0.895
Pre-BMI (means ± SD)	20.61 ± 2.62	19.80 ± 3.26	21.34 ± 2.22	1.279	0.280
Monthly income (CNY)					
<4,000 [*n* (%)]	99 (35.74)	8 (53.33)	4 (26.67)	0.281	0.756
4,000–8,000 [*n* (%)]	130 (46.93)	4 (26.67)	9 (60.00)		
>8,000 [*n* (%)]	48 (17.33)	3 (20.00)	2 (13.33)		
Passive smoking [*n*(%)]					
Yes	117 (42.24)	7 (46.67)	2 (13.33)	2.587	0.778
No	160 (57.76)	8 (53.33)	13 (86.67)		
Parity [*n*(%)]					
Primipara	145 (52.35)	7 (46.67)	10 (66.67)	1.406	0.495
Multipara	132 (47.65)	8 (53.33)	5 (33.33)		

NBW, normal birth weight group; LBW, low birth weight group; HBW, high birth weight group.

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Table 2. Comparison of hs-CRP levels and dietary intake in the second trimester of pregnant women

Variable	NBW	LBW	HBW	(*F*/*H*)	*p*
n (%)	277	15	15		
	–90.20%	–4.90%	–4.90%		
hs-CRP (mg/L)	1.6 (0.72, 3.30)	4.37 (1.50, 6.68)	2.9 (0.89, 10.22)	10.744	0.005
DII score	–3.47 ± 2.24	–1.44 ± 2.39	–2.53 ± 2.90	6.596	0.002
Energy (kcal)	2,467.19 ± 302.14	2,531.19 ± 268.06	2,559.11 ± 323.56	0.936	0.393
Protein (g)	110.76 ± 19.95	113.57 ± 22.96	111.63 ± 16.20	0.150	0.860
Carbohydrate (g)	398.32 ± 67.78	403.09 ± 58.24	388.56 ± 70.29	0.192	0.825
Fat (g)	55.07 ± 23.11	75.68 ± 29.88	64.65 ± 25.64	6.366	0.002
Saturated fatty acid (g)	6.02 ± 5.13	9.32 ± 9.86	5.39 ± 5.60	2.747	0.066
Monounsaturated fatty acid (g)	7.82 ± 7.40	10.26 ± 13.62	9.04 ± 12.70	0.779	0.460
Polyunsaturated (g)	5.14 ± 5.16	4.54 ± 3.66	5.28 ± 4.29	0.109	0.897
Cholesterol (mg)	694.77 ± 353.84	891.73 ± 621.93	743.75 ± 258.20	2.131	0.120
Dietary fiber (g)	17.61 ± 6.16	15.93 ± 6.79	18.08 ± 6.02	1.311	0.271
Folic acid (μg)	385.34 ± 162.15	353.74 ± 190.79	335.00 ± 175.22	0.891	0.411
Vit A (μg)	1,135.51 ± 569.02	769.71 ± 273.98	1,053.27 ± 731.19	3.191	0.043
Vit B1 (mg)	1.47 ± 0.31	1.45 ± 0.36	1.51 ± 0.34	0.126	0.882
Vit B2 (mg)	1.40 ± 0.33	1.65 ± 0.62	1.30 ± 0.32	4.602	0.011
Vit C (mg)	167.10 ± 55.57	136.26 ± 52.69	140.78 ± 48.12	3.663	0.027
Vit E (mg)	17.19 ± 4.75	17.19 ± 3.66	17.08 ± 5.24	0.004	0.996
Niacin (mg)	24.69 ± 5.75	23.11 ± 4.66	22.00 ± 6.79	1.992	0.138
Iron (mg)	30.97 ± 6.34	29.31 ± 4.60	29.03 ± 5.70	1.130	0.324
Zinc (mg)	16.66 ± 2.85	16.46 ± 2.84	15.03 ± 3.02	2.331	0.099
Selenium (μg)	84.38 ± 29.54	95.45 ± 40.55	90.11 ± 25.48	1.181	0.308
Magnesium (mg)	443.12 ± 74.54	423.80 ± 82.40	426.75 ± 60.69	0.786	0.457

Table 3. Logistic regression analysis of the DII and serum hs-CRP in the second trimester

DII	Normal hs-CPR (*n* = 211)	High hs-CPR (*n* = 96)	OR (95% CI)	*p*
T1: ≤–4.55	80 (74.47%)	26 (24.53%)	1.00 (control group)	
T2: –4.54 – –2.41	68 (68.00%)	32 (32.00%)	1.49 (0.81, 2.74)	0.234
T3: >–2.40	63 (62.38%)	38 (37.62%)	1.89 (1.05, 3.42)	0.043

T1: anti-inflammatory dietary group and as a control group, T2: The middle group, T3: pro-inflammatory dietary group.

Table 4. The relationship between DII, hs-CRP and birth weight in the second trimester

Birth outcomes[†]	Grouping variable	OR	95% CI	*p*
LBW	The 2nd tertiles of DII[‡]	4.44	0.48–40.99	0.189
	The 3rd tertiles of DII[‡]	10.44	1.29–84.61	0.028
	High hs-CRP[§]	3.81	1.26–11.56	0.018
HBW	The 2nd tertiles of DII[‡]	2.10	0.51–8.72	0.307
	The 3rd tertiles of DII[‡]	2.20	0.53–9.14	0.279
	High hs-CRP[§]	1.84	0.61–5.55	0.278

[†]The control group of birth outcome is NBW, [‡]The control group of mid pregnancy DII is the 1st tertiles (anti-inflammatory tendency dietary), [§]The control group of hs-CRP is normal (<3 mg/L).

Relationship between DII, serum hs-CRP levels and neonatal birth weight in the second trimester. Using the multinomial logistic regression model, the result showed that the risk of LBW in pregnant women with high serum hs-CRP levels in the second trimester is 3.81 times higher than that of normal hs-CRP (95% CI: 1.26, 11.56). The risk of LBW in the 3rd tertiles of DII socers in the second trimester (pro-inflammatory tendency dietary group) was 10.44 times higher than in the first tertiles (anti-inflammatory tendency dietary group) (95% CI: 1.29, 84.61). There was no statistically significant difference between the two factors in the risk of HBW (p>0.05). The pro-inflammatory tendency dietary of the second trimester and the higher hs-CRP increase the risk of low birth weight (Table 4).

Discussion

This study found that a pro-inflammatory diet in the second trimester was associated with higher maternal hs-CRP and an increased risk of low birth weight, similar to previous studies and inconsistent with the results of Moore BF.[28,29] However, the

difference is that we chose healthy pregnant women with a normal pre-pregnancy BMI and no classical inflammatory symptoms during pregnancy as subjects. Compared with obese pregnant women, this association was more reliable. The birth rate of LBW can be reduced by adjusting the diet during the second trimester, depending on the dietary composition or nutrients that have pro-inflammatory or anti-inflammatory effects.

The intake of nutrients such as total fat and saturated fatty acids in the diet increased with the increase of the DII score, while the intake of vitamin C and vitamin A decreased significantly. The DII score of the NBW diet was used as a control group. The diets of the LBW group and the HBW group had pro-inflammatory effects, and the pro-inflammatory trend of the LBW group was more obvious. Therefore, in the case of ensuring that various nutrients in pregnancy meet the needs of the body, the nutrition quality of pregnant women can be evaluated with the DII score to improve the dietary anti-inflammatory level of pregnant women.

This study found that a diet with a pro-inflammatory tendency in the second trimester was positively correlated with serum hs-CRP levels, which is consistent with other studies. A dietary intervention study of 14 menopausal women found that low-sugar and high-fiber, fish diets can reduce serum hs-CRP levels.[30] A cross-sectional survey of 8,607 men in the United States found a positive correlation between dietary DII total score and serum hs-CRP level.[31] Farhangi *et al*.[32] evaluated the dietary intake of 454 patients with cardiovascular disease and calculated DII score. After adjusting for confounding factors, the DII score was positively correlated with serum hs-CRP and other inflammatory factors. Intake of SFA (saturated fatty acids) in patients over 45 years of age can significantly increase hs-CRP levels, while supplementation with EPA (eicosapentaenoic acid) and DHA (twenty-two carbon six) can significantly reduced hs-CRP levels.[33] Therefore, pregnant women should take more anti-inflammatory foods, such as vegetables, soy products, fish, etc., and reduce the intake of pro-inflammatory foods such as sugar and red meat, thereby reducing serum hs-CRP levels.

Previous studies have found that pregnant women with pre-eclampsia and gestational diabetes had higher serum hs-CRP levels, but these diseases may increase the risk of LBW or HBW.[34–39] The innovation of this study is that we used healthy pregnant women with normal pre-BMI to exclude the effects of obesity and other complications such as gestational diabetes and eclampsia on birth weight. And we did not find a relationship between pro-inflammatory diet and HBW. As a result, we found that higher hs-CRP levels in the second trimester were independent risk factors for increased risk of LBW. The underlying mechanism might be disordered placental angiogenesis via Wnt5a-Flt1 activation triggered by inflammation.[40]

In the future clinical work, serum hs-CRP level can be included in routine prenatal examination to screen out pregnant women with low-grade inflammation, and targeted dietary intervention to avoid the occurrence of LBW.

This study found that the pro-inflammatory dietary and the higher hs-CRP level in the second trimester increased the risk of LBW. Compared with the NBW group, the DII score was higher in the HBW group, but there was no statistical difference. This may be due to the small sample size. Moreover, 15 HBW cases eventually occurred in this study and the incidence may actually be higher. This is because pregnant women in the late pregnancy will undergo ultrasound examination to check the development of the fetus. Once the ultrasound results suggest that the fetus is growing too fast, they will strictly follow the doctor's instructions to control and change the diet, and even hospitalization to avoid the occurrence of dystocia. Other study found that supplementation with DHA, folic acid, zinc and other nutrients during pregnancy can reduce the incidence of LBW.[41,42] Previous studies found the effects of maternal age, maternal history, and environmental factors on birth weight,[43,44] but they do not fully explain the causes of low birth weight. In recent years, studies have explained the occurrence of LBW from the perspective of low-grade inflammation. Pregnant women consume more types of dietary ingredients or nutrients during pregnancy. These ingredients or nutrients have pro-inflammatory or anti-inflammatory effects. Anti-inflammatory dietary contain more vitamins and antioxidants to improve the clinical inflammation of the body. Therefore, the more pro-inflammatory tendency in the diet of pregnant women, the higher the incidence of low birth weight in newborns.

However, due to the complexity of dietary survey and the limitation of blood sample collection, we failed to dynamically observe the changes of DII, serum hs-CRP levels and fetal development during pregnancy. Subsequently, we will further improve the research methods and provide new ideas and methods for clinical pregnant women nutrition guidance.

In summary, this study explored the relationship between DII, hs-CRP level and neonatal birth weight in the second trimester. The pro-inflammatory dietary in the second trimester affects the serum hs-CRP level, showing a positive correlation. The pro-inflammatory dietary and the higher hs-CRP in the second trimester increase the risk of low birth weight. Due to the complexity of dietary survey and the limitation of blood sample collection, this study only investigated the pregnant women in the second trimester, and did not investigate the dietary DII before and during the third trimester, which will be further improved in future studies. Therefore, the results of our study showed that while ensuring the nutritional needs of pregnant women, the dietary structure of pregnant women can be improved to reduce the incidence of low birth weight infants. To provide control for the formulation of health intervention strategies and measures in the second trimester, promote balanced diet, reasonable maintenance, maintain pregnancy and improve the quality of life.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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