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Inflammation and weight gain in reproductive-aged women

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Abstract

Aim—To investigate whether mid-pregnancy inflammation predicts rate of subsequent gestational weight gain (GWG), and whether inflammation at 3 years postpartum is associated with weight and waist circumference (WC) gain during a median of 4.4 years follow-up.

Subjects & methods—We quantified CRP, IL-6, and TNF-α in plasma of 886 women at ~28 weeks gestation, and calculated GWG rate (kg/week) from blood draw to delivery. At ~3 years postpartum, we assayed CRP and IL-6 from 351 women, and measured weight and WC at 3 and 7 years postpartum. We used linear regression to investigate the relation between mid-pregnancy inflammation and subsequent GWG rate, and the association of inflammation at 3 years postpartum with weight and WC change during follow-up.

Results—After accounting for confounders, we observed a small dose-response association of mid-gestation CRP with subsequent GWG; women in the 4th CRP quartile gained weight at 0.05 (95% CI: 0.01, 0.10) kg/week faster than those in the 1st quartile. Neither IL-6 nor TNF-α was related to GWG. Postpartum inflammation was not associated with subsequent weight or WC gain.

Conclusions—Higher mid-gestation CRP was related to modestly higher subsequent GWG rate. Future studies are warranted to confirm these findings.

Keywords

gestational weight gain; inflammation; reproductive-aged women; longitudinal; C-reactive protein

INTRODUCTION

Cross-sectional studies have consistently found a direct relation between inflammation and weight status (Fantuzzi, 2005). Because adipose tissue can secrete pro-inflammatory cytokines, inflammation is traditionally regarded as a consequence of adiposity. However,

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some epidemiological investigations (Engstrom et al., 2003, Holz et al., 2010) found that low-grade inflammation preceded weight gain, suggesting that it may play a role in adipose accumulation. Little is known of this relation in reproductive-aged women, a population of special concern considering the high prevalence of overweight/obesity in this group (Flegal et al., 2012) and the adverse consequences of excess weight entering and during pregnancy for both mother and child (Oken et al., 2009).

In a longitudinal cohort, we investigated the relation of inflammation quantified during mid-pregnancy with subsequent rate of gestational weight gain (GWG). We also examined whether inflammation at 3 years postpartum was associated with adiposity gain during four years of follow-up.

METHODS

Study population

This study included participants in Project Viva; details on recruitment and eligibility are previously reported (Oken et al., 2014). Women were recruited from a multi-specialty clinic in eastern Massachusetts (Harvard Vanguard Medical Associates) at ~10 weeks gestation. At enrollment, women reported their pre-pregnancy weight and height. At median 28 weeks gestation ('mid-pregnancy'), participants returned for an in-person visit during which they provided a blood specimen. At ~3 and ~7 years postpartum, we measured the women's weight (kg), waist circumference (WC; cm) using standard techniques. At the 3-year visit, we also collected a blood specimen.

Of the 2128 women who delivered a live singleton, we excluded those with type 1 or 2 diabetes (n=16) from all analyses. In the first portion of this study where mid-pregnancy inflammation was the exposure, we also excluded 504 women who did not provide a blood sample during the second trimester and 82 participants with gestational diabetes. Of the remaining women (n=1526), inflammation biomarkers were available for 901 participants whose bloods were previously analyzed for a study of corticotrophin-releasing hormone and offspring adiposity (Gillman et al., 2006). After excluding 15 women missing information on GWG rate, the final analytic sample was 886.

At 3 years postpartum, inflammation data were available for 585 women whose blood samples were analyzed previously in a study of breastfeeding and postpartum inflammation (Stuebe et al., 2010). We further excluded 135 mothers who were pregnant or became pregnant between 2 and 7 years postpartum, and 99 participants missing data on weight and WC change, leaving 351 women in the postpartum analysis, 155 of whom were also in the mid-pregnancy analysis.

All participants provided written informed consent. The institutional review board of Harvard Pilgrim Health Care approved all study protocols; all procedures were conducted in accordance with ethical standards.

Laboratory procedures

Blood samples were collected, processed within 24 hours, and stored at −80°C until analyses. Inflammatory biomarkers during mid-pregnancy (C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α]) were assayed using a multiplex method described elsewhere (Luminex Corporation) (Skogstrand, 2012). At 3 years postpartum, CRP was measured using an immunoturbidimetric high-sensitivity assay on a Hitachi 911 analyzer (Roche Diagnostics). Plasma IL-6 was measured via ultrasensitive ELISA (R&D Systems).

Anthropometric outcomes

We obtained serial pregnancy weights from medical records and calculated GWG rate (kg/week) as the difference between the last clinically-measured weight ≤4 weeks prior to delivery and weight at the time of mid-pregnancy blood draw, divided by the time difference. We determined weight and WC change by subtracting the anthropometric measurements at 3 years from those at 7 years postpartum.

Covariates

Using interviews and questionnaires, we collected information on race/ethnicity, age, education, parity, income, breastfeeding duration, physical activity, and partner's weight and height. Medical records provided information on infection during pregnancy (vaginitis and urinary tract infection [UTI]), birth characteristics, and delivery date. Infant birthweight-for-gestational-age z-scores ('fetal growth') were determined using U.S. reference data (Oken et al., 2003). We calculated GWG rate prior to blood draw by dividing the difference in weight at blood draw and self-reported pre-pregnancy weight (kg) by time elapsed (weeks).

Data analysis

Mid-pregnancy inflammation and GWG rate—First, we examined the distribution of CRP, IL-6, and TNF-α across categories of sociodemographic and perinatal characteristics to identify confounders. Next, we estimated mean differences and 95% confidence intervals (CI) in GWG rate between women in the 2nd, 3rd, and 4th vs. the 1st quartile of each inflammation biomarker using linear regression. In multivariable analyses, we adjusted for gestation length and BMI at the time of blood collection, previous GWG rate, age, race/ethnicity, education, partner's BMI, and parity. In sensitivity analyses, we excluded 119 women with vaginitis or UTI before or at the time of mid-pregnancy blood collection. We also examined associations after accounting for gestational glucose tolerance, fetal growth, smoking habits and physical activity during pregnancy, and preeclampsia.

Postpartum inflammation and adiposity gain—We examined the relations of CRP and IL-6 quartiles at 3 years postpartum with weight and WC change from 3 to 7 years postpartum using linear regression models that accounted for age, race/ethnicity, parity, education, delivery mode, breastfeeding duration, baseline anthropometry, and time elapsed between the anthropometric measurements. We also evaluated associations after inclusion of smoking habits and physical activity at 3 years postpartum. All analyses were performed using SAS software (v9.3; SAS Institute Inc., Cary, NC).

RESULTS

Among the women in the mid-pregnancy inflammation analysis, median age at enrollment was 32.2 years (range: 14.8–44.8); 72.2% were white. Mean±SD pre-pregnancy BMI was 24.5±5.3 kg/m^2 and GWG rate from mid-pregnancy blood draw to delivery was 0.45±0.22 kg/week.

In bivariate analyses (Table I), CRP was inversely related to education and pre-pregnancy physical activity; and positively associated with parity, pre-pregnancy BMI and BMI at time of blood draw, gestational glucose tolerance, partner's BMI, and fetal growth. Neither IL-6 nor TNF- α were associated with any background characteristics, except IL-6 was higher among multiparas and women who gained weight at a faster rate prior to blood draw, and TNF-α was directly related to pre-pregnancy BMI.

We observed a small dose-response relation between mid-pregnancy CRP levels and subsequent GWG rate after accounting for gestation length at blood draw (Table II Model 1). GWG rate for women in the 4th CRP quartile was 0.03 (95% CI: −0.01, 0.07) kg/week faster than those in the 1st quartile (predicted mean±SE rate for 1st quartile=0.43±0.02 kg/week, 4th quartile=0.46±0.01 kg/week). Adjustment for prior GWG rate and mid-pregnancy BMI slightly strengthened the association (Model 2). In the final model (Model 3), GWG rate for women in the 4th quartile was 0.05 (0.01, 0.10) kg/week greater than those in the 1st quartile, which corresponds to a difference of 0.7±0.3 kg total weight gain over 11.7±2.0 weeks. These relations were similar after excluding women with an infection before or at the time of mid-pregnancy blood collection (4th vs. 1st quartile: 0.05 [0.00, 0.09] kg/week; *P*-trend=0.04). Further adjustment for gestational glucose tolerance, fetal growth, smoking habits and physical activity during pregnancy, and preeclampsia did not attenuate the association (0.05 [0.01, 0.10] kg/week; *P*-trend=0.03). Neither IL-6 nor TNF-α was related to GWG rate.

At 3 years postpartum, sociodemographic characteristics and bivariate associations were similar to those presented in Table 1, with the expected increments in age and parity compared to the index pregnancy. Both weight (2.6±5.9 kg) and WC (2.4±6.5 cm) increased during the median 4.4 years follow-up, but there were no clear relations with CRP or IL-6. In multivariable analysis, weight change for women in the 2nd, 3rd, and 4th quartiles of CRP was −1.63 (−3.38, 0.12) kg, −1.36 (−3.16, 0.45) kg, and −0.95 (−2.93, 1.03) kg, as compared to those in the 1st quartile (*P*-trend=0.87). For WC change, estimates for participants in the 2nd, 3rd, and 4th CRP quartiles were −1.41 (−3.35, 0.53) cm, −1.51 (−3.53, 0.51) cm, and 0.23 (−1.93, 2.39) cm (*P*-trend=0.28). Similar associations were observed for IL-6 (data not shown).

DISCUSSION

In this study of U.S. reproductive-aged women, higher CRP during mid-pregnancy corresponded with slightly higher subsequent GWG rate. Women in the highest CRP quartile at mid-pregnancy gained approximately 0.6 kg more than those in the lowest

quartile from the time of blood draw to delivery. Neither TNF-α nor IL-6 were associated with weight gain during pregnancy.

Although mild inflammatory activity is normal in pregnancy (Palm et al., 2013), our finding with respect to CRP – although not IL-6 or TNF-α – parallels those of prospective investigations in non-pregnant populations (Engstrom et al., 2003, Holz et al., 2010), and could be explained by a few mechanisms. Researchers have speculated that although inflammatory cytokines initially stimulate thermogenesis through actions of regulatory hormones such as leptin (Bruun et al., 2002) and insulin (Xu et al., 2003), sustained inflammation paradoxically impairs thermogenesis by desensitizing beta-adrenergic signaling pathways, eventually leading to weight gain (Seals and Bell, 2004). Additionally, inflammation stimulates production of reactive oxidative species, which promote expansion and terminal differentiation of adipocytes (Lee et al., 2009). Alternatively, systemic inflammation may not be causally related to weight gain, but rather, marks disturbances in the gut microbiota that trigger hyphagia through vagal pathways between the satiety centers of the brain and the gastrointestinal tract (Tehrani et al., 2012).

Neither CRP nor IL-6 levels at 3 years postpartum predicted weight or WC change over 4 years. Although a study of middle-aged adults found a direct association between CRP and weight gain (Holz et al., 2010), the duration of follow-up was ~10 years, meriting further investigation of this relation over a longer timeframe.

Strengths of this study include the ability to examine associations of inflammation with weight gain both during and after pregnancy. Repeated anthropometric measurements enhanced our ability to explore the temporal relations between the biomarkers and weight gain. Limitations include potential bias due to exclusion criteria and attrition, and reliance on a single blood draw at each time point to characterize inflammation.

In conclusion, CRP during mid-pregnancy is related to modestly higher subsequent GWG rate. Although the effect size was small, it is still clinically-relevant as it corresponds to approximately 14%, 22%, and 30% of the recommended weekly weight gain rate for normal weight, overweight, and obese women, respectively, during the second and third trimesters (Institute of Medicine, 2009). Future studies are warranted to examine this relation in other populations, and to explore the influence of dietary modifications and exercise to moderate weight gain during pregnancy.

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Abbreviations

BMI	body mass index

CRP	C-reactive protein
GWG	gestational weight gain
IL-6	interleukin-6
TNF-α	tumor necrosis factor-α

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Table I

Distribution of inflammation biomarkers during mid-pregnancy according to background characteristics of 886 Project Viva mothers

		Mean ± SD		
	N*	**CRP (mg/L) *n* = 885**	**IL-6 (pg/mL) *n* = 879**	**TNF-α (units/mg) *n* = 878**
Overall		1.49 ± 1.23	33.9 ± 36.7	43.6 ± 51.1
Characteristics at enrollment				
Age at enrollment				
15–24 years	71	1.55 ± 1.35	29.2 ± 37.6	37.8 ± 34.2
25–34 years	577	1.52 ± 1.26	33.7 ± 34.5	43.2 ± 51.6
35–44 years	237	1.43 ± 1.11	35.9 ± 41.4	46.3 ± 54.0
P†		0.32	0.19	0.22
Race/ethnicity				
Black	129	1.80 ± 1.40	29.8 ± 39.7	41.4 ± 53.0
Hispanic	57	1.36 ± 1.08	38.3 ± 40.4	45.3 ± 40.7
White	635	1.47 ± 1.22	34.0 ± 35.0	43.4 ± 50.3
Asian	36	0.78 ± 0.54	33.2 ± 35.6	52.4 ± 67.0
Other	23	1.84 ± 0.82	41.1 ± 53.1	40.4 ± 40.6
P†		0.0001	0.51	0.83
Marital status				
Married/cohabiting	819	1.50 ± 1.23	33.8 ± 36.1	44.0 ± 49.8
Single	62	1.37 ± 1.12	36.0 ± 45.2	35.7 ± 60.0
P†		0.40	0.65	0.21
Education				
Primary	91	1.67 ± 1.29	39.5 ± 48.0	38.3 ± 50.1
Secondary	549	1.55 ± 1.28	31.3 ± 33.1	43.9 ± 52.2
University	242	1.30 ± 1.06	37.7 ± 39.3	44.6 ± 47.0
P†		0.004	0.53	0.40
Smoking habits				
Never	616	1.50 ± 1.25	33.9 ± 36.5	44.0 ± 52.8
Quit before pregnancy	165	1.39 ± 1.11	33.2 ± 33.2	42.1 ± 42.6
Smoked in early pregnancy	100	1.65 ± 1.28	35.4 ± 44.0	43.8 ± 54.5
P†		0.25	0.90	0.92
Partner's BMI				
Not overweight (<25 kg/m^2)	311	1.34 ± 1.18	32.1 ± 33.8	43.4 ± 53.9
Overweight (≥25 kg/m^2)	543	1.59 ± 1.24	34.6 ± 37.2	43.8 ± 48.5
P†		0.004	0.34	0.89
Parity				
0	432	1.41 ± 1.18	33.2 ± 32.1	43.0 ± 49.7
1	317	1.55 ± 1.23	31.6 ± 33.4	42.3 ± 52.4

		Mean ± SD		
	N*	**CRP (mg/L) *n* = 885**	**IL-6 (pg/mL) *n* = 879**	**TNF-α (units/mg) *n* = 878**
≥2	137	1.66 ± 1.36	41.7 ± 53.6	48.8 ± 52.5
P†		0.02	0.09	0.38
Pre-pregnancy BMI				
Underweight (<18.5 kg/m^2)	31	1.28 ± 1.00	41.7 ± 47.3	37.9 ± 49.4
Normal (18.5 to 24.9 kg/m^2)	553	1.22 ± 1.09	33.4 ± 34.4	42.4 ± 46.4
Overweight (25.0 – 29.9 kg/m^2)	180	1.80 ± 1.23	34.2 ± 38.6	39.9 ± 43.5
Obese (≥30.0 kg/m^2)	120	2.34 ± 1.37	33.6 ± 37.5	54.6 ± 72.9
P†		<0.0001	0.75	0.05
Pre-pregnancy physical activity				
Q1 (lowest)	185	1.66 ± 1.31	38.3 ± 47.6	45.3 ± 60.8
Q2	178	1.56 ± 1.26	30.7 ± 30.9	38.9 ± 45.7
Q3	173	1.31 ± 1.05	34.5 ± 36.0	49.0 ± 56.6
Q4 (highest)	200	1.49 ± 1.30	34.0 ± 33.1	44.1 ± 44.1
P†		0.05	0.45	0.72
Pregnancy conditions & outcomes				
GWG rate prior to blood draw (kg/week)				
Q1 (median: 0.22)	220	1.53 ± 1.31	29.0 ± 28.5	40.0 ± 51.0
Q2 (median: 0.34)	223	1.47 ± 1.22	33.0 ± 33.9	43.9 ± 49.1
Q3 (median: 0.41)	222	1.30 ± 1.11	36.8 ± 41.9	44.5 ± 55.6
Q4 (median: 0.53)	221	1.68 ± 1.25	37.0 ± 40.7	46.1 ± 48.5
P†		0.49	0.01	0.22
BMI at time of blood draw (kg/m^2)				
Q1 (median: 23.3)	222	1.07 ± 1.10	31.6 ± 31.9	40.1 ± 45.8
Q2 (median: 26.0)	220	1.27 ± 1.08	33.0 ± 33.3	41.6 ± 49.6
Q3 (median: 28.7)	220	1.48 ± 1.13	35.5 ± 39.6	45.8 ± 46.2
Q4 (median: 33.7)	222	2.14 ± 1.31	35.6 ± 41.3	46.3 ± 59.5
P†		<0.0001	0.19	0.14
Infection status				
Vaginitis or UTI	119	1.49 ± 1.04	34.8 ± 36.1	44.4 ± 52.9
Neither	767	1.50 ± 1.26	33.8 ± 36.8	43.5 ± 50.8
P†		0.99	0.78	0.87
Gestational glucose tolerance				
Normoglycemic	776	1.48 ± 1.22	33.8 ± 35.3	43.1 ± 50.6
Isolated hyperglycemia	86	1.43 ± 1.21	35.8 ± 44.1	48.5 ± 51.7
Impaired glucose tolerance	24	2.08 ± 1.35	33.0 ± 51.6	43.3 ± 64.4
P†		0.16	0.81	0.53
Mode of delivery				
Vaginal	695	1.46 ± 1.20	34.1 ± 36.5	43.2 ± 49.5

		Mean ± SD		
	N*	**CRP (mg/L) *n* = 885**	**IL-6 (pg/mL) *n* = 879**	**TNF-α (units/mg) *n* = 878**
C-section	191	1.61 ± 1.32	33.3 ± 37.7	45.2 ± 56.7
P†		0.14	0.80	0.63
Childs sex				
Male	432	1.52 ± 1.29	33.1 ± 37.5	42.2 ± 46.5
Female	454	1.47 ± 1.17	34.7 ± 36.0	45.0 ± 55.2
P†		0.48	0.50	0.40
Fetal growth				
SGA (<10th percentile)	53	1.48 ± 1.13	34.2 ± 28.2	42.5 ± 42.5
AGA (10 to <90th percentile)	720	1.45 ± 1.21	33.5 ± 36.2	43.1 ± 49.2
LGA (≥90th percentile)	113	1.81 ± 1.34	36.7 ± 43.2	47.2 ± 64.8
P†		0.02	0.53	0.48

*Totals may be <886 due to missing values.

†Represents a test for linear trend in which the ordinal predictor is entered into the model as a continuous variable, except for race/ethnicity, smoking habits, partner's BMI, and delivery method (Wald test).

Table II

Associations between mid-pregnancy inflammation and rate of subsequent gestational weight gain (GWG)

	Difference (95% CI) in GWG rate (kg/week)					
	N	**Model 1**	***N***	**Model 2**		**Model 3**
C-reactive protein, *mg/L*	885		883		851	
Q1 (median: 0.32)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)
Q2 (median: 0.83)		0.02 (−0.02, 0.06)		0.01 (−0.03, 0.05)		0.03 (−0.01, 0.07)
Q3 (median: 1.56)		0.04 (0.00, 0.08)		0.04 (−0.01, 0.08)		0.05 (0.01, 0.09)
Q4 (median: 2.86)		0.03 (−0.01, 0.07)		0.04 (0.00, 0.08)		0.05 (0.01, 0.10)
P trend *		0.15		0.06		0.02
Interleukin-6, *pg/mL*	879		877		845	
Q1 (median: 4.0)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)
Q2 (median: 18.0)		0.01 (−0.03, 0.05)		0.01 (−0.03, 0.05)		0.01 (−0.03, 0.05)
Q3 (median: 32.5)		0.01 (−0.03, 0.05)		0.00 (−0.04, 0.05)		0.01 (−0.03, 0.05)
Q4 (median: 64.0)		0.01 (−0.03, 0.06)		0.01 (−0.03, 0.05)		0.01 (−0.03, 0.05)
P trend *		0.52		0.74		0.69
TNF-α, *units/mg*	878		876		844	
Q1 (median: 4.0)		0.00 (Reference)		0.00 (Reference)		0.00 (Reference)
Q2 (median: 20.0)		0.00 (−0.04, 0.04)		0.00 (−0.04, 0.04)		0.01 (−0.03, 0.05)
Q3 (median: 49.0)		0.01 (−0.03, 0.05)		0.01 (−0.02, 0.05)		0.02 (−0.02, 0.06)
Q4 (median: 96.0)		0.00 (−0.04, 0.04)		−0.01 (−0.05, 0.03)		−0.01 (−0.04, 0.03)
P trend *		0.85		0.86		0.81

Model 1: Adjusted for gestation length at time of mid-pregnancy blood draw

Model 2: Model 1 + BMI at time of blood draw and GWG rate up until blood draw

Model 3: Model 2 + age at enrollment, race/ethnicity, education level, partner's BMI, and parity.

* Represents a test for linear trend in which an ordinal variable with each quartile set to the median value was entered into the model as a continuous variable.