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Association Between Adiponectin and Tumor Necrosis Factor-Alpha Levels at Eight to Fourteen Weeks Gestation and Maternal Glucose Tolerance: The Parity, Inflammation, and Diabetes Study

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Abstract

Objective: Inflammation may influence gestational hyperglycemia, but to date, the data from observational studies is largely limited to results from the third trimester of pregnancy. Our objective was to evaluate first trimester adipocytokine levels. We sought to determine whether first trimester adiponectin and tumor necrosis factor-alpha (TNF)-alpha concentrations were independently associated and predictive of maternal glucose tolerance, as measured by the 1-hour glucose challenge test (GCT), after adjustment for maternal lifestyle behaviors and body mass index (BMI).

Material and Methods: Prospective study of pregnant women ($n = 211$) enrolled in the Parity, Inflammation, and Diabetes Study. Nonfasting serum levels of adiponectin and TNF-r2 were measured at 8–14 weeks of pregnancy. GCT results were abstracted from electronic prenatal records. Multiple linear regression models were developed to determine the association of adiponectin and TNF-r2 levels with response to the GCT, adjusting for demographics, pregravid dietary intake and physical activity, first trimester BMI, and gestational weight gain.

Results: At baseline, higher adiponectin concentrations were inversely and statistically significantly associated with maternal response to the GCT [regression coefficient (β) −0.68; 95% confidence interval (CI): −1.29, −0.06). Adjustment for lifestyle factors did not alter the association of adiponectin with the GCT (β −0.74; 95% CI: −1.43, −0.05). After adjustment for first trimester BMI, the association of adiponectin was attenuated and no longer significant (β −0.46; 95% CI: −1.15, 0.24). TNF-r2 levels were not associated with the GCT (β −0.003; 95% CI: −0.011, 0.005).

Conclusions: First trimester adiponectin levels are not predictive of the 1-hour GCT response, but may be a marker for the effect of maternal BMI on glucose response to the GCT.

Introduction

It is estimated that 7%–14% of the 6 million pregnancies each year in the United States are complicated by gestational diabetes (GDM);[1] one-third of pregnancies each year are complicated by a positive 1-hour glucose challenge test (GCT), indicating some degree of glucose intolerance.[2] Results from the Hyperglycemia and Pregnancy Outcomes (HAPO) study[3] suggest that even mild glucose intolerance in pregnancy (i.e. hyperglycemic levels not diagnostic of GDM) is associated with accelerated intrauterine growth, adverse delivery outcomes,[3,4] metabolic alterations in the newborn, and maternal risk of type 2 diabetes in much the same fashion as GDM.[5] Moreover, a subset analysis of the HAPO data showed a statistically significant relationship between third trimester adipocytokine levels in the

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third trimester and glucose responses to the 2-hour 75-g oral glucose tolerance test (OGTT).[6]

Inflammatory peptides, such as adiponectin and tumor necrosis factor-alpha (TNF-α), have been linked to obesity and type 2 diabetes in general populations.[7–10] Adiponectin levels are lower in subjects with obesity and type 2 diabetes; lower third trimester levels are associated with gestational diabetes and lesser degrees of maternal hyperglycemia.[11–13] TNF-α levels correlate positively with body mass index, insulin resistance,[14] and gestational diabetes.[14,15]

The objective of the current study was to determine the feasibility of using inflammatory biomarkers in early pregnancy to identify women who are likely to develop third trimester glucose intolerance. With the growing epidemic of overweight/obesity and the parallel increase in glucose intolerance, screening tools to identify at-risk women in early pregnancy could improve clinical care. Using inflammatory biomarkers for early identification of women at risk of developing gestational diabetes could change the current paradigm of prenatal screening. To date, only one study has prospectively assessed the association of first trimester adiponectin levels with third trimester glucose tolerance;[16] no studies have assessed first trimester TNF-α levels. Also, few studies of adipocytokines in pregnancy adjust for the influence of pregravid lifestyle behaviors (dietary intake, physical activity) on glucose tolerance.[17,18]

We investigated the prospective association of first trimester adiponectin and tumor necrosis factor-receptor 2 (TNF-r2) levels with third trimester maternal glucose tolerance in a cohort of healthy pregnant women, adjusting for maternal body mass index (BMI) and pregravid factors. In light of the results of the HAPO study, our objective was to assess the relation of first trimester biomarker levels with varying levels of maternal glycemia, as measured by response to the 1-hour GCT. Our hypothesis was that first trimester adiponectin levels would be inversely associated and predictive of maternal response to the 1-hour GCT. We also hypothesized that TNF-r2 levels would be positively associated with response to the GCT.

Materials and Methods

The Parity, Inflammation, and Diabetes (PID) study is a prospective study of a diverse sample of urban-based pregnant women. The objective of the PID study is to examine the association of maternal prepregnancy lifestyle behaviors and four inflammatory biomarkers (high sensitivity C-reactive protein, interleukin-6, TNF-α, adiponectin) during pregnancy on maternal glucose tolerance, intrauterine fetal growth, and infant birth weight. We conducted an analysis of a subset of data from the PID study to examine the association of first trimester levels of adiponectin and tumor necrosis factor-receptor 2 (TNF-r2) and response to the GCT, adjusting for prepregnancy dietary intake and leisure activity. This study was approved by the Johns Hopkins institutional review board.

Participant recruitment and eligibility

The PID study is an ongoing prospective study of pregnant women recruited in the first trimester between 2006 and 2008 at an urban-based academic medical center. Women were eligible for recruitment if they (1) were at ≤14 weeks of gestation, (2) had no self-reported or documented history of preexisting diabetes mellitus, (3) had no history of chronic corticosteroid use, (4) had no history of HIV or cancer, (5) had no hypertension, (6) were able to provide written informed consent in English, and (7) did not anticipate leaving the area prior to delivery. Following consent, participants were officially enrolled in the study. Demographic and medical history information was obtained. Nonfasting glucose was measured at baseline and at 18–22 weeks' gestation to identify and exclude participants with preexisting glucose intolerance prior to the GCT. Although the 1-hour GCT followed by a 3-hour OGTT in those who screen positive is often used to identify preexisting diabetes in early pregnancy by clinicians, the use of this two-step process in the current study would have been logistically challenging since women are recruited and enrolled in the study at the first prenatal visit. We used a modified version of the American Diabetes Association criteria for diagnosing type 2 diabetes[19] and excluded women if the nonfasting glucose level was ≥200 mg/dL (11.1 mmol/L) 1–2 hours after a meal. We also examined diurnal adjusted nonfasting insulin levels using an exclusionary threshold value of >150 mU/L outlined in other investigations.[20] Women were also excluded if they had a spontaneous miscarriage, elective termination, or fetal death or had moved away from the area. Gestational age was determined through a review of the electronic medical record and was based on the obstetrician's assessment of the last menstrual period and prenatal ultrasound. If there was a discrepancy between the gestational age by the last menstrual period and ultrasound, the estimated gestational age determined by ultrasound was assigned to the participant. The power analysis is based on the continuous outcome of the glucose response to the 1-hour GCT regressed on the level of TNF-r2 and adiponectin as the independent variables. Based on the standard deviation of the glucose response to the 1-hour GCT of 26.7 and the observed standard deviation of 507.28 for TNF-r2, we had 80% power to detect a regression coefficient of 0.010 or greater in a linear regression analysis of the glucose response on TNF-r2. With the observed standard deviation of adiponectin levels of 6.40, we had 80% power to detect a regression coefficient of 0.79 or greater.

Exposure variables. Clinical data were abstracted from medical records were collected at baseline (8–14 weeks) and at the two follow-up visits in the second (18–22 weeks) and third (28–32 weeks) trimesters. Blood samples were obtained at baseline and at the third follow-up visit.

Serum biomarker assays. Nonfasting maternal blood was collected in serum separator tubes, centrifuged at 2000× for 15 minutes, pipetted into 3-cc polyethylene storage containers, and stored at −80°C. Samples were batch-transported on dry ice to the institution's core laboratory for analysis. Aliquots of the plasma samples were thawed and assayed for each inflammatory biomarker. Serum adiponectin levels were determined through radioimmunoassay (Linco; intra-assay coefficient of variation [CV] 2.11%; inter-assay CV 6.77%). TNF-r2 levels were measured using monoclonal antibody enzyme-linked immunosorbent assay assays. All blood samples were handled identically throughout the processes of blood collection, storage, retrieval, and assays. Assay results that were clearly out of range were considered outliers and excluded—2 study participants were considered outliers and excluded from analyses of TNF-r2.

Dietary intake and leisure activity

Dietary intake patterns prior to pregnancy were assessed using a modified version of the Block Rapid Food Screener[21] at the baseline interview. We calculated screener scores for dietary intake of fruit and vegetables, meat, and snacks using the Block algorithm. These scores were used in the calculation of daily servings of fruit and vegetables, daily total fat intake (grams), daily saturated fat intake (grams), daily dietary cholesterol intake (grams), and daily percent fat intake using equations derived and previously published by Block and colleagues.[21] The Block Rapid Food Screener ranks subjects similarly with respect to dietary intake from total fat, saturated fat, dietary cholesterol, and percentage of calories from fat with a Spearman rank-order correlation coefficient of $r > 0.60$ and fruit/vegetable intake ($r > 0.71$) as the gold standard.[21] Dietary intake variables were evaluated as continuous variables in the analysis. Pregravid leisure-time activity was assessed at baseline using a standardized questionnaire by Baecke and colleagues.[22] The Baecke questionnaire is commonly used in epidemiologic studies, is designed to measure habitual physical activity, and has reported test-retest reliability of the leisure time index of 0.74. A leisure activity index derived at baseline ranged from 1 (low activity) to 5 (high activity) and was modeled as a continuous variable.

Outcome variable

Maternal response to the GCT is a standard method[23] for measuring glucose tolerance during pregnancy and a well-established predictor of important fetal[4,24] and maternal outcomes.[25,26] Participants were screened for gestational diabetes between 24 and 28 weeks gestation as part of routine prenatal care using the nonfasting GCT. Venous blood was sampled 1 hour after a 50-g oral glucose load. The GCT was administered without regard to the time elapsed since the last meal, in accordance with the American College of Obstetricians and Gynecologists and American Diabetes Association[23] practice guidelines. Test results were abstracted from the electronic medical record. Maternal response to the 1-hour GCT was modeled as a continuous variable.

Assessment of covariates

Maternal age, race (white, black, other), marital status, years of education and income were obtained via self-report in a personal interview at the time of enrollment. Other covariates were accessed from the electronic patient record. Marital status was categorized into two groups: single/separated/divorced and married. Years of education completed was categorized as < 13 years, 13–16 years, and > 16 years. Parity was obtained via medical record abstraction and categorized into three groups: no previous live births, one live birth, and more than one live birth. Family history of diabetes was obtained via self-report. Participants were classified as having a family history of diabetes if they responded "yes" to having a first-degree relative (mother, father, or sibling) with diabetes. Baseline height and weight were measured at enrollment into the study using a calibrated stadiometer and scale. Maternal weight was determined using the same calibrated scale and was recorded at each follow-up visit for serum collection. We also collected data on prepregnancy weight, which was based on self-report. Gestational weight gain was defined as the difference in weight at enrollment into the study and weight at the time of the 1-hour GCT. Body mass index (BMI), defined as weight in kilograms divided by height in meters squared, and modeled as a continuous variable.

Statistical analysis

We examined each biomarker for outliers and categorized them into tertiles. Socio-demographic, clinical, and pregravid lifestyle characteristics were then compared across tertiles of adiponectin and TNF-r2 using analysis of variance and *p*-values for trend for continuous variables and chi-square analysis for categorical variables. Glucose response to the 1-hour GCT was examined across tertiles of TNF-r2 and adiponectin. We also examined the distribution of different GCT threshold results across tertiles of both biomarkers.

To explore the association of first trimester adiponectin and TNF-r2 levels with maternal response to the1-hour GCT, we developed separate multivariable models for each biomarker, including adiponectin and TNF-r2 levels as continuous variables and adjusting for demographics and covariates. Covariates were added to the model in a stepwise fashion in order to assess the contribution of each category of variables on the relationship between inflammatory biomarkers and glucose tolerance: sociodemographic variables first (age, race, parity, family history of type 2 diabetes), pregravid dietary intake and leisure activity scores second, then first trimester BMI, and finally, gestational weight gain from enrollment to the time of the GCT. Since heavier women can underreport their weight,[27] we examined the correlation between self-reported prepregnancy BMI and first trimester BMI based on clinically measured height and weight. The correlation between self-reported prepregnancy BMI and BMI at the first prenatal visit was 0.98, indicating a high correlation. For ease of interpretation, we adjusted for first trimester BMI in the multivariate analyses.

To assess potential dose–response relationships, additional multivariate models were developed comparing the association of the highest tertile of adiponectin and TNF-r2 to the lowest tertile. We also developed linear regression models stratified by first trimester BMI (normal, overweight, obese) to determine if the strength and direction of association of each biomarker varied across BMI categories. Finally, we developed multiple logistic regression models to assess the relationship of adiponectin to the GCT at varying threshold levels. All analyses were conducted using Stata statistical software (version 9.0; Stata Corporation).

Results

Of the 326 women approached for participation, 250 (77%) women met eligibility criteria and agreed to be enrolled in the study. A total of 37 (15%) women were subsequently excluded due to first trimester spontaneous miscarriage ($n = 34$) or delivery prior to completion of the GCT ($n = 3$). Two additional participants were excluded from the analysis due to outlying values of TNF-r2, leaving a total sample size for TNF-α analysis of 210 participants. A subset of these data ($n = 174$) were analyzed for adiponectin levels. There were no exclusions due to elevated non-fasting glucose levels, fetal aneuploidy early in pregnancy, or genetic anomalies noted at delivery. There were statistically significant differences in participant

Table 1. Maternal Demographics, Body Mass Index, Lifestyle Behaviors and Response to the 1-Hour Glucose Challenge Test Across Tertiles of Adiponectin

	*Tertiles of adiponectin**			
Covariates	*Lowest tertile*	*Middle tertile*	*Highest tertile*	p-*values for trend*
Age, (years), mean	28.9 ± 5.6	29.8 ± 5.2	31.4 ± 5.1	0.03
Race, *n* (%), white	10 (17)	32 (55)	42 (72)	< 0.001
Black	33 (57)	17 (29)	8 (14)	
Asian	8 (14)	5 (9)	5 (9)	
Other	7 (12)	4 (7)	3 (5)	
Total No. pregnancies	2.8 ± 2.1	2.2 ± 1.7	2.3 ± 1.4	0.11
Prepregnancy BMI**	30.8 ± 8.9	24.5 ± 5.4	23.8 ± 3.5	< 0.001
First trimester BMI	31.6 ± 9.3	25.3 ± 5.5	24.8 ± 4.2	< 0.001
Total weight gain (kg)	6.5 ± 3.5	8.1 ± 3.8	9.2 ± 3.3	0.0002
Positive family history DM	37 (65%)	23 (40%)	22 (38%)	0.006
Fruit and vegetable score	15.1 ± 5.6	15.0 ± 4.7	15.8 ± 4.7	0.65
Fruit and vegetable (servings/day)	4.8 ± 2.1	4.8 ± 1.7	5.1 ± 1.7	0.65
Meat score	24.4 ± 8.0	23.0 ± 9.1	21.3 ± 8.2	0.13
Saturated fat (g)	27.4 ± 7.0	26.2 ± 8.0	24.6 ± 7.2	0.13
Percent fat (%)	36.7 ± 4.8	35.9 ± 5.5	34.9 ± 4.9	0.13
Cholesterol (g)	286.1 ± 66.8	260.7 ± 76.9	241.9 ± 70.7	0.005
Total fat (g)	91.3 ± 19.1	87.9 ± 21.9	83.7 ± 19.7	0.13
Leisure activity score	2.5 ± 0.6	2.8 ± 0.6	2.7 ± 0.7	0.09

*$n = 57$ for each tertile.
**Based on self-reported weight.
BMI, body mass index; DM, diabetes mellitus.

characteristics across tertiles of adiponectin (Table 1). Fifty-seven percent of women in the lowest tertile of adiponectin were African American, while 72% of participants in the highest tertile were white. Participants in the lowest tertile of adiponectin had a higher average first trimester BMI compared with participants in the middle and highest tertiles. Sixty-five percent of participants in the lowest tertile had a positive history of type 2 diabetes compared to 38% of participants in the highest tertile of adiponectin. Cholesterol levels were inversely related to adiponectin, with an average value of 286.1 ± 66.8 in the lowest tertile to 241.9 ± 70.7 in the highest tertile.

As shown in Table 2, a larger proportion of participants in the highest tertile of TNF-r2 were white (56%), while the racial composition of participants in the middle tertile was similar (41% white; 43% African American). Maternal BMI, meat

Table 2. Maternal Demographics, Body Mass Index, Lifestyle Behaviors, and Response to the 1-Hour Glucose Challenge Test Across Tertiles of Tumor Necrosis Factor-Receptor 2

	*Tertiles of tumor necrosis factor-r2**			
Covariates	*Lowest tertile*	*Middle tertile*	*Highest tertile*	p-*Values for trend*
Age, mean	31.1 ± 4.8	29.3 ± 5.7	30.5 ± 5.6	0.12
Race, *n* (%), white	30 (43)	29 (41)	39 (56)	0.10
Black	19 (27)	30 (43)	22 (31)	
Asian	11 (16)	6 (9)	4 (6)	
Other	10 (14)	5 (7)	5 (7)	
Total No. pregnancies	2.2 ± 1.6	2.6 ± 2.0	2.7 ± 1.8	0.27
Prepregnancy BMI**	24.0 ± 4.3	27.6 ± 7.1	27.0 ± 8.1	0.004
First trimester BMI	24.7 ± 4.9	28.7 ± 7.0	28.0 ± 8.5	0.002
Total weight gain (kg)	8.7 ± 3.4	7.6 ± 4.3	7.6 ± 3.5	0.17
Positive family history DM	34 (50%)	36 (52%)	29 (41%)	0.41
Fruit and vegetable score	15.7 ± 5.2	15.6 ± 4.9	14.3 ± 5.2	0.20
Fruit and vegetable (servings/day)	5.0 ± 1.9	5.0 ± 1.8	4.5 ± 1.9	0.20
Meat score	22.1 ± 8.0	24.3 ± 8.6	20.6 ± 8.6	0.04
Saturated fat (g)	25.3 ± 7.0	27.3 ± 7.5	24.0 ± 7.6	0.04
Percent fat (%)	35.3 ± 4.8	36.7 ± 5.1	34.5 ± 5.2	0.04
Cholesterol (g)	258.4 ± 69.2	275.6 ± 73.8	242.8 ± 73.2	0.03
Total fat (g)	85.7 ± 19.2	91.0 ± 20.5	82.1 ± 20.7	0.04
Leisure activity score	2.8 ± 0.6	2.6 ± 0.6	2.6 ± 0.6	0.10

*$n = 70$ for each tertile.
**Based on self-reported weight.

Table 3. Response to the 1-Hour Glucose Challenge Test Across Tertiles of Adiponectin and Tumor Necrosis Factor-Alpha

	Tertiles[a] of adiponectin				*Tertiles[b] of tumor necrosis factor-alpha*			
Glucose measures	*Lowest tertile*	*Middle tertile*	*Highest tertile*	*Total* n = *171*	*Lowest tertile*	*Middle tertile*	*Highest tertile*	*Total* n = *210*
Response to 1-hour GCT, mean (SD)	121 ± 29	110.2 ± 23	108.8 ± 25*		113 ± 29.4	114.5 ± 24.2	114.8 ± 26.9**	
1-hour ≥ 140	15	5	5	25 (15%)	12	11	10	33 (17%)
1-hour ≥ 135	20	5	6	31 (18%)	14	14	13	41 (21%)
1-hour ≥ 130	22	9	9	40 (23%)	18	16	16	50 (26%)

[a] $n = 57$ per tertile.
[b] $n = 71$ per tertile.
*p for trend = 0.02.
**p for trend = 0.94.
GCT, glucose challenge test; SD, standard deviation.

scores, fat and cholesterol intake, and specific dietary intake were higher in the middle tertile of TNF-r2 compared with the lowest and highest tertiles. In particular, average first trimester BMI ranged from 24.7 ± 4.9 in the lowest tertile to 28.7 ± 7.0 kg/m^2 and 28.0 ± 8.5, respectively, in the middle and highest tertiles of TNF-r2. Average meat scores, dietary fat, and cholesterol intake were highest in the middle tertile of TNF-r2 compared to the highest and lowest tertiles of TNF-r2. There was no difference in average leisure activity scores across tertiles of TNF-r2.

Average glucose response to the GCT from 121 ± 29 mg/dL in the lowest tertile to 108 ± 25 mg/d: in the highest tertile of adiponectin (Table 3). Average maternal response to the GCT was similar across tertiles of TNF-r2. A larger proportion of participants with glucose levels that exceeded select threshold values were in the lowest tertiles for adiponectin and TNF-r2.

Multivariate analysis of adiponectin and TNF-r2 levels and the one-hour GCT

Adiponectin levels were inversely related to the glucose response to the GCT. In unadjusted analysis, every 1.0 μg/mL increase in first trimester adiponectin was associated with a 0.68 lower glucose level in response to the GCT (Table 4). After adjustment for maternal demographics (age, race, and parity), the association of adiponectin with maternal response to the GCT remained statistically significant. Adjustment for pregravid lifestyle factors did not alter the magnitude of association and the relationship remained statistically significant (β −0.74*; [95% confidence interval: −1.43, −0.05]). After adjustment for first trimester BMI, the association of adiponectin was attenuated and no longer statistically significant (−0.46; [−1.15, 0.24]). In the fully adjusted model after gestational weight gain up to the time of the GCT, the association of adiponectin with response to the GCT was further attenuated (−0.42; [−1.12, 0.28]) and not statistically significant.

We also examined the relation of TNF-r2 with response to the GCT. In the unadjusted model, higher TNF-r2 concentrations were associated with lower glucose levels in response to the GCT (−0.003; [−0.011, 0.005]). In the fully adjusted model, the association of TNF-r2 with the GCT was small and not statistically significant. TNF-r2 with glucose levels in response to the GCT. In sensitivity analyses, we included prepregnancy BMI rather than first trimester BMI in Model 4 (Table 4) and found no substantial difference in the direction or magnitude of the regression coefficients for the relation of adiponectin (−0.49; −0.22, 1.19) or TNF-r2 (−0.003; −0.005, 0.11) with response to the GCT.

There was no statistically significant dose response relationship of adiponectin or TNF-r2 with glucose response to the GCT. In analyses stratified by first trimester BMI categories adiponectin and TNF-r2 levels were inversely related to maternal response to the 1-hour GCT, but these relationships were not statistically significant (data not shown).

*Indicates that regression coefficient is statistically significant because the 95% confidence interval does not include zero.

Table 4. Multivariable Association of Adiponectin and Tumor Necrosis Factor-r2 Concentrations at 8- to 12-Weeks Gestation with Maternal Response to the 1-Hour GCT

	Regression coefficient [95% confidence interval]	
Regression models	*Adiponectin (μg/mL)*	*Tumor necrosis factor-r2 (pg/mL)*
Model 1: unadjusted	−0.68* [−1.29, −0.06]	−0.003 [−0.011, 0.005]
Model 2: sociodemographics (age, race, parity, fhx diabetes)	−0.72* [−1.41, −0.04]	−0.002 [−0.010, 0.006]
Model 3: model 2 + pregravid dietary intake[a] and leisure activity[b]	−0.74* [−1.43, −0.05]	−0.001 [−0.010, 0.007]
Model 4: model 3 + first trimester BMI	−0.46 [−1.15, 0.24]	−0.004 [−0.012, 0.004]
Model 5: model 4 + gestational weight gain[c]	−0.42 [−1.12, 0.28]	−0.005 [−0.013, 0.003]

*Indicates that regression coefficient is statistically significant because the 95% confidence interval does not include zero.
[a]Dietary intake was assessed using the Block Food Frequency Questionnaire.[21]
[b]Leisure activity was assessed with the Baecke Questionnaire.[22]
[c]Represents weight gained from enrollment to the time of the GCT.

Table 5. Association of First Trimester Adiponectin Levels and Varying Thresholds of Glucose Response to the 1-Hour GCT from Multiple Logistic Regression Models

	Odds ratio[a] *(95% confidence intervals)*	
Logistic regression models	*≥140 mg/dL*	*≥135mg/dL*
Model 1 (unadjusted)	0.90* (0.83, 0.98)	0.90* (0.84, 0.97)
Model 2: sociodemographics (age, race, parity, fhx diabetes)	0.90* (0.82, 0.98)	0.90* (0.82, 0.97)
Model 3: model 2 + pregravid dietary intake[b] and leisure activity[c]	0.90* (0.83, 0.99)	0.90* (0.83, 0.98)
Model 4: model 3 + first trimester BMI	0.93 (0.85, 1.01)	0.92* (0.85, 1.00)
Model 5: model 4 + gestational weight gain[d]	0.92 (0.84, 1.02)	0.91 (0.83, 1.00)

*Denotes a statistically significant odds ratio because the 95% confidence interval does not include 1.
[a]An odds ratio less than 1 indicates less odds of a 1-hour glucose response of 140 or greater and 135 or greater.
[b]Dietary intake was assessed using the Block Food Frequency Questionnaire.[21]
[c]Leisure activity was assessed with the Baecke Questionnaire.[22]
[d]Represents weight gained from enrollment to the time of the GCT.

Logistic regression analysis of adiponectin levels and glucose thresholds

As shown in Table 5, an increase in adiponectin levels was statistically significantly associated with a lower likelihood of a glucose level above 140 in response to the 1-hour GCT in the unadjusted model. After adjustment for first trimester BMI, the relationship was no longer statistically significant. Similarly, an increase in adiponectin was associated with lesser odds of a glucose level above 135 in response to the GCT (Table 5). However, after adjustment for first trimester BMI and gestational weight gain, the relationship was no longer statistically significant. There were no relation between TNF-r2 levels and varying thresholds of the response to the GCT.

Discussion

Prior investigations[12,16,28] have reported an inverse relationship of third trimester plasma concentrations of adiponectin with maternal response to the 1-hour GCT and the diagnosis of GDM. The current study extends our understanding of the relation of first trimester levels with lesser degrees of maternal glycemia. Adiponectin levels between 8 and 14 weeks of pregnancy were inversely related, but not independently associated with maternal response to the GCT. In multivariate analysis, the regression coefficient was moderately attenuated and became nonsignificant after the addition of first trimester maternal BMI to the model. These findings suggest that adiponectin is likely a marker for the relation of prepregnancy or first trimester BMI on third trimester glucose intolerance. Early maternal BMI has been shown to be predictive of third trimester glucose tolerance in several observational studies. Obesity is a known predictor of glucose intolerance and inflammation and obesity share common mechanistic pathways that can influence glucose tolerance. The current study helps to better elucidate the influence of maternal BMI on the association of adiponectin with maternal glycemia.

Our findings differ from those reported in prior studies conducted in late pregnancy (24–28 weeks gestation). Several factors may account for this difference. First, while insulin resistance begins in early pregnancy, the severity of insulin resistance at the time adiponectin was measured (8–12 weeks gestation) may not have substantially affected adiponectin concentrations. It may be that women who develop varying levels of maternal glycemia do not exhibit the same decrease in adiponectin levels early in pregnancy that have been reported in the third trimester among women with overt GDM. Second, it may be that the decrease in adiponectin levels in response to increasing insulin resistance may be cumulative, occurring over the course of pregnancy and culminating in the third trimester. Longitudinal studies that show the pattern of adiponectin levels and glucose tolerance from the first through the third trimester may further inform the relation of adiponectin levels with glucose response to the GCT.

We also assessed the role of TNF-r2, a novel inflammatory marker whose association with varying levels of maternal glycemia has not been completely investigated.[28,29] In contrast to studies in late pregnancy, there was a weak, negative relationship between TNF-r2 and maternal response to the GCT. It may be that early TNF-r2 levels are not associated with glycemic levels below the threshold for GDM. Alternatively, the effect of TNF-r2 on the inflammatory milieu may be diminished by adiponectin levels at this stage of pregnancy. Evidence suggests that adiponectin inhibits the production of TNF-α and its effect on the insulin signaling cascade.[30,31] Longitudinal studies that assess levels across the course of pregnancy may provide further insight into the role of TNF-α.

The current study is particularly relevant when viewed within the current context of the ongoing discussions about the best strategies to diagnose gestational diabetes. The American Diabetes Association[32] published new guidelines for evaluating glucose tolerance and gestational diabetes in 2011, based on recommendations of the International Association of Diabetes and Pregnancy Study Group.[23] These recommendations could result in a 2- to 3-fold increase in the number of women with GDM or glucose intolerance. The proposed change in criteria reflects growing concerns about the effect of maternal glycemia on the developing fetus and further emphasizes the need for alternative diagnostic markers for early identification of women at risk for glucose intolerance.

Strengths of the PID study include the prospective study design, diverse cohort, and recruitment and enrollment in the first trimester. We were able to rule out early insulin resistance in the first and second trimesters by assessment of random glucose levels. Also, we were able to adjust for first trimester BMI in addition to gestational weight gain up to the time of the GCT. In contrast to prior investigations, we adjusted for prepregnancy dietary intake and leisure activity, factors that have been shown to affect inflammatory markers and glucose tolerance.

Our study has several limitations that deserve attention. First, the study is limited by the absence of additional adiposity measures (e.g., triceps skin folds, waist circumference) that might be important factors to incorporate into the regression models. Also, the study was conducted in one academic hospital among women of relative high socioeconomic levels, which may limit the generalizability of the findings. The lower prevalence of GDM within our cohort despite the strong family history of type 2 diabetes may be due, in part, to the higher socioeconomic status and access to care. Also, the prepregnancy activity level of our cohort was higher than that reported in other studies of pregnant women. While we were only able to adjust for prepregnancy/first trimester lifestyle behaviors, our analysis represents one of the first investigations of inflammatory markers to include adjustment for these factors. Finally, the ratio of leptin, another relevant adipocytokine, to adiponectin has been associated with type 2 diabetes in nonpregnant adults. Further studies are needed to assess the relation of the leptin/adiponectin ratio in pregnancy.[33]

Conclusions

The main implication of this study is that the role of early pregnancy levels of adiponectin and TNF-α in the development of glucose intolerance of pregnancy deserves further attention. Additional investigations that examine the effect of preconception lifestyle factors on early levels of these adipocytokines may improve our understanding of pregravid characteristics and the inflammatory milieu of pregnancy. Because of the effect of varying levels of maternal glycemia on infant birth weight, further studies that examine the combined influence of maternal BMI and inflammation on early in utero growth may provide additional insight.

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Disclosure Statement

No competing financial interests exist.

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