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Low Adiponectin Concentration in Pregnancy Predicts Postpartum Insulin Resistance, Beta-cell Dysfunction, and Fasting Glycaemia

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Abstract

Aims/Hypothesis—The postpartum following gestational diabetes (GDM) is characterized by subtle metabolic defects, including beta-cell dysfunction that is believed to mediate the increased future risk of type 2 diabetes in this patient population. Recently, low circulating levels of adiponectin and increased leptin and C-reactive protein (CRP) have emerged as novel diabetic risk factors, although their relevance to GDM and subsequent diabetes has not been characterized. Thus, we sought to determine whether adiponectin, leptin and CRP in pregnancy relate to the postpartum metabolic defects linking GDM with type 2 diabetes.

Methods—487 women underwent metabolic characterization, including oral glucose tolerance test (OGTT), in pregnancy and at 3-months postpartum. Based on the antepartum OGTT, there were 137 women with GDM, 91 with gestational impaired glucose tolerance, and 259 with normal glucose tolerance.

Results—Adiponectin levels were lowest ($p<0.0001$) and CRP levels highest ($p=0.0008$) in women with GDM. Leptin did not differ between the glucose tolerance groups ($p=0.4483$). Adiponectin ($r=0.41, p<0.0001$), leptin ($r=-0.36, p<0.0001$) and CRP ($r=-0.30, p<0.0001$) in pregnancy were all associated with postpartum insulin sensitivity (IS_{OGTT}). Intriguingly, adiponectin was also related to postpartum beta-cell function (insulinogenic index/HOMA-IR) ($r=0.16, p=0.0009$). Indeed, on multiple linear regression analyses, adiponectin in pregnancy independently predicted both postpartum insulin sensitivity ($t=3.97, p<0.0001$) and beta-cell function ($t=2.37, p=0.0181$), even after adjustment for GDM. Furthermore, adiponectin emerged as a significant negative independent determinant of postpartum fasting glucose ($t=-3.01, p=0.0027$).

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Conclusions—Hypoadiponectinemia in pregnancy predicts postpartum insulin resistance, beta-cell dysfunction, and fasting glycaemia, and hence may be relevant to the pathophysiology relating GDM with type 2 diabetes.

Keywords

adiponectin; gestational diabetes; type 2 diabetes; beta-cell function; leptin; CRP

INTRODUCTION

The diagnosis of gestational diabetes mellitus (GDM) identifies a population of young women at high risk of subsequently developing type 2 diabetes [1,2]. As such, it is not surprising that detailed postpartum evaluation of women with a history of GDM typically reveals subtle metabolic defects, including the pathologic hallmarks of type 2 diabetes: chronic insulin resistance and beta-cell dysfunction [1]. The chronic beta-cell defect, in particular, is believed to play a central role in determining the future risk of type 2 diabetes [1,3]. Importantly, however, the precise pathophysiologic mediators of postpartum metabolic dysfunction and diabetic risk in this patient population remain to be fully elucidated.

Identifying specific metabolic intermediates during pregnancy that are associated with future risk of T2DM may provide insight into the pathophysiology underlying this relationship. Antepartum factors that have been linked to the future development of type 2 diabetes in women with GDM include pre-pregnancy BMI, the severity of hyperglycaemia at diagnosis, earlier gestational age at diagnosis, recurrent GDM, parity, and non-white ethnicity [1,4–6]. Of these, pre-pregnancy BMI appears to be particularly important, having emerged as the factor with the highest attributable risk fraction [6]. Thus, obesity-mediated factors potentially may be relevant to the pathophysiologic relationship between GDM and subsequent type 2 diabetes.

In the past decade, a growing body of evidence has identified two pathologic sequelae of obesity that may link adiposity to diabetic risk: (i) chronic sub-clinical inflammation, as characterized by increased serum levels of inflammatory bio-markers such as C-reactive protein (CRP), and (ii) dysregulation of adipokines, including increased serum leptin and low circulating levels of the insulin-sensitizing protein adiponectin [7,8]. Indeed, CRP, leptin and hypoadiponectinemia have each emerged as novel risk factors for T2DM in the general population [8–11]. Considering these data, we hypothesized that these factors may also be relevant to GDM and subsequent type 2 diabetes, a setting in which their role has not been characterized. Thus, our objective in this study was to determine whether CRP, leptin, and adiponectin in pregnancy relate to postpartum insulin resistance, beta-cell dysfunction, and glycaemia in a cohort of women representing the full spectrum of glucose homeostasis in pregnancy, ranging from normal to impaired glucose tolerance to GDM.

METHODS

This analysis was conducted in the context of an ongoing observational study of early events in the natural history of type 2 diabetes, in which a cohort of women recruited at the time of antepartum screening for GDM is undergoing longitudinal metabolic characterization in

pregnancy and in the postpartum period [12–14]. The study protocol, which was approved by the Mount Sinai Hospital Research Ethics Board, has been described in detail previously [12–14] and all participants have provided written informed consent. In brief, participants have undergone (i) a 3-hour 100g oral glucose tolerance test (OGTT) in late 2nd trimester for determination of glucose tolerance status in pregnancy and (ii) a 2-hour 75g OGTT at 3-months postpartum, with completion of interviewer-administered questionnaires, a physical examination, and assessment of cardio-metabolic risk factors on both occasions (12–14).

Laboratory Measurements and Physiologic Indices

All OGTTs were performed in the morning after an overnight fast, with venous blood samples drawn for measurement of glucose and insulin at fasting and at 30, 60 and 120 minutes (and 180 minutes in pregnancy) following ingestion of the glucose load. As previously described [12,14], the application of National Diabetes Data Group (NDDG) criteria [15] to the antepartum OGTT stratified subjects into the following 3 glucose tolerance groups in pregnancy: (i) GDM (defined by exceeding 2 or more NDDG glycemic thresholds); (ii) gestational impaired glucose tolerance (GIGT) (a designation that was not originally described by NDDG but that we have previously applied to describe those women exceeding only 1 NDDG glycemic threshold on the OGTT); and (iii) normal glucose tolerance (NGT).

Specific insulin was measured using the Roche Elecsys 1010 immunoassay analyzer and the electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Quebec, Canada). This assay shows 0.05% cross-reactivity to intact human proinsulin and the primary circulating split form (Des 31,32). Total adiponectin was measured from fasting serum samples by enzyme-linked immunosorbent assay (Linco, St. Louis, Missouri, USA). High-sensitivity CRP was measured by endpoint nephelometry using the Dade-Behring BN Prospec and the N high sensitivity CRP reagent (Dade-Behring, Mississauga, Ontario, Canada). Leptin was measured using the human leptin ELISA assay #EZHL-80SK (Linco Research, St. Charles, Missouri, USA).

Insulin sensitivity was measured using the insulin sensitivity index (IS_{OGTT}) of Matsuda and DeFronzo [16]. The Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR) was calculated as described by Matthews et al [17]. Beta-cell function was assessed by the insulinogenic index divided by HOMA-IR (insulinogenic index/HOMA-IR) [18,19].

Statistical Analyses

All analyses were conducted using the Statistical Analysis System (SAS, Version 9.1, SAS Institute, Cary, North Carolina, USA). Continuous variables were tested for normality of distribution and natural log transformations of skewed variables were used, where necessary, in subsequent analyses. In Table 1, univariate differences across the 3 gestational glucose tolerance groups were assessed in pregnancy and at 3-months postpartum using Analysis of Variance for continuous variables and χ^2 test for categorical variables. Univariate correlations between metabolic variables in pregnancy and at 3-months postpartum were assessed by Spearman correlation analysis (Table 2). Multiple linear regression analysis (Table 3) was used to determine independent relationships between factors in pregnancy and

the following dependent variables at 3-months postpartum: log IS_{OGTT} (Model A), log insulinogenic/HOMA-IR (Model B), and log fasting glucose (Model C). The antepartum variables that were included in these models consisted of (i) those that have been linked to future diabetic risk in pregnant women (age, weeks gestation, pre-pregnancy BMI, gestational weight gain preceding the OGTT, ethnicity, family history of diabetes, personal history of previous GDM, parity, GIGT in current pregnancy, GDM in current pregnancy) and (ii) the biochemical factors under study (CRP, leptin, adiponectin). In these models, the reference groups were Caucasian for ethnicity and nulliparous for parity, respectively.

RESULTS

Characteristics of Study Groups in Pregnancy and at 3-months Postpartum

Table 1 shows the baseline demographic, clinical and metabolic characteristics of the study population in pregnancy, stratified into the following 3 gestational glucose tolerance groups: NGT (n=259), GIGT (n=91), and GDM (n=137). There were no significant differences between the groups with respect to age, ethnicity and parity. The antepartum OGTT was performed slightly later in the women with NGT (median 30 weeks gestation) than in the other two groups (both median 29 weeks) (overall p=0.002). As glucose tolerance status worsened, both family history of diabetes and personal history of previous GDM were more prevalent (p=0.0271 and p=0.0144, respectively). Similarly, pre-pregnancy BMI progressively increased with worsening glucose tolerance status (p=0.0114), varying from median 23.1 kg/m^2 in the NGT group to 23.5 kg/m^2 in GIGT to 25.0 kg/m^2 in the GDM group. Gestational weight gain preceding the OGTT showed the opposite pattern, being greatest in NGT (likely reflecting the later OGTT in this group, as gestational weight gain did not differ between the three groups after adjustment for weeks gestation at the time of the OGTT (p=0.1967)). Of note, leptin concentration in pregnancy did not differ significantly between the 3 groups (p=0.4483), whereas CRP levels were highest (p=0.0008) and adiponectin levels lowest (p<0.0001) in the women with GDM. These group differences in CRP and adiponectin concentration also persisted after adjustment for weeks gestation at the time of the OGTT (Online Table).

At 3-months postpartum, there remained significant metabolic differences between the groups (Table 1). Specifically, as expected, both insulin sensitivity (IS_{OGTT}) and beta-cell function (insulinogenic index/HOMA-IR) progressively decreased from the NGT group to GIGT to GDM (both p<0.0001), while fasting glucose showed the opposite pattern (being lowest in NGT) (p<0.0001). Furthermore, the NGT group exhibited the highest adiponectin concentration (overall p=0.0463) and the lowest CRP and leptin levels (overall p=0.0003 and p=0.0006, respectively).

Relationships between Metabolic Variables in Pregnancy and those at 3-months Postpartum

CRP, leptin, and adiponectin levels in pregnancy were each strongly correlated with their respective concentrations at 3-months postpartum (CRP: r=0.60, p<0.0001; leptin: r=0.71, p<0.0001; adiponectin: r=0.78, p<0.0001). When measured at 3-months postpartum, these proteins were cross-sectionally associated with parameters of glucose homeostasis (Table 2).

Specifically, CRP and leptin were both positively associated with fasting glucose and inversely related to IS_{OGTT}, while adiponectin showed the opposite relationships (inverse with fasting glucose and positive with IS_{OGTT}). In addition, postpartum leptin was negatively associated with insulinogenic index/HOMA-IR, while adiponectin was positively related.

Since CRP, leptin and adiponectin in pregnancy were strongly correlated with their respective levels at 3-months postpartum, which in turn were associated with parameters of glucose homeostasis at that time, we queried whether the antepartum concentrations of these proteins may relate to postpartum metabolic function. Indeed, on Spearman univariate correlation analysis, adiponectin, leptin, and CRP in pregnancy were all associated with postpartum IS_{OGTT} ($r=0.41$, $r=-0.36$, and $r=-0.30$, respectively; all $p<0.0001$) (Table 2). Intriguingly, adiponectin was also related to postpartum insulinogenic index/HOMA-IR ($r=0.16$, $p=0.0009$). Furthermore, adiponectin in pregnancy was more strongly associated with postpartum fasting glucose ($r=-0.31$, $p<0.0001$) than were antepartum levels of either leptin ($r=0.23$, $p<0.0001$) or CRP ($r=0.14$, $p=0.0021$). Thus, on univariate analysis, adiponectin in pregnancy was positively associated with postpartum insulin sensitivity and beta-cell function, and inversely associated with postpartum fasting glycaemia (Figure 1).

Multiple Linear Regression Analyses

Having demonstrated that GDM is characterized by antepartum hypoadiponectinemia, which in turn relates to postpartum insulin resistance, beta-cell dysfunction and fasting glycaemia, we next queried whether adiponectin levels in pregnancy may account for the postpartum metabolic dysfunction observed in women with GDM. In this context, multiple linear regression analyses (Table 3) were performed to elucidate independent relationships between antepartum variables and each of the following 3 postpartum outcome measures: (Model A) insulin sensitivity (log IS_{OGTT}); (Model B) beta-cell function (log insulinogenic index/HOMA-IR); and (Model C) glycaemia (log fasting glucose). The following antepartum variables were included in all of these models: age, weeks gestation, pre-pregnancy BMI, gestational weight gain preceding the OGTT, ethnicity, family history of diabetes, personal history of previous GDM, parity, GIGT in the current pregnancy, GDM in the current pregnancy, CRP, leptin, and adiponectin. Importantly, after adjustment for all of these variables (including notably GDM and GIGT), adiponectin in pregnancy emerged as a significant independent determinant of both postpartum insulin sensitivity ($t=3.97$, $p<0.0001$) (Table 3 Model A) and postpartum beta-cell function ($t=2.37$, $p=0.0181$) (Table 3 Model B). Furthermore, unlike CRP and leptin in pregnancy, antepartum adiponectin emerged as a significant negative independent determinant of postpartum fasting glucose ($t=-3.01$, $p=0.0027$) (Table 3 Model C). Thus, hypoadiponectinemia in pregnancy, as occurs in GDM, is an independent predictor of postpartum insulin resistance, beta-cell dysfunction and fasting glycaemia.

Subgroup and Sensitivity Analyses

The multiple linear regression analyses in Table 3 were repeated with stratification of subjects into subgroups based on pre-pregnancy BMI and gestational glucose tolerance status. Amongst lean women (defined by pre-pregnancy BMI<25 kg/m^2) (n=288),

adiponectin remained a significant predictor of postpartum insulin sensitivity (t=2.56, p=0.0111), beta-cell function (t=2.23, p=0.0269), and fasting glucose (t=−2.19, p=0.0298). In the overweight/obese group (defined by pre-pregnancy BMI >/= 25 kg/m^2), adiponectin was a significant predictor of postpartum insulin sensitivity (t=3.19, p=0.0018), and fasting glucose (t=−2.37, p=0.0192), but not beta-cell function (t=0.92, p=0.3599). The latter finding may be partly due to power limitations with the smaller sample size of the overweight/obese group (n=185), particularly since no significant interaction was detected between adiponectin and BMI group (lean vs overweight/obese) with respect to postpartum beta-cell function (p=0.5674 for interaction term) (data not shown).

We next repeated the multiple linear regression analyses within the gestational glucose tolerance groups. Amongst women with NGT (n=259), adiponectin remained a significant independent predictor of postpartum insulin sensitivity (t=2.34, p=0.0204), beta-cell function (t=2.03, p=0.0438) and fasting glycaemia (t=−2.38, p=0.0182). These relationships were less robust in the smaller subsets of GIGT and GDM. Amongst women with GIGT (n=91), adiponectin maintained significance as an independent predictor of postpartum beta-cell function only (t=2.30, p=0.0250). Amongst women with GDM (n=137), adiponectin maintained significance as an independent predictor of postpartum insulin sensitivity only (t=2.79, p=0.0064). Importantly, formal tests of interaction between adiponectin and gestational glucose tolerance group in the Table 3 models showed no significant interactions (p=0.3398, p=0.4688, and p=0.9595 for interaction terms in the insulin sensitivity, beta-cell function and fasting glycaemia models, respectively) (data not shown). As such, the differences observed in the GIGT and GDM groups (compared to the NGT group) are likely due to their much smaller sample sizes.

Finally, while the relationship between adiponectin and postpartum insulin sensitivity in Table 3 Model A could be attenuated by further adjustment for IS_{OGTT} in pregnancy (t=1.30, p=0.1948), the significant independent relationship between antepartum adiponectin and postpartum beta-cell function in Table 3 Model B persisted even after adjustment for insulinogenic index/HOMA-IR in pregnancy (t=2.11, p=0.0357) (data not shown).

DISCUSSION

In this report, we demonstrate that GDM is characterized by increased CRP concentration and low levels of adiponectin in pregnancy and in the postpartum. Importantly, multiple linear regression analyses reveal that antepartum hypoadiponectinemia predicts postpartum insulin resistance, beta-cell dysfunction, and fasting glycaemia. These findings thus implicate adiponectin deficiency as a potential factor in the pathophysiology linking GDM with the subsequent development of type 2 diabetes, providing insight which may be relevant to both risk stratification and modification in this patient population.

Previous studies have demonstrated that, in pregnancy, women with GDM exhibit evidence of sub-clinical inflammation and dysregulation of adipokines, including low circulating levels of both adiponectin and its high-molecular-weight (HMW) multimeric form [20–23]. In fact, both sub-clinical inflammation and hypoadiponectinemia may be chronic defects in this patient population, as increased CRP and low adiponectin in the first trimester have each

been shown to independently predict the subsequent development of GDM later in pregnancy [22,23]. Moreover, a limited number of studies following pregnancy have also reported increased levels of inflammatory markers and decreased adiponectin in women with a history of GDM [24–26]. By documenting their existence both in pregnancy and at 3-months postpartum, the current study supports the potential chronic nature of these defects, and thereby suggests that they may be of pathophysiologic relevance to diabetic risk in this patient population.

In this context, the key finding of the current study is the demonstration that hypoadiponectinemia in pregnancy is an independent predictor of postpartum metabolic dysfunction, including insulin resistance and beta-cell dysfunction. Indeed, as chronic beta-cell dysfunction is believed to mediate the considerable long-term risk of type 2 diabetes in women with a history of GDM [1,3], these data suggest that hypoadiponectinemia may be a pivotal abnormality linking these conditions. This possibility is further supported by the demonstration that, unlike dysregulation of CRP and leptin, low adiponectin in pregnancy is an independent determinant of fasting glucose at 3-months postpartum.

Several lines of evidence support the plausibility of a role for adiponectin in the relationship between GDM and type 2 diabetes. Firstly, although not previously studied in women with a history GDM, hypoadiponectinemia has emerged as a robust predictor of incident type 2 diabetes in a variety of settings and populations [11]. Secondly, low adiponectin has been repeatedly associated with insulin resistance, consistent with the known insulin-sensitizing bio-activity of the protein [8,11]. This inverse relationship between adiponectin and insulin resistance has also been consistently observed in pregnancy and in GDM [20,21,27]. Finally, a growing body of literature has recently queried a link between adiponectin and beta-cell function, although conclusive resolution of this question remains elusive owing to some conflicting observations in this as-yet modest literature. Specifically, adiponectin receptors are expressed on beta cells [28,29], although *in vitro* studies have reported conflicting findings with respect to the ability of adiponectin to stimulate insulin secretion [29,30]. In humans, low circulating adiponectin concentration has been associated with beta-cell dysfunction in some [21,31–34] but not all [29,35] studies, possibly due to differences in (i) the methods used to evaluate beta-cell function, (ii) the populations under study, and (iii) their sample sizes. Of note, the only two previous studies examining this question in pregnancy have indeed linked hypoadiponectinemia and beta-cell dysfunction in women with and without GDM [21,31]. Thus, in relating antepartum hypoadiponectinemia to postpartum beta-cell dysfunction, the current study extends these earlier data and highlights the need for further longitudinal study of this relationship.

The significance of the current findings rests in the potential implications that a relationship between antepartum adiponectin and future type 2 diabetes could hold for diabetic risk stratification and modification. Specifically, it follows from these data that antepartum adiponectin concentration may provide a means of stratifying women with GDM with respect to their future risk of type 2 diabetes. Ideally, this information could help to target postpartum surveillance efforts to those women at the highest risk of developing diabetes. The availability of this predictor at the time of diagnosis in pregnancy may be particularly important, in light of the well-recognized sub-optimal rates of postpartum metabolic follow-

up in women with GDM [36]. Secondly, the current data also suggest that chronic hypoadiponectinemia could provide a therapeutic target for risk modification in this patient population. In this respect, it is of interest to note that thiazolidinedione therapy, which has been shown to preserve beta-cell function and significantly reduce the risk of developing type 2 diabetes in women with a history of GDM [37], is also known to increase adiponectin levels [38]. It thus emerges that a pathophysiologic relationship between hypoadiponectinemia and diabetic risk following GDM could hold important clinical implications.

A limitation of this study is the use of surrogate (rather than direct) measures of insulin resistance and beta-cell function. However, direct measures (such as clamp studies) would be difficult to implement in a study of this size (n=487) given their cost, invasiveness, and time requirements, which may be particularly burdensome for new mothers at 3-months postpartum. Moreover, both the IS_{OGTT} index and insulinogenic index/HOMA-IR have been widely used in large clinical studies [19]. A second limitation is that the observational nature of these data cannot conclusively establish causality in the relationship between antepartum adiponectin and postpartum metabolic dysfunction. Nevertheless, the identification of adiponectin in this context represents a biochemical advance on our existing clinical understanding of the link between GDM and subsequent type 2 diabetes, and should lead to further study.

In summary, GDM is characterized by increased CRP concentration and low levels of adiponectin in pregnancy and in the postpartum. Importantly, antepartum hypoadiponectinemia predicts postpartum insulin resistance, beta-cell dysfunction, and fasting glycaemia. Thus, adiponectin deficiency may be a factor in the pathophysiology linking GDM with the subsequent development of type 2 diabetes, and hence may be relevant to strategies for both risk stratification and risk modification in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CRP	C-reactive protein
GDM	Gestational diabetes
GIGT	Gestational impaired glucose tolerance

IS_{OGTT}	Insulin sensitivity index of Matsuda and DeFronzo
NDDG	National Diabetes Data Group
NGT	Normal glucose tolerance

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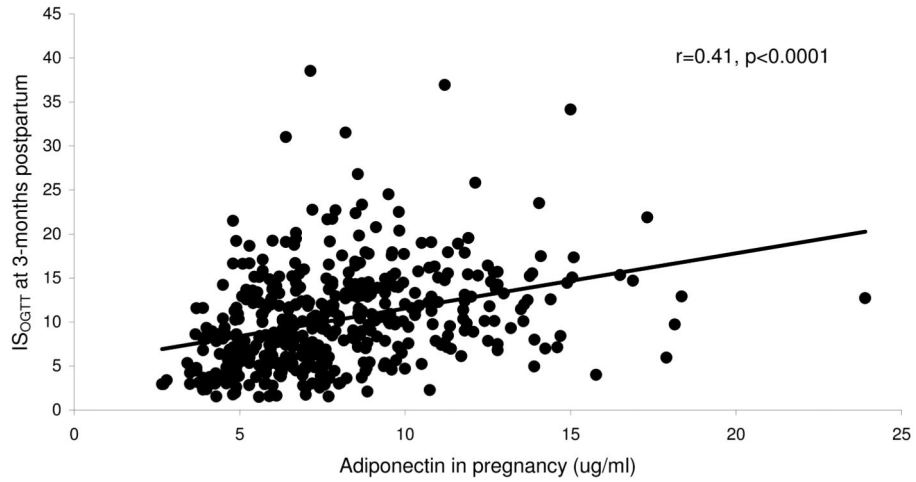
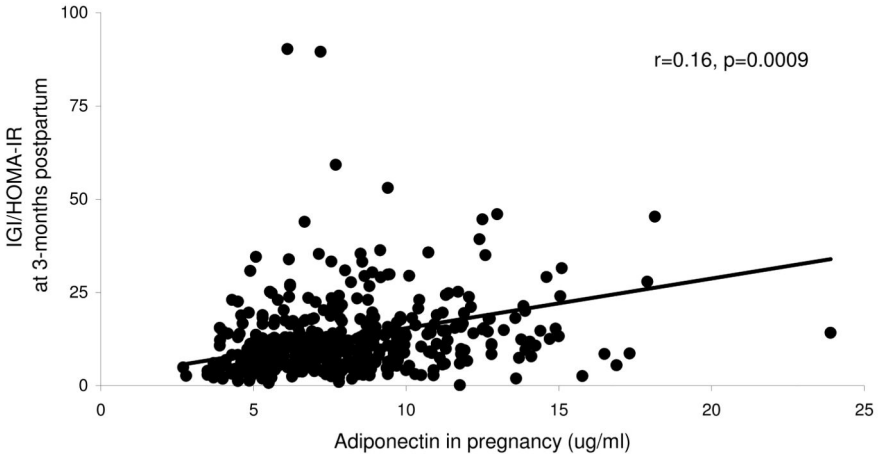
Panel a: Adiponectin in pregnancy and postpartum insulin sensitivity



Panel b: Adiponectin in pregnancy and postpartum beta-cell function



Note: A single outlying point with IGI/HOMA-IR 230.77 is not shown on this plot but was included in the analyses.

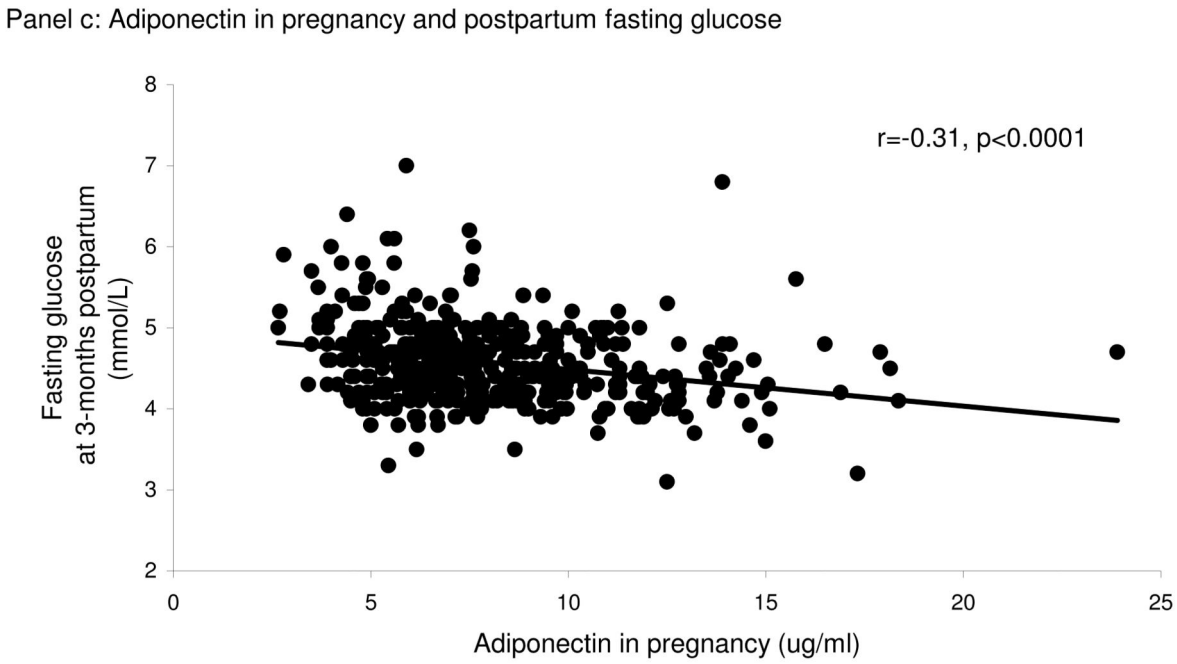


Figure 1.

Plots of relationships between adiponectin in pregnancy and the following parameters of glucose homeostasis at 3-months postpartum: (panel a) IS_{OGTT} (r=0.41, p<0.0001); (panel b) insulinogenic index/HOMA-IR (r=0.16, p=0.0009); and (panel c) fasting glucose (r= −0.31, p<0.0001).

Table 1

Characteristics of study subjects stratified by glucose tolerance status in pregnancy

	NGT n=259	GIGT n=91	GDM n=137	p
At OGTT in pregnancy				
Age (yrs)	33.9 [4.3]	34.2 [4.2]	34.5 [4.3]	0.3606
Weeks gestation (weeks)	30 [28 – 32]	29 [28 – 31]	29 [28 – 31]	0.0002
Ethnicity:				0.0835
Caucasian (%)	79.5	71.4	71.5	
Asian (%)	8.5	19.8	11.0	
Other (%)	12.0	8.8	17.5	
Pre-pregnancy BMI (kg/m^2)	23.1 [21.3 – 26.9]	23.5 [21.8 – 27.7]	25.0 [22.0 – 30.1]	0.0114
Weight gain in pregnancy (kg)	11.4 [8.6 – 14.5]	10.0 [7.3 – 14.5]	9.1 [5.9 – 12.7]	0.0019
Family history of DM (%)	47.5	52.8	59.1	0.0271
Previous GDM/macrosomia (%)	2.3	12.1	7.3	0.0144
Parity:				0.3978
Nulliparous (%)	46.7	55.3	50.4	
One or greater (%)	53.3	44.7	49.6	
CRP (mg/L)	4.7 [2.6 – 7.5]	4.1]2.4 – 8.6]	5.8 [3.5 – 10.7]	0.0008
Leptin (ng/ml)	32.9 [23.0 – 49.1]	35.7 [23.3 – 47.6]	35.8 [25.4 – 43.4]	0.4483
Adiponectin (ug/ml)	8.0 [6.2 – 10.0]	7.0 [5.2 – 8.7]	7.0 [5.3 – 8.5]	<0.0001
At 3-months postpartum				
Breastfeeding (%)	93.1	87.9	95.6	0.5131
BMI (kg/m^2)	25.4 [23.0 – 28.9]	26.0 [23.2 – 30.1]	26.6 [23.7 – 31.1]	0.0701
CRP (mg/L)	1.6 [0.9 – 3.6]	2.5 [1.0 – 5.4]	2.7 [1.5 – 4.9]	0.0003
Leptin (ng/ml)	16.8 [8.4 – 30.9]	23.9 [11.6 – 35.3]	23.8 [13.0 – 38.7]	0.0006
Adiponectin (ug/ml)	8.6 [6.6 – 10.6]	7.6 [5.4 – 9.9]	8.2 [6.1 – 10.4]	0.0463
IS_{OGTT}	11.9 [8.0 – 16.9]	8.9 [6.0 – 12.6]	8.5 [5.7 – 12.5]	<0.0001
Insulinogenic Index/HOMA-IR	11.4 [7.5 – 17.4]	8.9 [5.2 – 12.4]	8.1 [4.4 – 12.3]	<0.0001
Fasting glucose (mmol/L)	4.4 [4.2 – 4.7]	4.7 [4.4 – 5.0]	4.7 [4.4 – 5.0]	<0.0001

Data are presented as median followed by interquartile range, with the exception of (i) age (presented as mean followed by standard deviation) and (ii) ethnicity, family history of DM, previous GDM, parity and breastfeeding (presented as percentages). p-values refer to overall differences across groups as derived from ANOVA for continuous variables or χ^2 test for categorical variables

Table 2

Spearman univariate correlations between (i) adiponectin, CRP, and leptin in pregnancy and at 3-months postpartum with (ii) insulin sensitivity (IS_{OGTT}), beta-cell function (IGI/HOMA-IR), and fasting glucose at 3-months postpartum

	Parameters of Glucose Homeostasis at 3-months Postpartum					
	IS_{OGTT}		IGI/HOMA-IR		Fasting Glucose	
	r	p	r	p	r	p
CRP at 3-months postpartum:	−0.39	<0.0001	−0.05	0.31	0.22	<0.0001
Leptin at 3-months postpartum:	−0.59	<0.0001	−0.13	0.007	0.43	<0.0001
Adiponectin at 3-months postpartum:	0.47	<0.0001	0.12	0.01	−0.25	<0.0001
CRP in pregnancy:	−0.30	<0.0001	−0.05	0.24	0.14	0.0021
Leptin in pregnancy:	−0.36	<0.0001	−0.03	0.51	0.23	<0.0001
Adiponectin in pregnancy:	0.41	<0.0001	0.16	0.0009	−0.31	<0.0001

Table 3

Multiple linear regression analyses of the relationships between antepartum variables and the following parameters of glucose homeostasis at 3-months postpartum: (Model A) log IS_{OGTT}, (Model B) log IGI/HOMA-IR, and (Model C) log fasting glucose.

	Beta Coefficient	Standard Error	t	p
Model A: Dependent variable -- log IS_{OGTT} at 3-months postpartum				
Age	−0.001	0.006	−0.17	0.8643
Weeks gestation	0.020	0.010	2.03	0.0427
Pre-pregnancy BMI	−0.032	0.007	−4.57	<0.0001
Weight gain up to OGTT	−0.003	0.004	−0.74	0.4575
Ethnicity:				
Asian	−0.322	0.084	−3.84	0.0001
Other non-white	−0.197	0.084	−2.35	0.0194
Family history of diabetes	−0.025	0.052	−0.48	0.6345
Parity	0.025	0.053	0.47	0.6361
Previous GDM	−0.176	0.133	−1.32	0.1878
GIGT in current pregnancy	−0.130	0.069	−1.90	0.0587
GDM in current pregnancy	−0.123	0.062	−1.99	0.0475
CRP	−0.006	0.004	−1.41	0.1600
Leptin	−0.003	0.001	−1.78	0.0758
Adiponectin	0.038	0.010	3.97	<0.0001
Model B: Dependent variable -- log insulinogenic index/HOMA-IR at 3-months postpartum				
	Beta Coefficient	**Standard Error**	**t**	**p**
Age	−0.010	0.010	−1.02	0.3094
Weeks gestation	0.047	0.016	2.93	0.0036
Pre-pregnancy BMI	−0.020	0.011	−1.75	0.0810
Weight gain up to OGTT	−0.008	0.007	−1.09	0.2778
Ethnicity:				
Asian	0.142	0.138	1.03	0.3025
Other non-white	0.173	0.141	1.23	0.2211
Family history of diabetes	−0.112	0.085	−1.33	0.1852
Parity	0.177	0.087	2.03	0.0431
Previous GDM	−0.107	0.214	−0.50	0.6177
GIGT in current pregnancy	−0.342	0.113	−3.02	0.0027
GDM in current pregnancy	−0.294	0.101	−2.92	0.0037
CRP	−0.011	0.007	−1.73	0.0843
Leptin	0.007	0.002	2.98	0.0031
Adiponectin	0.037	0.016	2.37	0.0181
Model C: Dependent variable -- log fasting glucose at 3-months postpartum				
	Beta Coefficient	**Standard Error**	**t**	**p**
Age	0.003	0.001	2.47	0.0139
Weeks gestation	−0.005	0.002	−2.52	0.0123

Model A: Dependent variable -- log IS_{OGTT} at 3-months postpartum				
	Beta Coefficient	**Standard Error**	**t**	**p**
Pre-pregnancy BMI	0.006	0.001	4.63	<0.0001
Weight gain up to OGTT	0.002	0.001	2.51	0.0123
Ethnicity:				
Asian	0.023	0.016	1.47	0.1416
Other non-white	0.029	0.015	1.92	0.0553
Family history of diabetes	−0.008	0.010	−0.81	0.4192
Parity	−0.010	0.010	−1.02	0.3078
Previous GDM	0.008	0.025	0.32	0.7489
GIGT in current pregnancy	0.047	0.013	3.65	0.0003
GDM in current pregnancy	0.042	0.012	3.68	0.0003
CRP	−0.001	0.001	−1.46	0.1459
Leptin	−0.00003	0.0003	−0.14	0.8872
Adiponectin	−0.005	0.002	−3.01	0.0027

Note that reference groups are (i) Caucasian for ethnicity and (ii) nulliparous for parity, respectively.