Lower Adiponectin Levels at First Trimester of Pregnancy Are Associated With Increased Insulin Resistance and Higher Risk of Developing Gestational Diabetes Mellitus

Marilyn Lacroix, bsc[1]
Marie-Claude Battista, phd[1]
Myriam Doyon, msc[2]
Julie Ménard, phd[2]
Jean-Luc Ardilouze, md, phd[1,2]
Patrice Perron, md, msc[1,2]
Marie-France Hivert, md, mmsc[1,2,3]

OBJECTIVE—To evaluate the associations between adiponectin levels and *1*) the risk of developing gestational diabetes mellitus (GDM), and *2*) insulin resistance/sensitivity, β-cell function, and compensation indices in a prospective cohort representative of the general population of pregnant women.

RESEARCH DESIGN AND METHODS—We performed anthropometric measurements and collected blood samples at 1st (6–13 weeks) and 2nd (24–28 weeks) trimesters. Diagnosis of GDM was made at 2nd trimester based on a 75-g oral glucose tolerance test (International Association of the Diabetes and Pregnancy Study Groups criteria). Insulin was measured (ELISA; Luminex) to estimate homeostasis model assessment of insulin resistance (HOMA-IR), β-cell function (HOMA-B), insulin sensitivity (Matsuda index), insulin secretion ($AUC_{insulin/glucose}$), and β-cell compensation (insulin secretion sensitivity index-2). Adiponectin was measured by radioimmunoassay.

RESULTS—Among the 445 participants included in this study, 38 women developed GDM. Women who developed GDM had lower 1st-trimester adiponectin levels (9.67 ± 3.84 vs. 11.92 ± 4.59 μg/mL in women with normal glucose tolerance). Lower adiponectin levels were associated with higher risk of developing GDM (OR, 1.12 per 1 μg/mL decrease of adiponectin levels; $P = 0.02$, adjusted for BMI and HbA_{1c} at 1st trimester). Adiponectin levels at 1st and 2nd trimesters were associated with HOMA-IR (both: $r = -0.22$, $P < 0.0001$) and Matsuda index ($r = 0.28$, $P < 0.0001$, and $r = 0.29$, $P < 0.0001$). After adjustment for confounding factors, we found no significant association with HOMA-B and $AUC_{insulin/glucose}$.

CONCLUSIONS—Pregnant women with lower adiponectin levels at 1st trimester have higher levels of insulin resistance and are more likely to develop GDM independently of adiposity or glycemic measurements.

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Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition determined during pregnancy (1). In normal pregnancy, there is a progressive physiologic increase of insulin resistance, compensated by an increase of insulin secretion by pancreatic β-cells (2). Among GDM women, there is an imbalance between insulin resistance and insulin secretion capacity, resulting in increased circulating glucose levels (3). Over the past decades, GDM has drawn scientific attention because of its growing incidence and deleterious consequences for mothers and offspring (4,5). Nevertheless, the exact mechanisms implicated in its pathophysiology remain poorly understood.

Adiponectin is an adipokine suspected to have insulin-sensitizing properties (6). Furthermore, lower adiponectin levels have been repeatedly and consistently associated with increased risk of type 2 diabetes incidence (7–9), but reports on GDM are inconsistent. Few studies investigated the association between adiponectin levels measured early in pregnancy and GDM incidence: some showed that low adiponectin levels are associated with increased risk of GDM (10–13), while others showed no association (14,15). Contradictory findings between studies can be partly explained by limited power and different study designs. Also, these studies inconsistently accounted for potential confounding factors like adiposity and baseline impaired glucose regulation in pregnant women. Therefore, larger prospective studies are needed, designed to take into account potential confounding factors to adequately assess whether there is an independent association between adiponectin levels and the risk of developing GDM.

Thus, in the current study, we evaluated whether 1st-trimester adiponectin levels are associated with higher risk of developing GDM during pregnancy. Also, we assessed whether there is an association between adiponectin at both 1st and 2nd trimesters (or the change [Δ] over 1st to 2nd trimester) and insulin resistance/sensitivity or pancreatic β-cell function/compensation indices at 2nd trimester of pregnancy.

RESEARCH DESIGN AND METHODS

—In this prospective cohort study, 445 women were recruited

From the [1]Faculty of Medicine, Université de Sherbrooke, Sherbrooke, Québec, Canada; the [2]Centre de Recherche Clinique Étienne-Le Bel, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec, Canada; and the [3]General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts.
Corresponding author: Marie-France Hivert, marie-france.hivert@usherbrooke.ca.
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between 6 and 13 weeks of pregnancy (1st trimester). Pregnant women were invited to participate when visiting the blood-sampling clinic for their 1st-trimester blood samples if they were planning to deliver at the Centre Hospitalier Universitaire de Sherbrooke (CHUS). Exclusion criteria were as follows: age <18 or >40 years, multiple pregnancy, pregestational diabetes (type 1 or 2), drug and/or alcohol abuse, uncontrolled endocrine disease, renal failure, or other major medical conditions that would affect glucose regulation. This study was part of a cohort study evaluating the usefulness of the O'Sullivan test at 1st trimester, so we excluded women with abnormal glucose regulation detected early in pregnancy (defined as glycemia ≥10.3 mmol/L at 1 h post 50 g glucose ingestion, according to Canadian Diabetes Association guidelines) (16). The project was approved by the CHUS ethics review board, and written informed consent was obtained from all women before their inclusion in the study in accordance with the Declaration of Helsinki.

Demographics and baseline characteristics were collected at 1st trimester and included maternal age, gestational weeks, medications, and personal and familial medical history. Specific details about nutrition and physical activity were assessed by validated questionnaires adapted from the Canadian Community Health Survey (17). Anthropometric measurements were made according to standardized procedures: weight (kilograms) was measured by calibrated electronic scale, with bare feet, in light clothing; height (meters) was measured with a wall stadiometer without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. Body fat percentage (BFP) was estimated based on lean body mass measured by bioimpedance using a standing (foot-to-foot) scale (model no. TBF-300A; Tanita). Waist circumference (WC) was measured with a flexible measuring tape (in centimeters) above the top of the iliac crest (18); the average of two measurements was used for analyses. Systolic and diastolic blood pressures were measured in the sitting position after 5 min of rest; the average of three measurements was used for analyses. During the 1st-trimester visit, all women also underwent a 50-g glucose challenge test (O'Sullivan test). Glucose levels were measured at 1 h post glucose ingestion, and extra blood samples were collected.

At 2nd trimester (between 24 and 28 weeks of gestation), data concerning any medical update since the beginning of pregnancy were collected, the nutrition and physical activity questionnaires were repeated, and weight (kilograms) and estimated BFP according to the same standardized procedures were measured. Each participant performed a 75-g oral glucose tolerance test (OGTT) under fasting state (>8 h). Diagnosis of GDM was based on the results of the OGTT, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (one or more values equal to or exceeding the following thresholds: fasting plasma glucose ≥5.1 mmol/L; at 1 h, ≥10.0 mmol/L; and at 2 h, ≥8.5 mmol/L [19]). Extra blood samples were collected in the fasted state and at 1 h and 2 h during the OGTT for biochemical analyses. Each blood sample was maintained at 4°C and centrifuged, and plasma was distributed in aliquots and stored at −80°C until measurements.

Laboratory measurements

Plasma glucose levels were measured by glucose hexokinase (Roche Diagnostics, Indianapolis, IN). HbA_{1c} levels were measured by high-performance liquid chromatography (Bio-Rad VARIANT, Hercules, CA). Insulin levels were measured by ELISA (Luminex Technology; Millipore, Billerica, MA). Total adiponectin levels were measured by radioimmunoassay (Millipore). Fasting total cholesterol, triglycerides (TG), and HDL cholesterol levels were measured by a colorimetric method (Johnson & Johnson Clinical Diagnostics, Rochester, NY), and LDL cholesterol levels were determined using the Friedewald formula (20).

Physiologic indices. Homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) and HOMA of β-cell function (HOMA-B) were calculated, respectively, as follows: HOMA-IR (validated in pregnancy [21]), fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5, and HOMA-B, [20 × fasting insulin (μIU/mL)]/[fasting glucose (mmol/L) − 3.5] (22). Measures of glucose and insulin over the course of the OGTT allowed determination of dynamic indices of insulin sensitivity and secretion, respectively; Matsuda index (validated in pregnancy [21]), 10,000/[square root (fasting glucose × fasting insulin) × (mean glucose × mean insulin)] (23); and total area under the curve $(AUC)_{insulin/glucose}$, total AUC/total AUC (calculated using the trapezoidal rule applied to the insulin and glucose curves during the OGTT). The two dynamic indices were used to estimate an OGTT-based measure of the integrative β-cell function in relation to insulin sensitivity (β-cell compensation, analogous to the disposition index) (the insulin secretion sensitivity index [ISSI]-2: total $AUC_{insulin/glucose}$ × Matsuda index) (24,25).

Statistical analyses

Characteristics of pregnant women included in the study are presented as percentage for dichotomous variables; continuous variables are presented as means ± SD if normally distributed or as median and interquartile ranges (IQR) otherwise. Adiponectin levels were normally distributed. After log transformation, glycemic indices were normally distributed; log-transformed variables were used for correlations and linear regression analyses. We compared characteristics of pregnant women who had a normal glucose tolerance (NGT) with characteristics of women who developed GDM using χ^2 for categorical variables, Mann-Whitney *U* test for continuous variables not normally distributed, and Student *t* tests for continuous variables normally distributed. To assess whether adiponectin levels were associated with risk of developing GDM independently of confounding factors, we used logistic regression analyses. (Odds ratios [ORs] are reported per 1 μg/mL adiponectin.) We first assessed both age and parity in the same model; since parity was not statistically associated with GDM, we kept only age for all subsequent multivariable models. We adjusted for BMI measured at 1st trimester to account for adiposity; we additionally adjusted for glucose level 1 h post 50 g glucose challenge to test whether adiponectin levels were associated with risk of GDM independently of glucose regulation at 1st trimester. Sensitivity analyses were performed using WC or BFP instead of BMI and HbA_{1c} instead of 1-h glucose levels (all measured at 1st trimester). We also performed sensitivity analyses adding triglycerides measured at 2nd trimester to the models adjusted for age and adiposity. Pearson correlations were used to assess the association between adiponectin levels (at 1st and 2nd trimesters) and indices of glucose regulation including HOMA-IR, HOMA-B, Matsuda index, total $AUC_{insulin/glucose}$, and ISSI-2 (all log transformed). Linear regression analyses were used to adjust for potential confounders of correlations. In all analyses, $P < 0.05$ was considered

statistically significant. All statistical analyses were performed using SPSS for Windows, version 18.

RESULTS—Characteristics of participating women at 1st and 2nd trimesters are presented in Table 1. Participants were mainly of European descent, were 28.4 ± 4.3 years old on average, and had a mean BMI of 25.4 ± 5.6 kg/m^2 at 1st trimester—similar to the general population of pregnant women delivering at our institution (26). Women gained a mean of 6.78 ± 3.10 kg between 1st and 2nd trimesters. Mean blood pressure and lipids profile were in the normal ranges. Over the 1st and 2nd trimesters, women reported being moderately active (median [IQR] energy expenditure of 1.1 [0.5–1.9] and 0.9 [0.5–1.6] kcal/kg/day) and increased slightly their fruit and vegetable consumption from 5.6 ± 2.3 to 6.1 ± 2.5 portions per day. The majority of pregnant women reported eating breakfast on a daily basis (88.4 and 94.8% at 1st and 2nd trimesters, respectively), and they reported going to a restaurant approximately once per week.

Overall, 38 participants developed GDM (8.5%) during follow-up. Women who developed GDM had lower levels of adiponectin both at 1st trimester (GDM 9.67 ± 3.84 μg/mL vs. NGT 11.92 ± 4.59 μg/mL; $P = 0.004$) and 2nd trimester (GDM 9.70 ± 5.18 μg/mL vs. NGT 11.67 ± 4.72 μg/mL; $P = 0.02$) compared with women with NGT. In cross-sectional analyses, lower adiponectin levels were correlated with higher adiposity measurements at 1st trimester ($r = -0.30$, $r = -0.28$, and $r = -0.24$ for BMI, BFP, and WC, respectively; all $P < 0.0001$) and 2nd trimester ($r = -0.26$ and $r = -0.23$ for BMI and BFP; all $P < 0.0001$), elevated triglycerides ($r = -0.28$; $P < 0.0001$), and lower HDL levels ($r = 0.33$; $P < 0.0001$) (Supplementary Table 1). The change in adiponectin levels between 1st and 2nd trimesters was not significant either within each group (NGT −0.25 ± 4.55 μg/mL, $P = 0.27$; GDM

Table 1—*Characteristics of participants (all), pregnant women with NGT, and pregnant women who developed GDM*

	All participants	NGT	GDM	*P**
n	445	407	38	
1st trimester				
Age (years)	28.4 ± 4.3	28.2 ± 4.3	30.3 ± 4.0	0.005
Ethnic background (% European descent)	95.9	96.1	94.6	0.41
Parity (% primiparous)	50.6	52.3	31.6	0.01
Gestational weeks	9.0 ± 1.7	9.0 ± 1.6	8.9 ± 2.1	0.69
WC (cm)	90.4 ± 13.5	90.0 ± 12.9	94.8 ± 18.6	0.12
BMI (kg/m^2)	25.4 ± 5.6	25.3 ± 5.4	27.3 ± 7.4	0.13
BFP (%)	31.5 ± 8.6	31.3 ± 8.3	33.6 ± 11.4	0.24
Physical activity (kcal/kg/day)	1.1 (0.5–1.9)	1.1 (0.5–1.9)	1.0 (0.4–2.0)	0.73
Nutrition				
Fruits and vegetables (per day)	5.6 ± 2.3	5.6 ± 2.3	5.7 ± 2.4	0.66
Breakfasts (% daily)	88.4	88.8	84.2	0.40
Restaurant meals (per week)	1.0 (0.5–2.0)	1.0 (0.5–2.0)	1.0 (1.0–2.0)	0.43
S/D BP (mmHg)	113/70 ± 10/7	113/70 ± 10/7	116/72 ± 10/7	0.08/0.11
Total adiponectin (μg/mL)	11.73 ± 4.57	11.92 ± 4.59	9.67 ± 3.84	0.004
2nd trimester				
Gestational weeks	26.5 ± 1.1	26.4 ± 1.1	26.7 ± 1.3	0.24
BMI (kg/m^2)	27.9 ± 5.3	27.7 ± 5.1	29.9 ± 7.0	0.08
BFP (%)	35.8 ± 6.6	35.6 ± 6.4	37.5 ± 8.4	0.19
Physical activity (kcal/kg/day)	0.9 (0.5–1.6)	0.9 (0.5–1.6)	1.1 (0.4–1.6)	0.86
Nutrition				
Fruits and vegetables (per day)	6.1 ± 2.5	6.1 ± 2.5	6.4 ± 2.7	0.42
Breakfasts (% daily)	94.8	94.8	94.7	0.99
Restaurant meals (per week)	1.0 (0.5–2.0)	1.0 (0.5–2.0)	1.0 (0.9–2.0)	0.83
S/D BP (mmHg)	109/68 ± 9/7	109/68 ± 9/7	111/69 ± 10/8	0.15/0.55
Triglycerides (mmol/L)	1.96 ± 0.64	1.94 ± 0.63	2.22 ± 0.70	0.008
HDL cholesterol (mmol/L)	1.92 (1.61–2.17)	1.93 (1.62–2.16)	1.79 (1.44–2.27)	0.18
LDL cholesterol (mmol/L)	3.43 (2.83–4.10)	3.43 (2.83–4.10)	3.35 (2.69–4.60)	0.83
Total cholesterol (mmol/L)	6.26 (5.58–7.02)	6.24 (5.60–7.00)	6.41 (5.34–7.09)	0.51
Total adiponectin (μg/mL)	11.51 ± 4.78	11.67 ± 4.72	9.70 ± 5.18	0.02
Differences 2nd vs. 1st trimester				
Weight gain (kg)	6.8 ± 3.1	6.8 ± 3.1	7.0 ± 3.2	0.63
ΔAdiponectin (μg/mL)	−0.23 ± 4.61	−0.25 ± 4.55	0.03 ± 5.24	0.72

Data are presented as means ± SD or median (IQR). Variables not normally distributed were log transformed. Ranges of adiponectin levels were 2.94–32.86 μg/mL at 1st trimester and 0.45–32.87 μg/mL at 2nd trimester. For ethnic background: $n = 407$ for NGT and 37 for GDM. For WC: $n = 400$ for NGT and 38 for GDM. For nutrition: $376 \leq n \leq 404$ for NGT and $37 \leq n \leq 38$ for GDM. For lipid levels: $380 \leq n \leq 405$ for NGT and $34 \leq n \leq 38$ for GDM. S/D BP, systolic/diastolic blood pressure. *Comparison between NGT and GDM groups: independent *t* tests for continuous variables normally distributed, Mann-Whitney test for continuous variables not normally distributed, or χ^2 for categorical variables.

0.03 ± 5.24 μg/mL, $P = 0.97$) or between groups ($P = 0.72$). Few differences in clinical characteristics between GDM and NGT were noted (Table 1). Women who developed GDM were older ($P = 0.005$) and more likely to be multiparous ($P = 0.01$). Comparing adiposity measurements, WC, BMI, and BFP tended to be higher in women with GDM, but the differences did not reach statistical significance.

The glucose and insulin measurements, as well as the various indices of glucose regulation, are compared between NGT and GDM women in Supplementary Table 2. At 1st trimester, women who developed GDM had higher levels of glucose 1 h post 50 g glucose load ($P < 0.0001$) and of HbA_{1c} ($P = 0.001$) compared with NGT participants. At 2nd trimester, participants with GDM had higher levels of blood glucose and insulin at all time points of the OGTT (respectively, $P < 0.0001$ and $P < 0.05$), higher levels of HbA_{1c} ($P = 0.001$), higher insulin resistance (HOMA-IR; $P = 0.0002$), and lower levels of β-cell function (HOMA-B [$P = 0.01$]), insulin sensitivity (Matsuda index [$P < 0.0001$]), and β-cell compensation (ISSI-2 [$P < 0.0001$]).

Adiponectin levels and risk of GDM

With use of logistic regression, lower adiponectin levels at 1st trimester were associated with an increased risk of developing GDM (OR 1.14 [95% CI 1.04–1.25] per 1 μg/mL decrease in adiponectin levels; unadjusted $P = 0.004$), and this remained statistically significant after adjustment for age and adiposity represented by BMI (1.13 [1.03–1.24]; $P = 0.01$), by BFP (1.14 [1.04–1.25]; $P = 0.007$), or by WC (1.13 [1.03–1.24]; $P = 0.01$ [Table 3]). The association also remained significant when we further adjusted for glycemic regulation at 1st trimester based on 1-h glucose levels post 50 g glucose intake or based on HbA_{1c} (all shown in Table 2). Adding triglycerides levels did not modify substantially the models (adiponectin levels remained statistically significant: $P = 0.01$–0.03), and triglyceride levels were not statistically significant in any of the models.

Adiponectin levels and insulin resistance/sensitivity indices

Next, we investigated the correlations between adiponectin levels and indices of glucose regulation to understand the potential pathophysiologic role of adiponectin in gestational glycemic regulation (Table 3). Adiponectin levels at 1st and 2nd trimesters were inversely associated with insulin resistance measured by HOMA-IR at 2nd trimester (both, $r = -0.22$; $P < 0.0001$), and all correlations remained significant after adjustment for age and adiposity (Table 3). HOMA-IR was strongly correlated with Matsuda index ($r = -0.90$; $P < 0.0001$). Adiponectin levels at 1st and 2nd trimesters were associated with insulin sensitivity measured by Matsuda index at 2nd trimester (respectively, $r = 0.28$, $P < 0.0001$, and $r = 0.29$, $P < 0.0001$) (Fig. 1). The correlations between adiponectin levels and Matsuda index remained statistically significant after adjustment for age, BMI, and total $AUC_{insulin/glucose}$ ($P = 0.009$ and $P = 0.001$ for 1st and 2nd trimesters, respectively). For all the insulin resistance/sensitivity indices analyses, replacing BMI by other adiposity measures did not change the results.

Adiponectin levels and indices of β-cell function or insulin secretion

There was no correlation between adiponectin levels and β-cell function measured by HOMA-B (Table 3). There were significant correlations between 1st- and 2nd-trimester adiponectin levels and insulin secretion measured by total $AUC_{insulin/glucose}$ (respectively, $r = -0.16$, $P = 0.0008$, and $r = -0.17$, $P = 0.0003$), but these correlations were no longer significant once we adjusted for age, BMI, and Matsuda index (respectively, $P = 0.43$ and $P = 0.47$).

Adiponectin levels and β-cell compensation for insulin resistance

Finally, total adiponectin levels at 1st and 2nd trimesters were associated with β-cell compensation measured by ISSI-2 (respectively, $r = 0.21$, $P < 0.0001$; and $r = 0.22$, $P < 0.0001$). These correlations remained statistically significant after adjustment for age and adiposity measurements (all $P < 0.02$) (Table 3).

CONCLUSIONS—We demonstrated that lower 1st-trimester adiponectin levels are associated with increased risk of developing GDM during the 2nd trimester independent of early pregnancy major risk factors. Numerous previous prospective studies in nonpregnant populations have demonstrated that low adiponectin levels were associated with risk of developing type 2 diabetes (7). Studies investigating the association between adiponectin levels in early pregnancy and risk of developing GDM are fewer and more controversial. In line with our results, Williams et al. (10) showed that adiponectin levels measured at 13 weeks were associated with increased risk of GDM independently of age and BMI at the time of blood sampling. It is noteworthy that the differences in adiponectin levels between GDM and normoglycemic women are very similar in the two studies (2.5 μg/mL in the study by Williams et al. and 2.2 μg/mL in our report). In a nested

Table 2—*Multivariable logistic regression models using adiponectin levels and covariables measured at 1st trimester predicting GDM at 2nd trimester*

	Model 1			Model 2			Model 3			Model 4		
	Unadjusted			Adjusted for age and BMI			Adjusted for age and BFP			Adjusted for age and WC		
Variables at 1st trimester	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Total adiponectin (per μg/mL decrease)	1.14	1.04–1.25	0.004	1.13	1.03–1.24	0.01	1.14	1.04–1.25	0.007	1.13	1.03–1.24	0.01
Total adiponectin and glucose post 50 g	1.12	1.02–1.23	0.02	1.11	1.00–1.22	0.04	1.11	1.01–1.23	0.03	1.11	1.00–1.22	0.04
Total adiponectin and HbA_{1c}	1.13	1.03–1.24	0.009	1.12	1.02–1.23	0.02	1.13	1.03–1.24	0.01	1.12	1.02–1.23	0.02

For HbA_{1c}, $n = 405$ for NGT and 38 for GDM. For WC, $n = 400$ for NGT and 38 for GDM.

Table 3—*Correlations between adiponectin levels at 1st or 2nd trimester and glycemic regulation indices at 2nd trimester*

Glycemic regulation indices measured at 2nd trimester	Adiponectin levels at 1st trimester			Adiponectin levels at 2nd trimester		
	r	*P*	*P* adjusted*	*R*	*P*	*P* adjusted**
HOMA-IR	−0.22	<0.0001	0.04	−0.22	<0.0001	0.01
Matsuda index	0.28	<0.0001	0.0002	0.29	<0.0001	<0.0001
HOMA-B	−0.02	0.74	0.61	0.03	0.59	0.14
Total $AUC_{ins/gluc}$	−0.16	0.0008	0.03	−0.17	0.0003	0.01
ISSI-2	0.21	<0.0001	0.02	0.22	<0.0001	0.004

$AUC_{ins/gluc}$, $AUC_{insulin/glucose}$. *Adjusted for age and BMI at 1st trimester. **Adjusted for age and BMI at 2nd trimester.

case-control study, Nanda et al. (13) suggested that adding adiponectin levels measured at 6–13 weeks would improve a clinical prediction model for screening performance. Also in line with our results, Georgiou et al. (11) and Lain et al. (12) found, in small case-control studies matched for BMI, that 1st-trimester adiponectin levels were lower in women who developed GDM. Adding to the current knowledge, our results demonstrate that the association was still significant when additionally adjusted for 1st-trimester glycemic regulation indices (1-h glucose levels during 50-g test or HbA_{1c} levels). In contrast to those studies and our results, the findings of Paradisi et al. (14) did not show a significant difference in 1st-trimester adiponectin levels in GDM versus control women. Their negative findings might be explainable by limited sample size (12 GDM and 38 control subjects) or by the difference in the bioassay used to measure adiponectin. Adding to the controversy, Savvidou et al. (15) found that women who developed GDM had lower levels of adiponectin at 1st trimester, but the difference was not significant after adjustment for confounding factors.

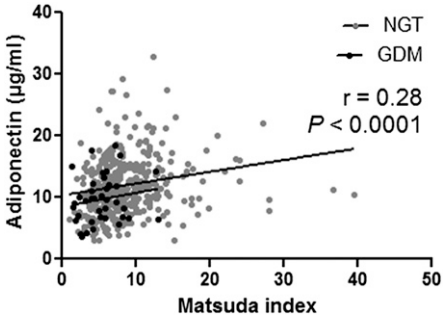

Figure 1—*Correlation between total adiponectin at 1st trimester and insulin sensitivity measured by Matsuda index at 2nd trimester. NGT,* n = *407; and GDM,* n = *38.*

In summary, our results clarified the link between 1st-trimester adiponectin levels and the risk of GDM by testing its association in a large prospective cohort of pregnant women, representative of the general population receiving care in our institution.

The nature of our design also allowed us to investigate the evolution of adiponectin levels during pregnancy and its potential contribution to gestational glycemic physiology in a population of women with a full spectrum of glucose regulation. It is well established that pregnancy is characterized by an increase in insulin resistance that starts to rise during mid-pregnancy and reaches a level similar to that associated with early type 2 diabetes at the end of the third trimester (2). Some authors have suggested that adiponectin could contribute to the regulation of pregnancy-induced insulin resistance. In fact, adipose tissue biopsies have demonstrated lower adiponectin expression in late pregnancy versus in the pregravid state (27). A few studies reported that adiponectin levels decrease over the course of normal pregnancy (14,27,28). Initially, we hypothesized a decrease in adiponectin levels between the 1st and 2nd trimesters and that the decrease would be more pronounced in women who develop GDM. This was not the case, as the adiponectin levels were not significantly different between 1st and 2nd trimester in either normoglycemic or GDM women. The difference in observations between our study and existing literature might be related to the fact that we assessed adiponectin levels at 9 and 26 weeks, while previous studies observed the decrease in adiponectin levels during the 3rd trimester (27,28). In line with this, Paradisi et al. (14) observed a larger decrease in adiponectin levels between 2nd to 3rd trimester and 1st to 2nd trimester. If adiponectin was implicated in the pregnancy-related rise in insulin resistance, we would expect a decrease of adiponectin levels before the known rise in insulin resistance characteristic of 2nd trimester. Nevertheless, our results demonstrate that low adiponectin levels at 1st trimester are independently associated with risk of developing GDM and suggest that they are likely the reflection of baseline insulin resistance.

Indeed, we demonstrated that low adiponectin levels were associated with higher insulin resistance assessed by HOMA-IR or by Matsuda index derived from dynamic measures obtained during the OGTT. Those associations were validated for both 1st- and 2nd-trimester adiponectin levels and remained significant after adjustment for age, adiposity, and insulin secretion indices. Our results are consistent with the results from the study of Retnakaran et al. (29) showing that adiponectin levels in late pregnancy were associated with insulin sensitivity based on Mastuda index. This group also demonstrated that low adiponectin levels were associated with lower ISSI, an index of β-cell function in the face of insulin resistance (considered as a proxy of the disposition index), which is similar to our results (29,30). We added to the understanding of the association between adiponectin and ISSI by demonstrating that the observation was mainly driven by the link between adiponectin levels and insulin resistance/sensitivity while having no association with insulin secretion indices (after adjustment for the level of insulin sensitivity). The ISSI is the product of insulin secretion and insulin sensitivity: both components influence the results, and so it is important to assess the implication of adiponectin with each component to understand the association between adiponectin and ISSI. Our results suggest that adiponectin is likely part of insulin resistance pathways, reflecting the "health" of adipose tissue in pregnant women, which is similar to observations in nonpregnant women (8,9,31).

Adiponectin levels vary within a wide range in pregnancy. In our cohort, adiponectin levels at 1st trimester ranged from 2.94 to 32.86 μg/mL. Also, as illustrated in Fig. 1, adiponectin levels in women who developed GDM had levels that overlapped with those observed in women who remained NGT. Thereby, it would be difficult to determine a clinically applicable threshold to identify pregnant women who will develop

GDM during pregnancy solely on the basis of adiponectin levels.

Our study has many strengths. First, we report here the largest prospective cohort of pregnant women with first assessment at the 1st trimester and measured adiponectin levels that we are aware of. Our cohort is representative of the general population of pregnant women receiving care in our institution (26), increasing our confidence that our results represent adiponectin's physiologic role in free-living humans. We excluded preexisting diabetes at 1st trimester to make sure to investigate glucose regulation related to pregnancy and GDM exclusively. Diagnosis of GDM was based on a standard 75-g OGTT and the most recent cutoffs recommended by IADPSG (19); none of the previous reports about adiponectin and GDM mentioned above were using the newest criteria. All laboratory and clinical measurements were performed under standardized procedures with high reliability. Nevertheless, our study also has limitations. First-trimester adiponectin was measured under the nonfasting state, but adiponectin levels are not influenced by acute food intake (32). Total adiponectin—not high molecular weight—fraction was measured. However, previous studies in pregnant women population demonstrated similar strength of associations between various glycemic indices and adiponectin levels using either total or high–molecular weight adiponectin (29). Clamps and frequently sampled intravenous glucose tolerance test are considered gold-standard measures of insulin resistance and insulin secretion, but this was impossible for us based on our large sample. We used indices of insulin resistance/sensitivity, based on fasting and dynamic measures obtained during OGTT, which are strongly correlated with gold-standard measures and were validated in the past in a pregnant population (21). Finally, since our population was composed mainly of women of European descent, our findings might not apply to other ethnic background and might explain some of the differences with the findings of previous reports that included mixed ethnicities.

In conclusion, our results suggest that low adiponectin levels early in pregnancy are associated with risk of GDM independently of adiposity and glycemic levels at 1st trimester. Low adiponectin levels already present at 1st trimester are likely a reflection of preexisting insulin resistance, which predisposes those women to develop GDM later in pregnancy if they have an insufficient β-cell capacity to respond to the increased demand related to pregnancy. It is unlikely that adiponectin regulation is the cause of pregnancy-related increase in insulin resistance (either in normoglycemic or GDM women), based on the stable levels from 1st to 2nd trimester. We hope that better understanding of the pathophysiology of insulin resistance during pregnancy and of pathways involved in GDM development will lead to adapted preventive approaches to improve the health of mothers and offspring in the future.

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M.L. performed data collection, data analysis and interpretation, and wrote the manuscript. M.-C.B., M.D., and J.M. participated in recruitment and data collection and revised and edited the manuscript. J.-L.A. and P.P. participated in study design conception and revised and edited the manuscript. M.-F.H. conceived the study design, provided assistance with the statistical analysis, actively participated in data interpretation, and revised and edited the manuscript. M.-F.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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