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Adiponectin and leptin as first trimester markers for gestational diabetes mellitus: a cohort study

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Abstract

Background: Gestational diabetes mellitus (GDM) is increasing partly due to the obesity epidemic. Adipocytokines have thus been suggested as first trimester screening markers for GDM. In this study we explore the associations between body mass index (BMI) and serum concentrations of adiponectin, leptin, and the adiponectin/leptin ratio. Furthermore, we investigate whether these markers can improve the ability to screen for GDM in the first trimester.

Methods: A cohort study in which serum adiponectin and leptin were measured between gestational weeks 6 + 0 and 14 + 0 in 2590 pregnant women, categorized into normal weight, moderately obese, or severely obese.

Results: Lower concentrations of adiponectin were associated with GDM in all BMI groups; the association was more pronounced in BMI < 35 kg/m^2 (p = 0.30 for interaction). Leptin was inversely associated with GDM in severely obese (p = 0.033), but showed no association in women with BMI < 35 kg/m^2. The adiponectin/leptin ratio was associated with GDM in women with BMI < 35 kg/m^2 but not in severely obese women (p = 0.79). In regard to predicting GDM, maternal characteristics combined with adiponectin alone, adiponcetin and leptin, and adiponcetin/leptin ratio had the strongest associations in women with BMI < 35 kg/m^2. These models had a detection rate of 77.3%–80.3% when the false positive rate was fixed at 25%.

Conclusions: Low adiponectin measured in the first trimester is associated with the development of GDM; higher BMI was associated with lower performance of adiponectin, though this was insignificant. Leptin had an inverse relationship with GDM in severely obese women and did not improve the ability to predict GDM.

Keywords: adiponectin; body mass index; first trimester screeing; gestational diabetes mellitus; leptin; obesity; pregnancy trimester.

Introduction

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance recognized during pregnancy. The prevalence ranges from 1% to 14% depending on the population screened and the diagnostic tests used [1]. In the first trimester, insulin sensitivity increases, whereas it decreases continuously during the second and third trimester. GDM develops when pancreatic β-cells are unable to increase insulin secretion appropriately to compensate for the corresponding fall in tissue insulin sensitivity seen during pregnancy [2, 3]. Randomized controlled trials have shown that detecting and treating GDM can reduce the risk of fetal macrosomia, preeclampsia, and shoulder dystocia. However, there is no international consensus regarding diagnostic tests and screening methods of GDM [4]. Knowledge is lacking regarding the most efficient screening models; selective screening or population screening, method and time of performance and the cost benefit of these different approaches [5, 6]. Identifying and treating women at risk in early pregnancy would potentially have a preventive effect on complication rates.

The obesity epidemic has led to an increased prevalence of GDM [7]. Women with a body mass index (BMI) >30 kg/m^2 exhibit a 6–12 times higher risk of developing

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GDM [8]. A combination of obesity and GDM is associated with an increased risk of adverse maternal and fetal outcomes, longer hospital stay, and higher healthcare costs [9].

Adipocytokines such as adiponectin and leptin are proteins secreted by adipocytes and are involved in a number of endocrine processes, e.g. body weight regulation, insulin resistance, insulin secretion, and inflammation. Therefore, the metabolic disturbances in obesity caused by adipocytokines may be involved in the development of GDM; although the causality is poorly understood [3, 10, 11].

Adiponectin can reduce fat storage by stimulating lipid oxidation and inhibit lipolysis in adipose tissue, and it is involved in inflammation and regulates insulin activity [12]. It increases insulin sensitivity, reduces glucose synthesis and glucose uptake, and is negatively correlated with the metabolic syndrome [13]. Most studies show a decrease in adiponectin concentrations in women with GDM [3, 14, 15], whereas other studies found no association [16, 17]. However, one study found that adiponectin combined with other hormones (follistatin-like-3 and sex hormone-binding globulin) was a useful marker for GDM in the first trimester [18].

Leptin plays a role in body weight regulation and glucose metabolism by regulating food intake. Low leptin concentrations elicit a starvation response, and high concentrations are permissive for a higher basal metabolic rate and induce satiety [19]. Studies investigating the relationship between serum leptin concentrations and the development of GDM show conflicting results [3, 10, 14, 20].

The adiponectin/leptin ratio has been reported to be a surrogate marker of insulin sensitivity and has been shown to be a more effective marker for metabolic disorders, such as type 2 diabetes mellitus, polycystic ovarian syndrome, and obesity, than either of the hormones alone [21–24]. Although one study has shown that the adiponectin/leptin ratio in pregnant women correlated with insulin sensitivity, no studies have examined the use of the first trimester adiponectin/lepin ratio as a marker for the development of GDM later in the pregnancy [25].

We hypothesized that the adiponectin/lepin ratio measured in the first trimester could serve as a marker for insulin sensitivity in obese women and thus potentially improve the early detection of GDM.

The aim of this study was to evaluate whether the concentrations of adiponectin and leptin or the adiponectin/leptin ratio could be used as screening markers for GDM in normal-weight and obese pregnant women.

Materials and methods

Study population

A cohort study selected from a population of 14,591 pregnant women attending their first routine visit at the ultrasound unit of Holbæk Hospital, Holbæk, Denmark, between January 2006 and December 2011 and who had a serum sample from the first trimester stored frozen at the State Serum Institute (SSI), Copenhagen, Denmark. Obese women with a BMI ≥ 30 kg/m^2 were identified and matched randomly with normal-weight women. We did not include underweight and overweight women, as the focus of this study was moderate to severe obesity.

The study was reported according to the STROBE recommendations and approved by the Danish Data Protection Agency (6 June 2013 reg. no. SJ-HO-01) and the regional Research Ethics board (3 April 2013 SJ-335).

Outcome measures

In Denmark, all pregnant women are offered a first trimester screening for trisomy 21 between gestational age (GA) 11 + 0 and 14 + 0 weeks. Data are registered prospectively and stored in a database (Astraia) that comprises information on all ultrasound fetal biometries, mothers' medical history, parity, maternal age, pre-pregnancy maternal weight and height, and smoking habits. In addition, all pregnant women included in the study had serum samples analyzed for PAPP-A and β-HCG before inclusion, and the samples were stored at SSI.

Screening for GDM was performed according to national guidelines in women with the following risk factors: GDM in previous pregnancies, BMI ≥ 27 kg/m^2, family history of diabetes mellitus, glycosuria, or previous delivery of infant with birth weight ≥4500 g [26]. The women were screened by an oral glucose tolerance test (OGTT) with a 75-g oral glucose load. GDM was defined as a plasma glucose ≥9 mmol/L after 2 h. BMI was classified according to WHO's definition as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), moderately obese (30–34.9 kg/m^2), and severely obese (≥35 kg/m^2) [27].

Sample analysis

The serum samples were collected at GA 6 + 0–14 + 0 weeks, processed, and afterwards stored at –20 °C at the prenatal biobank at SSI for subsequent biochemical analyses. Plasma adiponectin concentrations were determined using the DuoSet® ELISA Development System for human adiponectin/Acrp30 (Catalog no.: DY1065, R&D System, TX, USA). The detection rate of the assay was 62.5 pg/mL–4000 pg/mL. The lab performed controls for variation between batches, variation due to storage temperature, and freeze-thaw cycles, which did not significantly influence the concentrations [28]. Plasma leptin concentrations were determined using the Human Leptin Elisa Development Kit, DuoSet (DY398, R&D Systems, MN, USA). The lower limits of detection of the assays were 0.03 μg/L. Assay calibrator was purified with *Escherichia coli* expressed recombinant human leptin, produced by the manufacturer (AF398, R&D Systems, MN, USA). Leptin's intra- and inter-assay coefficients of variations were <5% and the analyses were stable for 3 months at –20 °C and for 10 freeze-thaw cycles [29].

Statistical analysis

Descriptive statistics are presented as mean, standard deviation (SD), median, interquartile range, and percentages. Comparisons between BMI groups were done by χ^2-test for categorical variables and the Kruskal-Wallis test for continuous or ordinal variables for skewed distributions with a *post hoc* Bonferroni correction.

Adiponectin and leptin concentrations and the adiponectin/leptin ratio were logarithmically transformed into a Gaussian distribution. Multiple regression analyses were performed to determine which factors predicted the log concentrations of the adipocytokines. We accounted for clustering introduced by assessing more than one birth by the same mother by using random effect models. Logistic regression analyses were used to determine the factors predicting GDM. GDM was the dependent variable, while BMI groups (normal weight, moderate-, and severely obese women), smoking habits (smoker/non-smoker), age of the mother (years), ethnicity (Caucasian/other) and parity (1–9) were used as independent variables. The women were divided into BMI groups, and tested for interactions between BMI groups and biomarkers; if an interaction were significant the interaction was a part of the final model. To evaluate the predictive power of the identified predictors of GDM, we used receiver operating characteristic (ROC) curves and in particular the associated area under the curve (AUC). The ROC curves were made with maternal factors alone and combined with different biomarkers (log leptin, log adipnectin, log adiponectin/leptin ratio and log leptin combined with log adiponectin) to find the best performing model. The models were also tested within different BMI groups and were evaluated using bootstrapping. p-Value <0.05 was considered statistically significant. The statistical package STATA (version 14.2) was used for data analyses.

Results

We identified 2205 moderately to severely obese women and selected randomly 2205 normal-weight women. We excluded 877 obese and 889 normal-weight women in whom maternal serum samples were unavailable. Other exclusion criteria were pre-pregnancy hypertension (n = 9), intrauterine fetal death or termination of pregnancy at GA < 22 + 0 weeks (n = 15), diabetes mellitus diagnosed before pregnancy (type 1 or 2) (n = 2), or serum samples taken at GA > 14 + 0 weeks (n = 28). Accordingly, 2590 pregnant women were included in the study.

The maternal characteristics and pregnancy outcomes are presented by BMI groups in Table 1. The moderately and severely obese women were significantly different from women with normal weight regarding parity, smoking habits, birth weight of child, and GDM.

In multiple regression analyses, we found that the log concentration of adiponectin was significantly dependent on smoking habit (regression coefficient [coef] = −1.34, p < 0.001), parity (coef = 0.03, p = 0.001), maternal age (coef = 0.01, p = 0.007), BMI (coef = −0.02, p < 0.001), and ethnicity (coef = −0.16, p < 0.001). There was a significant random effect of repeated mothers of 0.28 (CI = 0.25–0.32). The log leptin concentrations were dependent on BMI (coef = 0.08, p < 0.001), parity (coef = −0.04, p < 0.001), smoking (coef = −0.14, p < 0.001), but not maternal age or ethnicity. The random effect was 0.33 (CI = 0.27–0.39), p < 0.001 in mothers with several births. The log adiponectin/leptin ratio was dependent on maternal age (coef = 0.01, p = 0.004), ethnicity (coef = −0.16, p = 0.001) and BMI (coef = −0.09, p < 0.001), a random effect of 0.41 (CI = 0.35–0.48), p < 0.001 was reported. The adiponectin and leptin concentrations and the adiponectin/leptin ratio were not dependent on fetal sex or GA at the time of sample collection.

Figures 1–3 show scatter plots of log adiponectin, log leptin, and log adiponectin/leptin ratio in relation to BMI in pregnant women.

The associations between log adiponectin, log leptin, and log adiponectin/leptin ratio for each BMI

Table 1: Maternal characteristics and pregnancy outcomes.

BMI group	Normal weight (n = 1298)[a]	Moderately obese (n = 870)	Severely obese (n = 422)
Maternal age in years, median (IQR)	29 (26–33)	29 (26–33)	29 (26–33)
Gestation at sampling in days, median (IQR)	68.8 (63.4–75.4)	69.7 (64.3–77.7)	69.0 (63.2–77.1)
Gestation at delivery in days, median (IQR)	280.3 (273.2–286.4)	280.7 (272.3–287.2)	279.8 (272.1–286.4)
Birth weight in g median (IQR)	3500 (3146–3840)	3600 (3264–3950)[b]	3675 (3340–4010)[b]
Parity			
Nulliparous, n (%)	540 (41.6)	352 (40.5)[b]	162 (38.4)[b]
Para 1, n (%)	512 (39.4)	309 (35.5)[b]	158 (37.4)[b]
Para ≥2, n (%)	246 (19.0)	209 (24.0)[b]	102 (24.2)[b]
Smoker, n (%)	216 (16.6)	161 (18.5)[b]	95 (22.5)[b]
GDM, n (%)	11 (0.9)	55 (6.3)[b]	41 (9.7)[b]
Ethnicity			
Caucasian	1.212 (93.4)	818 (94.0)	405 (96.0)
Other	86 (6.6)	52 (6.0)	17 (4.0)

[a]Normal weight was the reference, IQR, interquartile range; [b]Significant different compared to reference, p < 0.05.

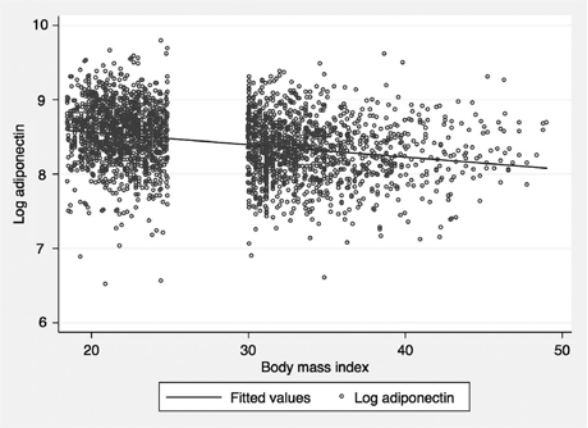

Figure 1: Scatter plot of log adiponectin in relation to body mass index.

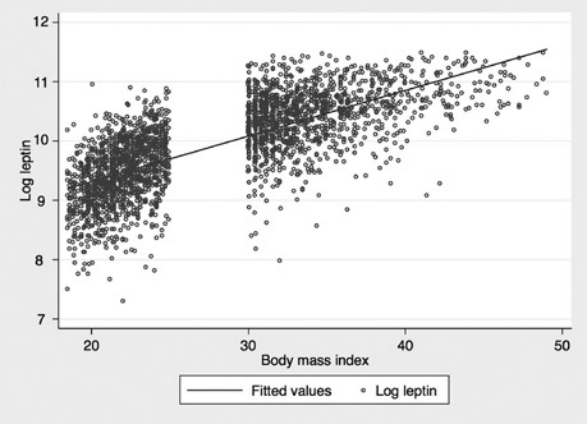

Figure 2: Scatter plot of log leptin in relation to body mass index.

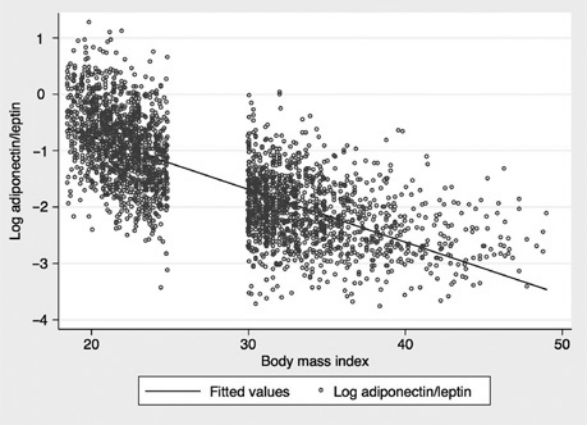

Figure 3: Scatter plot of the log adiponectin/leptin ratio in relation to body mass index.

group and the development of GDM in the final model are displayed in Table 2. The adiponectin concentrations were significantly associated with GDM (Exp (B) = 0.19–0.40), although the interaction between the BMI groups

Table 2: Effect of log adiponectin, log leptin and log adiponectin/leptin ratio for development of GDM (final models of logistic regressions).

BMI group	Normal weight			Moderately obese			Severely obese			Interaction[a]
	B	p-Value	Exp (B)	95% CI for Exp (B)	B	p-Value	Exp (B)	95% CI for Exp (B)	B	p-Value	Exp (B)	95% CI for Exp (B)	p-Value
Log adiponectin	−1.64	0.004	0.19	0.06–0.60	−1.58	<0.001	0.21	0.10–0.40	−0.91	0.029	0.40	0.18–0.91	0.302
Log leptin	0.58	0.310	1.78	0.59–5.42	0.18	0.530	1.21	0.67–2.16	−0.74	0.033	0.48	0.24–0.94	0.041
Log adiponectin/leptin ratio	−1.12	0.013	0.33	0.14–0.79	−0.91	<0.001	0.40	0.25–0.66	−0.08	0.790	1.08	0.61–1.92	0.026

B, β-coefficent; Exp (B), exponential β; [a]p-Value of interaction between BMI groups and biomarkers.

Table 3: Discrimination between GDM and non-GDM pregnancies with different prediction models; maternal factors alone and combined with adiponectin, leptin, the adiponectin/leptin ratio or adiponcetin. and leptin.

Screening test	AUROC (SE; CI)	Detection rates (%) for fixed FPR			
		5%	10%	20%	25%
All pregnancies					
Maternal factors	0.775 (0.731–0.818)	20.6	38.3	57.0	65.4
Maternal factors plus adiponectin	0.806 (0.770–0.843)[a]	26.2	43.0	57.0	70.1
Maternal factors plus leptin	0.784 (0.764–0.838)	26.2	37.4	58.9	65.4
Maternal factors plus adiponectin/leptin ratio	0.801 (0.775–0.838)[a]	20.6	40.2	58.9	72.9
Maternal factors plus adiponectin and leptin	0.812 (0.775–0.848)[a]	25.2	43.9	61.7	70.1
Normal weigthed and moderate obese					
Maternal factors	0.768 (0.709–0.827)	22.7	39.4	57.6	66.7
Maternal factors plus adiponectin	0.820 (0.774–0.864)[a]	27.3	43.9	68.2	78.8
Maternal factors plus leptin	0.771 (0.714–0.829)	19.7	37.9	54.5	71.2
Maternal factors plus adiponectin/leptin ratio	0.813 (0.764–0.861)[a]	21.2	39.4	74.2	80.3
Maternal factors plus adiponectin and leptin	0.824 (0.778–0.870)[a]	33.3	42.4	71.2	77.3

AUC, area under the ROC curve; FPR, false positive rate; [a]Significant different compared to maternal factors, $p < 0.05$.

and log adiponectin was not significant ($p = 0.302$). The adiponectin/leptin ratio was significantly associated with GDM in women with normal weight and moderately obese women, but not in women with severe obesity (BMI ≥ 35 kg/m^2), a significant interaction was included in the analysis ($p = 0.026$). Leptin was significantly associated with GDM only in the severely obese, with an inverse relationship (Exp (B) = 0.48) and interactions between log leptin and BMI groups was significant ($p = 0.041$).

The predictive values of adiponectin, adiponectin/leptin ratio, adiponectin combined with leptin and maternal characteristics for diagnosing GDM are presented in Table 3. There was a significant difference between the model only including maternal characteristics and the models including adiponectin ($p = 0.011$), adiponectin/leptin ratio ($p = 0.014$) and a combination of adiponcetin and leptin ($p = 0.005$). There was no significant difference between the model containing characteristics and leptin alone ($p = 0.12$). Normal-weight and moderately obese women had the largest AUC 0.813–0.824 (Figure 4), for adiponcetin/leptin ratio, adiponectin alone and combined with leptin, thus giving the best performing prediction models. Using bootstrapping, similar AUC, SE and p-values were obtained with 1000 and 5000 replicates.

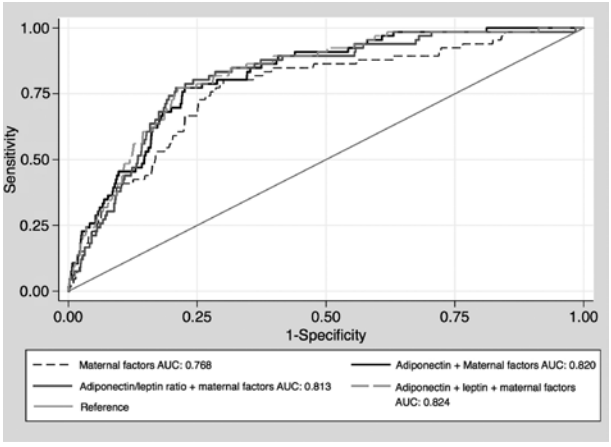

Figure 4: ROC curves for different predictive models in normal-weight and moderately obese women.

Discussion

The present study investigated the associations between the concentrations of adiponectin and leptin and the adiponectin/leptin ratio measured in the first trimester as predictors of GDM in pregnant women. We found an inverse association between the adiponectin/leptin ratio and development of GDM, although with decreased efficacy in obese women. Adiponectin alone exhibited the strongest association with the development of GDM. There was no association between leptin and GDM except in women with severely obesity where lower leptin concentrations were associated with GDM ($p = 0.03$).

The strength of the present study is the large number of pregnancies ($n = 2590$) with a high prevalence of obesity. Earlier studies are mainly case-control studies and a few cohort studies with a limited number of participants (maximum 817) with a low percentage of women with obesity [3, 30].

There are also limitations to our study; the OGTT was performed only in women with risk factors, according to Danish national guidelines [26]. This could have resulted in selection bias due to undiagnosed GDM in the pregnancies in which OGTT was not performed. This bias would be most pronounced in the normal-weight group who were offered an OGTT only if risk factors or symptoms of the disease were present. Another limitation is that underweight and overweight women were not included in the study. In this study we focused on women with moderate and severe obesity, as we know that there is a clear relationship between increasing BMI and the development of GDM. Based on our results, we cannot define at which BMI level the difference between normal and moderately obese occur.

We found no significant correlation between GDM and leptin concentrations, except for an inverse correlation in women with severe obesity. The literature is inconsistent regarding leptin's role in GDM [3, 14, 20, 25, 30, 31]. Leptin is found to correlate with BMI, total body fat during pregnancy, and insulin resistance [30, 32, 33]. There is growing evidence that regulation of leptin is different in pregnant women with obesity compared to normal-weight [34, 35]. Misra et al. [33] found that the increase of leptin/body mass during pregnancy is lower in obese than in women with normal weight, suggesting that the regulation of leptin concentrations during pregnancy is dependent on BMI. Park et al. investigated leptin, insulin resistance, and GDM and found that the development of GDM in normal-weight women was primarily associated with low capacity of insulin secretion, whereas in the obese, GDM was associated with both insulin resistance and inadequate insulin secretion. It seems that obesity is associated with a diminished metabolic efficacy of leptin, since elevated concentrations in the serum are less efficient to induce a normal response in the brain, suggesting that leptin in patients with obesity may be at its physiologically functional maximum, which has been termed leptin resistance [36, 37]. In pregnant mice, specific hormones (i.e. progesterone and prolactin) may cause a central leptin resistance in which the brain fails to respond to high leptin concentrations, enabling the mice to preserve energy for the fetus and birth [38]. The mechanisms concerning leptin, obesity, pregnancy, and insulin resistance are therefore complex and not yet fully understood. Mapel-Brown et al. [30] found in a cohort study of 817 human pregnancies that BMI was the strongest determinant of serum leptin concentrations during both the second and the third trimester and exhibited no association with the glucose tolerance status in the pregnancies, which is consistent with our findings in the first trimester. Further, we found an inverse association between leptin concentrations and GDM in severely obese women. This finding prompted us to examine the relationship between GDM and the deviation of leptin concentrations by comparing actual with expected leptin concentrations given the actual BMI in the pregnant women, which, however, did not reveal any other associations (data not shown). Thus, higher leptin concentrations were not associated with GDM.

Analyses of adiponectin concentrations exhibited as expected an inverse correlation with BMI. Interestingly, the efficacy of adiponectin as a marker of the later development of GDM decreased with increasing BMI. This is in contrasts with previous studies [39–42]. Though the decrease was not significant, the linear decrease in the difference between GDM and normal pregnancies with higher BMI support a relationship though our study might be underpowered to prove it.

Yamauchi et al. [43] showed that intravenous administration of adiponectin in a rat model of insulin resistance caused normalization of insulin sensitivity, illustrating that low adiponectin concentrations may contribute to GDM.

Svranca et al. [21] hypothesized that the adiponectin/leptin ratio was a more reliable marker of insulin resistance in normal weight pregnant women, and showed that it correlated with the homeostasis model assessment for insulin resistance (HOMA-IR). In our study the adiponectin/leptin ratio could be used as a predictor for GDM, but the efficacy decreased with increasing BMI and had to be adjusted for that. The performance of adiponectin was equal to that of the adiponectin/leptin ratio. Combining maternal characteristics, leptin and adiponectin we exhibited the best performance, though there were no significant difference between the three models containing adioponectin. Adiponectin/leptin ratio did not provide extra information; and had poor performance in women with severe obesity.

An early identification of women with increased risk of GDM may provide a window of opportunity for the clinician to improve outcomes and optimize glycemic control by diet and physical activity [44–46]. In a study using HbA_{1c} to screen for GDM in the first trimester, treatment with a low calorie diet in screening-positive women lowered the incidence of GDM in the non-obese [47]. Jensen et al. [26] offered GDM screening to all pregnant women according to the Danish program with a OGTT and had a participation rate of 77% in the high-risk group and only 25% in the low-risk group [48]. The sensitivity of screening by risk indicators is around 60%, with a false-positive rate of 30%–40% [5]. The prevalence of GDM depends on the performance of screening tests, the diagnostic criteria for

GDM, screening methods employed, and the participation rate [5, 49]. In a large population study, the prevalence of GDM varied between 4.2% and 18.5% depending on the diagnostic criteria used [50]. In countries screening by risk stratification, BMI is a strong parameter though early evaluation of adiponectin in women with BMI < 27 kg/m^2 may prove valuable for identifying pregnancies at risk in a low-risk group where the participation rate is low, and diagnosing GDM is difficult hopefully motivating the women to complete an OGTT and participate in preventive interventions. However, randomized trials are needed to determine whether early identification of women with increased risk of GDM has any effect on the incidence and complications related to GDM.

In conclusion, we found that adiponectin concentration is a marker for GDM. The performance of the adiponectin/leptin ratio is equal to that of adiponectin; although it is more imprecise in women with an increasing degree of obesity than adiponectin alone. In first trimester screening for GDM, leptin has a small contribution since it is only effective in women with severe obesity.

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