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Low adiponectin in overweight/obese women: association with diabetes during pregnancy

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Abstract. – BACKGROUND: Overweight/obese (OW/OB) women are at high risk to develop gestational diabetes mellitus (GDM) in pregnancy.

AIM: To investigate, in pregnant OW/OB women, the longitudinal changes of adiponectin plasma levels, carbohydrate and lipid metabolism, and to identify if there is any association between adipokines and subsequent development of GDM.

SUBJECTS AND METHODS: Thirty-two OW/OB normotensive normoglycaemic women at the beginning of pregnancy were studied. Adiponectin, insulin sensitivity (homeostasis model assessment, HOMA) and lipid panel were measured at 1st, 2nd and 3rd trimesters of pregnancy. The bioelectrical impedance to estimate the subject's body composition was also performed.

RESULTS: Sixteen OW/OB women developed GDM. There were no significant differences with regard to age, BMI and body composition. Glycaemic and insulinaemic plasma levels, HOMA and lipid panel were comparable in the two groups. Systolic, diastolic and mean blood pressure at the 1st trimester were higher in OW/OB women with GDM ($p < 0.05$). GDM group showed adiponectin levels significantly lower than control group, at each trimester ($p < 0.05$). Adiponectin, fat mass, diastolic blood pressure and HOMA are independent predictors of GDM.

CONCLUSIONS: OW/OB women who will develop GDM show lower adiponectin than euglycaemic group, across all pregnancy. Furthermore, at first trimester, they showed higher body fat and blood pressure levels than NGT group. Adiponectin, body fat, DBP and HOMA are independent predictors of GDM in OW/OB pregnant women. These results suggest the possibility of using adiponectin as early marker of GDM risk, at least in this cohort of women.

Key Words:
Adiponectin, Gestational diabetes mellitus, Overweight, Obesity, Pregnancy, HOMA.

Introduction

Obesity is one of the greatest public health challenges of the 21st century: its prevalence has tripled in many Countries of the WHO European Region since the 1980s[1]. Recent ISTAT (National Institute for Statistics) data reported that overweight and obesity (body mass index (BMI) = 25-29.9 kg/m^2 and BMI > 30 kg/m^2, respectively) affected 35.5% and 9.9% of italian population, respectively[2]. Obesity is the strongest risk factor for the development of type 2 diabetes in the non-pregnant individual and for the development of glucose intolerance during gestation. Pregnancy acts as metabolic stress test to evaluate the future risk of metabolic syndrome: thus, pregnant overweight/obese (OW/OB) women, constitutionally insulin resistant, could be considered at higher risk of glycometabolic and hypertensive disorders than normal-weight pregnancies.

Adipose tissue has recently been found to secrete biologically active proteins including leptin, TNF-α, IL-6, PAI-1 and resistin. Adiponectin, a 30-kD adipocytokine, is first described as the most abundant protein produced exclusively by adipocytes[3]. It appears to have a central regulatory role in many of the physiological pathways, controlling lipid and carbohydrate metabolism and to mediate various vascular processes. In the general population adiponectin plasma concentration is positively related to High-density lipoprotein (HDL)-cholesterol levels and inversely related to blood pressure, Low-density lipoprotein (LDL)-cholesterol, triglycerides and body weight[4]. Paradoxically, it decreased in subjects with obesity and insulin-resistance states, including metabolic syndrome and diabetes, as well as hypertension and coronary heart disease[5-10].

Recently, interest in adiponectin has also been focused on pregnancy. In a series of studies, adiponectin plasma concentration has been shown to be lower in pregnant women than in non-pregnant women[11-13] and, more interestingly, that pregnant women who successively developed gestational diabetes mellitus (GDM) presented a decreased adiponectin value than euglycaemic pregnancies[14-18].

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On these assumptions, it has been speculated that reduced adiponectin at the beginning of pregnancy could be considered a risk factor for the development of GDM.

There is little information regarding adiponectin trend in OW/OB pregnant women and, to date, no studies were prospectively designed to identify a prognostic risk marker for the development of GDM in this population.

Whether the effect of body mass on the development of GDM is primarily through changes in adipocyte metabolism or insulin resistance is still unknown. Moreover, it has been extensively debated whether impaired insulin action is the cause or the consequence of hypoadiponectinaemia[7,13,19].

Information on adiponectin concentration throughout gestation is, therefore, important.

The purpose of this study was to prospectively evaluate the longitudinal changes of adiponectin, carbohydrate and lipid metabolism in euglycaemic and GDM OW/OB women during pregnancy, and to discriminate their association with the development of GDM. To this end we measured adiponectin levels, insulin sensitivity, blood pressure and lipid panel at the beginning of pregnancy, repeating all the evaluations at second and third trimesters.

Subjects and Methods

A prospective cohort study in OW/OB women (BMI > 25 kg/m^2) at high risk for GDM was performed. This study was conducted at the Catholic University of the Sacred Heart (Rome, Italy) and was approved by the Institutional Review Board. Informed consent was obtained from each subject before the study.

Thirty-two consecutive OW/OB women with clinical characteristics consistent with a high risk for GDM (personal history of GDM, glycosuria or a strong family history of diabetes, according to the American Diabetes Association) were enrolled at the 1st trimester[20]. All patients had singleton pregnancy. All subjects where caucasian. None had hypertension or type 2 diabetes. None took medications known to affect glycaemic and lipid metabolism. None smoked during pregnancy. Demographic information from each subject included maternal age, parity, pre-pregnancy body mass index [BMI, calculated as the ratio between habitual weight (in kilograms) and height (in meters) squared], weight gain during gestation, family history of diabetes and hypertension and previous history of GDM. Neonatal data included week of delivery, birth weight and birth weight percentile. The study protocol performed at 1st (range 8-11 weeks), 2nd (range 23-25 weeks) and 3rd (range 33-36 weeks) trimesters, included the evaluation of blood pressure, body weight, bioelectrical impedance. At each trimester venous blood sample were made to evaluate fasting glycaemia and insulinemia, cholesterol levels (total, HDL and LDL), triglycerides, free fatty acids, and adiponectin. Glucose and insulin were measured at fasting and after 100 g OGTT performed after 2 days of a standard diet containing at least 250 g of carbohydrate per day. Samples were collected at 8.00 a.m. (after an overnight fast) and at 60, 120, 180 minutes after glucose ingestion and were centrifugated immediately.

Four aliquots of plasma were stored at –80°C pending adiponectin and insulin assay. GDM was diagnosed by two abnormal values following the 100 g load with normal values of 95, 180, 155 and 140 mg/dl for the fasting 1, 2 and 3 h postload, respectively[21].

Analytical Methods

Serum adiponectin levels were determined by the Human ELISA kit (B-Bridge International, Sunnyvale, CA, USA), according to the manifacturer's instructions.

Plasma glucose levels were measured using the glucose oxidase method (Beckman Glucose Analyzer, Fullerton, CA, USA); plasma insulin concentrations were measured by commercial radioimmunoassay kits (Radim, Rome, Italy). Insulin resistance was calculated by homeostasis model assessment [HOMA: fasting plasma insulin (microunits per milliliter) × fasting plasma glucose (millimoles per liter)/22.5].

Total cholesterol and triglyceride concentrations were determined by an enzymatic assay (Bristol, Paris, France). HDL-cholesterol was determined after precipitation with polyethylene glycol 6000 (Delchimica Scientific, Naples, Italy). LDL-cholesterol was isolated by sequential flotation in a Beckman model L7-65 ultracentrifuge using a type 70 rotor (Beckman, Palo Alto, CA, USA). Free fatty acids (FFAs) were determined using an acyl-coenzyme A oxidase-based colorimetric method.

Body Composition

Bioelectrical impedance to estimate the subject's body composition was performed with a

tetrapolar impedance plethysmograph (Soft Tissue Analyzer (STA/BIA), Akern Bioresearch, Florence, Italy) according to Lukaski et al[26]. Briefly, at 07.00 h, each woman was supine on a bed made of nonconductive materials. Detecting electrodes (Red Dot, 3M Health Care, St. Paul, MN, USA) were placed in the middle of the dorsum of hands and feet proximal to the metacarpal-phalangeal and metatarso-phalangeal joints, respectively, and also medially between the distal prominences of the radius and the ulna and between the medial and lateral malleoli at the ankle. The current-introducing electrodes were placed at a minimum distance of the diameter of the wrist or ankle beyond the paired detector electrode. An excitation current of 800 mA alternating current at 50 kHz was introduced at the distal electrodes, and the voltage drop across the patient was detected by the proximal electrodes. The percentage of body fat, fat-free mass, and total body water were calculated using the appropriate software (Bodygram, Akern Bioresearch, Florence, Italy).

Statistical Analysis

Descriptive statistics were performed using frequencies, percentages, frequency tables for qualitative variables and mean ± standard error (SE) for quantitative variables. Statistical significance was accepted at a level of $p \leq 0.05$. For the univariate analysis, Student's unpaired *t*-test was performed to compare quantitative variables between groups, as they were normally distributed. Comparison within the group was performed by Student's paired *t*-test. Comparisons between frequencies were assessed by Chi Square analysis. Repeated measures ANOVA were performed to evaluate adiponectin trend during pregnancy. Linear regression analysis was used for relationships between the development of GDM and the metabolic characteristics studied. Subsequently, variables whose correlation with the development of GDM achieved statistical significance ($p \leq 0.05$) were entered into a stepwise regression model to assess the magnitude of their individual effects. Statistical analysis was performed using the Statview II (SAS Institute Version 5, Cary, NC, USA) statistical package.

Results

During pregnancy, 16 of 32 OW/OB patients developed GDM. Demographic and pregnancy characteristics of normal glucose tolerance (NGT) subjects and GDM women are shown in Table I.

There were no significant differences between groups regarding the maternal age, parity, family history of diabetes and hypertension, previous GDM, pre-pregnancy BMI, weight gain during gestation, birth weight and birth weight percentile. No statistically significant differences between groups was seen regarding gestational age at delivery.

Table I. Demographic and pregnancy characteristics.

Variables	Mean ± SE		
	OW/OB NGT (n = 16)	OW/OB GDM (n = 16)	*p*-value*
Age (years)	31.62 ± 2.24	32.00 ± 0.80	0.8759
Pre-pregnancy BMI (Kg/m^2)	30.64 ± 0.85	32.72 ± 1.97	0.3399
Birth weight (g)	3510 ± 191.12	3645 ± 136.66	0.5699
Birth weight percentile	57.50 ± 5.77	72.37 ± 5.91	0.0817
Gestation at delivery (weeks)	39.50 ± 0.34	39.75 ± 0.33	0.6035
Weight gain during gestation	7.22 ± 1.15	6.46 ± 1.04	0.6301
	Frequencies		*p*-value§
Parity (1/>1 pregnancies)	4/16	5/16	0.6942
Family history of diabetes	5/16	8/16	0.0614
Family history of hypertension	3/16	4/16	0.4589
Previous GDM	4/16	2/16	0.1167

OW/OB: overweight/obese; NGT: normal glucose tolerance; GDM: gestational diabetes mellitus. *Student's unpaired *t*-test. §Chi Square test.

Longitudinal Evaluation of Metabolic Characteristics

The intra and intergroup comparisons of adiposity, blood pressure, glycaemic and lipid values between NGT and GDM OW/OB women are shown in Table II.

In both groups, there were an increase in BMI across trimesters, with higher values at 2nd and 3rd trimesters with respect to the 1st, and at the 2nd with respect to the 3rd ($p < 0.05$ in all trimesters).

At the 1st trimester, OW/OB GDM women showed a higher fat mass and a lower lean mass with respect to NGT group ($p < 0.05$). In NGT women, there was an increase in body fat and a decrease in lean mass from 1st to 2nd trimester ($p < 0.05$).

All OW/OB patients, NGT and GDM, were normotensive. However, GDM OW/OB women showed a 1st trimester systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) higher than NGT group ($p < 0.05$). In NGT women, there was a constant and significant increase in SBP from 1st to 3rd trimester and in MAP from 2nd to 3rd trimester ($p < 0.05$).

No statistically significant difference between groups was seen regarding fasting glucose and insulin levels and HOMA in all trimesters. Fasting glucose of GDM subjects was lower in the 1st than 2nd trimester, whereas in NGT we did not observe changes during pregnancy.

In NGT group, fasting insulin levels and HOMA showed a significant increase across trimesters, whereas in GDM group this trend was significant only from 1st to 3rd and from 2nd to 3rd trimester ($p < 0.05$).

Area under the glucose curve (glucose AUC) in OW/OB GDM group was higher at 2nd and 3rd trimester than the NGT group ($p < 0.05$ in both groups). As expected, glucose AUC showed a constant and significant increase across trimesters in GDM group. In NGT group this trend was significant only from 1st to 3rd and from 2nd to 3rd trimester ($p < 0.05$).

No differences between groups were observed regarding all lipids. In both groups, total cholesterol and triglycerides increased across trimesters ($p < 0.05$ at each trimester in both groups). HDL and LDL cholesterol showed a significant increase from 1st to 2rd and from 1st to 3rd trimester.

Adiponectin levels during pregnancy are depicted in Figure 1. In GDM group, adiponectin showed lower levels than NGT group, at each trimester ($p < 0.05$ in all trimesters). In NGT group, but not in GDM group, adiponectin decreased from 1st to 2nd and 3rd trimester reaching the statistical significativity ($p < 0.05$).

Regression Analyses

To better investigate the factors playing a role in the development of GDM in high-risk pregnant OW/OB women, we performed linear regression analysis between adiponectin and adiposity, blood pressure, carbohydrate and lipid metabolism at 1st trimester.

Linear regression analysis showed that adiponectin had a strong negative association with glucose AUC (r = –0.611; $p < 0.0105$), fasting insulin levels ($r = –0.576$; $p = 0.0179$) and HOMA ($r = –0.578$; $p = 0.0174$). A similar, if less robust, correlation was found between adiponectin and triglycerides ($r = –0.519$; $p = 0.0383$), NEFA ($r = –0.500$; $p = 0.0474$) and DBP ($r = –0.491$; $p = 0.0530$). Conversely, adiponectin exhibited positive relations with HDL cholesterol ($r = 0.532$; $p = 0.0326$). A significant correlation was also found between adiponectin and BMI ($r = –0.513$; $p = 0.0409$).

To evaluate the independent contributions of the various parameters examined to prediction of development of GDM, we performed stepwise regression analysis. The analysis revealed that adiponectin accounted for 21.3 % of the variance ($p = 0.0079$), whereas fat mass, DBP and HOMA contributed an additional 15.6%, 1.1% and 0.09 %, respectively ($p = 0.0013$ for fat mass, $p = 0.0011$ for DBP and $p = 0.0010$ for HOMA). The other variables analyzed did not contribute to the regression model.

Discussion

The results of this study reveal the following new findings:

1. Adiponectin in OW/OB pregnant women is characterized by a constant reduction across gestation: obese women who successively developed GDM showed lower adiponectin levels than NGT group, at each trimester.
2. At the beginning of pregnancy, OW/OB women who developed GDM showed higher body fat and blood pressure levels than NGT group.
3. Adiponectin, body fat, DBP and HOMA are independent predictors of GDM in OW/OB pregnant women.

Table II. Longitudinal evaluation of adiposity, blood pressure, carbohydrate and lipid metabolism, and adiponectin in NGT and GDM OW/OB women.

	OW/OB NGT (n = 16)			OW/OB GDM (n = 16)		
	1st trimester	2nd trimester	3rd trimester	1st trimester	2nd trimester	3rd trimester
Fat mass (%)	38.13 ± 0.69†,‡	41.80 ± 0.37	42.27 ± 1.53	42.67 ± 1.56	45.30 ± 3.54	38.67 ± 3.10
Lean mass (%)	61.46 ± 0.69†,‡	58.24 ± 0.39	57.65 ± 1.48	57.32 ± 1.56	55.52 ± 3.41	61.32 ± 3.10
SBP (mm Hg)	113.94 ± 2.76†,§	117.06 ± 2.61	120.06 ± 3.41	126.87 ± 3.17	124.75 ± 3.06	126.06 ± 2.27
DBP (mm Hg)	72.25 ± 2.02†	72.50 ± 3.10	75.00 ± 2.89	78.12 ± 2.03	78.12 ± 1.70	81.25 ± 2.21
MAP (mm Hg)	85.48 ± 1.78†	87.35 ± 2.70§	90.02 ± 2.72	94.37 ± 2.27	93.67 ± 2.01	96.19 ± 1.98
Fasting glucose (mg/dl)	80.25 ± 1.44	82.83 ± 2.38	83.60 ± 1.18	83.12 ± 1.48‡	87.87 ± 2.54	84.40 ± 2.39
Fasting insulin (μU/ml)	12.75 ± 1.60*	15.36 ± 1.25§	16.20 ± 1.39	16.15 ± 1.84§	13.87 ± 2.64§	21.97 ± 4.22
Glucose AUC	16171.87 ± 849.77§	17036.25 ± 617.18†,§	19210.62 ± 517.58†	17936.25 ± 678.17‡,§	20803.12 ± 1046.38§	22083.75 ± 763.11
HOMA	2.58 ± 0.34*	3.25 ± 0.33§	3.78 ± 0.31	3.26 ± 0.35§	3.32 ± 0.42§	4.46 ± 0.43
Triglyceride (mg/dl)	121.50 ± 7.2*	162.00 ± 9.08§	204.25 ± 7.58	146.62 ± 15.06*	212.21 ± 29.70§	234.37 ± 28.05
Total cholesterol (mg/dl)	184.37 ± 6.34*	228.75 ± 10.50§	259.62 ± 9.16	179.12 ± 6.22*	244.50 ± 13.42§	272.37 ± 14.06
HDL-cholesterol (mg/dl)	57.00 ± 2.47*	71.87 ± 4.01	79.37 ± 2.52	59.75 ± 3.54	67.75 ± 3.96	73.34 ± 4.53
LDL-cholesterol (mg/dl)	103.50 ± 5.46*	126.50 ± 8.63	141.25 ± 7.09	104.12 ± 10.07	116.86 ± 6.55	145.04 ± 8.55
FFA (mg/dl)	0.41 ± 0.05	0.31 ± 0.45	0.42 ± 0.04	0.39 ± 0.04	0.33 ± 0.05	0.38 ± 0.03
Adiponectin (μg/ml)	2.27 ± 0.27†,*	1.56 ± 0.13†	1.52 ± 0.07†	1.41 ± 0.14	1.22 ± 0.09	1.12 ± 0.12

OW/OB, overweight/obese; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; AUC, area under the glucose curve; HOMA, homeostasis model assessment; FFA, free fatty acids. Values are expressed as mean ± standard error of the mean. *p*-values at Student's unpaired t-test, Student's paired t-test and ANOVA for repeated measures (when appropriate). *$p < 0.05$ vs 2nd and 3rd trimester; †$p < 0.05$ vs similar trimester in the other group; ‡$p < 0.05$ vs 2nd trimester; §$p < 0.05$ vs 3rd trimester.

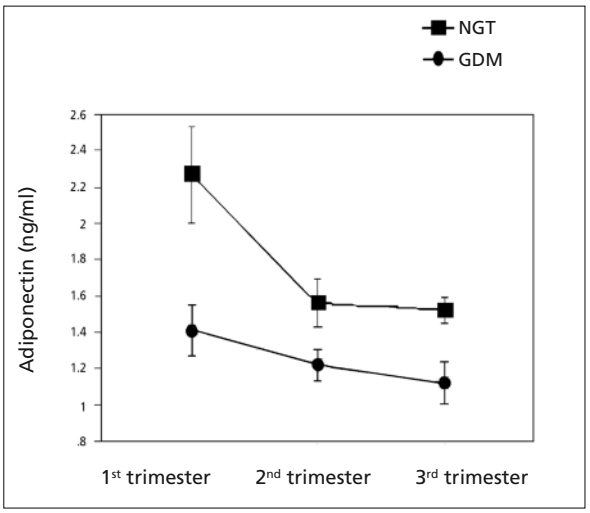

Figure 1. Adiponectin levels during pregnancy in NGT and GDM/OB women.

Pregnancy is a situation of hypoadiponectinaemia[11]. Recently, two Authors described longitudinal changes of adiponectin during normal pregnancy[12,13]. All studies, performed on small samples of euglycaemic women, showed a progressive decline of plasma adiponectin levels as the pregnancy advanced.

More interestingly, in a series of five cross-sectional case-control studies, adiponectin plasma concentration has been shown to be lower in pregnant women who successively developed GDM than euglycaemic pregnancies[14-18].

Renheim et al[15] categorized GDM and NGT pregnant women according to their pre-pregnancy BMI into two classes (BMI < 25 and BMI ≥ 25) and showed lower adiponectin plasma levels in GDM group. Additionally, they found that adiponectin mRNA levels in adipose tissue biopsies, obtained by excision at caesarean delivery from GDM subjects, were reduced.

Williams et al[16], according to maternal adiponectin concentrations and pre-pregnancy BMI, found that adiponectin levels less than 6.4 mcg/ml did correlate with a 4.6-fold increased risk of GDM and, furthermore, that overweight women with low adiponectin concentrations experienced a 11-fold increased risk of GDM.

More recently, Lain et al[17], in a nested case-control study performed on 30 GDM and 29 controls, did confirm these results: after categorizing women by quartile of adiponectin, they showed that women with adiponectin concentrations less than the 25th quartile were 11 times more likely to develop GDM, and this persisted after controlling for BMI.

Kinalski et al[18] did suggest that hypoadiponectinaemia in GDM may not simply reflect maternal adiposity and insulin resistant state, but may contribute to the impaired glucose metabolism during pregnancy, with potential implications for screening and prevention of the disease.

Thus, on these bases, it has been speculated that reduced adiponectin levels at the beginning of pregnancy could be considered a risk factor for the development of GDM.

To date, the mechanism by which low adiponectin should be related to GDM is still unclear. It seems like that, as in metabolic syndrome, reduced adiponectin expression could be associated to insulin resistance, and to the abnormalities of glucose metabolism. Therefore, to test this hypothesis, we have recently performed a longitudinal study[23] in a cohort of 50 high-risk women: we found a significant decrease in adiponectin concentrations, across gestation, in both NGT and GDM subjects, thus extending the previous knowledge on euglycaemic women, also to diabetic pregnancies. Interestingly, no difference emerged between NGT and GDM women. Therefore, the similarity between the adiponectin levels of women who remained NGT and those of GDM subjects was not consistent with the findings of the five previously cited Authors[14-18]. This lack of association, in both eugly-

Table III. Stepwise regression analysis: relationship between adiponectin, fat mass, DBP and HOMA, and development of GDM.

	Regression coefficients	R^2	*p*
Indipendent variables			
Adiponectin	-0.227 ± 0.079	0.213	0.0079
% fat mass	0.038 ± 0.014	0.369	0.0013
DBP	0.023 ± 0.010	0.380	0.0011
HOMA	0.090 ± 0.064	0.389	0.0010
Intercept	-0.621 ± 0.611		

DBP: diastolic blood pressure; HOMA: homeostasis model assessment.

caemic and GDM women, was in agreement with the only other recent longitudinal report[24].

Obesity is a well known risk factor for GDM: however BMI could represent an important potential confounding variable. On the other hand, pregnancy is a physiological condition of insulin resistance, strictly related to obesity. In obesity and diabetes, hypoadiponectinaemia appeared to be associated to the degree of hyperinsulinaemia and to the severity of insulin resistance.

There is little information regarding adiponectin trend in OW/OB pregnant women and, to date, no studies were prospectively designed to identify a prognostic risk marker for the development of GDM in these pregnancies.

We found that, as in normal-weight pregnant women, adiponectin trend is characterized by a constant reduction across gestation, but OW/OB women who will develop GDM showed significantly lower adiponectin levels than NGT group, at each trimester (see Table II). Furthermore, hypoadiponectinaemia has shown to be the strongest independent risk factor for GDM at begin of pregnancy. Thus, at early pregnancy OW/OB women who will develop GDM reveal a lower expression of adiponectin than obese euglycaemic women. Whether this difference is due to a different distribution of body fat in the two groups has not been well elucidated. We noted that, at the beginning of pregnancy, OW/OB women who will develop GDM, showed higher body fat than NGT group.

Ten techniques of body composition assessment are described: (1) anthropometric techniques including skinfold thicknesses and waist-hip ratio; (2) total body water (isotopically labeled); (3) hydrodensitometry (underwater weighing); (4) air-displacement plethysmography; (5) bio-impedance analysis (BIA); (6) total body potassium (TBK); (7) dual-energy x-ray absorptiometry (DEXA); (8) computed tomography (CT); (9) magnetic resonance imaging (MRI); and (10) ultrasound (USS). Most methods estimate total adiposity. Regional fat distribution-central (truncal) compared with peripheral (limb) or visceral compared with subcutaneous-is important because of regional variation in adipocyte metabolism. Skinfolds, DEXA, CT, MRI, or USS can distinguish central from peripheral fat. CT, MRI, or USS can further subdivide central fat into visceral and subcutaneous.

In our study we performed bio-impedance analysis (BIA), a technique executable also in pregnancy, to evaluate body composition, but that cannot provide data regarding compartmentalisation of body fat. Actually, we can only speculate that a lower expression of adiponectin in OW/OB GDM women could depend on a different distribution of body fat and, therefore, on a reduction of adipocytes metabolically active.

Whether the effect of body mass on the development of GDM is primarily through changes in adipocyte metabolism or insulin resistance is still unknown.

Two studies conducted in a non pregnant population[7,19] demonstrated that adiponectin concentrations are more closely related to insulin resistance than obesity.

The decrease of adiponectin during pregnancy appeared to inversely mirror the changes in adiposity: indeed, according to this concept, we did find a significant negative correlation between fat mass and adiponectin. When we performed the stepwise regression analysis to identify the main parameters determining the development of GDM, BMI did not enter, thus supporting the concern that body fat, independently to BMI, seemed to be a strong prognostic risk factor for the GDM.

According to Catalano et al[13], our findings suggested that in OW/OB pregnant women, likely to normal-weight pregnancies, adipose tissue accretion is associated with signals for lowering adiponectin production or secretion. Probably, these signals are strongest in overweight or obesity conditions, as demonstrated by lower adiponectin levels, at each trimester. Other situation of hypoadiponectinaemia, such as lipodystrophy and liver disease, are consistent with the view that a redistribution of adipose tissue is critical in lowering adiponectin levels[25].

It has been extensively debated whether impaired insulin action is the cause or the consequence of hypoadiponectinaemia. Our results didn't clarify this question, but they seemed to propose hypoadiponectinaemia as a somewhat specific predictive parameter for the development of GDM in OW/OB pregnant women.

At the beginning of pregnancy, OW/OB women who will develop GDM showed higher blood pressure levels than NGT group.

It's known that adiponectin levels are significantly lower in patients with essential hypertension[26] and it was observed an inverse correlation between adiponectin concentration and mean systolic and diastolic blood pressure.

In pregnancy, as suggested by D'Anna et al[27], a strong association between hypoadiponecti-

naemia and the risk of hypertensive disorders in pregnancy, especially with preeclampsia, was documented.

Hendler et al[28] extended these knowledges to OW/OB women, concluding that adiponectin level decreases in women with severe preeclampsia and BMI ≥ 25 kg/m^2, while increases in normal weight women with preeclampsia.

Frequently hypertension coexists with diabetes, given that both pathologies share similar pathways[29,30]. Thus, it is not surprising that diastolic blood pressure resulted to be an independent predictive parameter to the development of GDM.

Finally, the stepwise regression analysis revealed a minimal contribution of HOMA (0.09%, p = 0.0010) in determining the development of GDM.

Thus, in our hand, hypoadiponectinaemia early in pregnancy is the strongest independent risk factor for GDM: this findings is consistent with a prediabetic state of women who later will develop GDM. Body fat at early pregnancy was a second highly significant risk factor for GDM, independently to BMI. DBP and HOMA added a slow contribution to the global variance. The fact that adiponectin and body fat are the two main prognostic factors for the development of GDM among OW/OB pregnant women could suggest the role of adipose tissue, more than insulin resistance, in the development of glycometabolic disorders in this population: a lower expression of adiponectin in obese GDM women could depend on a different distribution of body fat and, probably, on a reduction of metabolically active adipocytes.

We are aware that the current study is limited by the lack of information on pre-pregnancy adiponectin, carbohydrate and lipid metabolism, that cannot give us the possibility to establish whether some differences were present before pregnancy. Furthermore, the use of bio-impedance analysis (BIA) cannot provide data regarding compartmentalisation of body fat.

We also do not have information following gestation to determine if they returned to the baseline metabolic state.

In summary, these data show that OW/OB women who will develop GDM have lower adiponectin levels, across gestation, than OW/OB euglycaemic women. At the beginning of pregnancy, women who will develop GDM showed higher body fat and blood pressure levels than NGT group. Adiponectin, body fat, DBP and HOMA are independent predictors of GDM in OW/OB pregnant women. These results increase the possibility of use of adiponectin as an early marker of GDM risk, at least in this cohort of women.

Conclusions

OW/OB women who will develop GDM show lower adiponectin than euglycaemic group, across all pregnancy. Furthermore, at first trimester, they showed higher body fat and blood pressure levels than NGT group. Adiponectin, body fat, DBP and HOMA are independent predictors of GDM in OW/OB pregnant women. These results suggest the possibility of using adiponectin as early marker of GDM risk, at least in this cohort of women.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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