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Serum adiponectin and lipid concentrations in pregnant women with polycystic ovary syndrome

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BACKGROUND: We aimed to evaluate the serum adiponectin and lipid concentrations in normal and polycystic ovary syndrome (PCOS) women during pregnancy in order to establish whether PCOS induces abnormal lipid and adiponectin levels that could constitute potential metabolic risk factors for pregnancy complications. METHODS: Women with singleton pregnancies and of similar age were included (48 pregnant PCOS and 51 normal pregnant women). During gestational weeks 10–16 and 22–28, a 2 h, 75 g oral glucose tolerance test was performed, with measurement of glucose and insulin in each sample. Adiponectin and lipid concentrations were determined in the fasting sample. RESULTS: The incidence of gestational diabetes mellitus (GDM) was significantly higher in the PCOS group (12.2%) compared with the control group (2%). In PCOS patients, triglyceride (TG) concentrations and area under the curve of glucose and insulin were higher in both study periods and adiponectin concentrations were significantly lower in the second period, compared with normal women. Moreover, adiponectin concentrations were lower in women with GDM than in those with normal glucose tolerance in the two study periods. CONCLUSION: Low adiponectin and high insulin levels are associated with GDM in pregnant PCOS patients. High TG levels seem not to be directly related to pregnancy complications in these patients.

Keywords: pregnancy; PCOS; adiponectin; blood lipids; gestational diabetes

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting ~5–8% of reproductive aged women (Franks, 1995; Asunción *et al.*, 2000; Azziz *et al.*, 2004) and characterized by irregular menses, chronic anovulation, infertility and hyperandrogenism. Approximately 50% of the PCOS women are overweight or obese, and most of them exhibit abdominal fat distribution (Gambineri *et al.*, 2002; Norman *et al.*, 2004). In addition, women with PCOS may also have other metabolic abnormalities such as insulin resistance (Holte, 1996; Dunaif, 1997), glucose intolerance, type 2 diabetes (Ehrmann *et al.*, 1999; Legro *et al.*, 1999; Gambineri *et al.*, 2002) and an increased prevalence of lipid-related abnormalities (Wild, 1997; Legro *et al.*, 2001; Cenk Sayin and Yardim, 2003; Banaszewska *et al.*, 2006).

Thus, women with PCOS constitute a high-risk group for pregnancy complications such as gestational diabetes mellitus (GDM) and pregnancy-induced hypertension (Urman *et al.*, 1997; Bjercke *et al.*, 2002; Homburg, 2006; Boomsma *et al.*, 2006).

Lipid abnormalities described in PCOS patients include reduced high-density lipoprotein cholesterol (HDL-C) and increased low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) concentrations (Legro *et al.*, 2001; Talbott *et al.*, 2004; Apridonidze *et al.*, 2005). Hyperinsulinaemia due to insulin resistance has been associated with decreased HDL-C and elevated TG (Legro *et al.*, 2001; Cenk Sayin and Yardim, 2003). Other investigators have found that circulating androgen levels affect lipid and lipoprotein concentrations in women with PCOS. In these women, hyperandrogenaemia plays an important role in the pathogenesis of LDL-C elevations (von Eckardstein *et al.*, 1996).

During normal pregnancy, changes in carbohydrate and lipid metabolism occur to ensure a continuous supply of nutrients to the growing fetus despite intermittent maternal food intake. Longitudinal studies of glucose tolerance during gestation show a progressive increase in nutrient-stimulated insulin responses despite only a minor deterioration in glucose tolerance, consistent with progressive insulin resistance (Ryan *et al.*, 1985; Catalano *et al.*, 1991; Butte, 2000).

Simultaneously, a significant progressive elevation of serum total cholesterol (TC), TG, LDL-C and HDL-C is observed in normal pregnancy (Chiang *et al.*, 1995; Saarelainen *et al.*, 2006).

Adiponectin is a 29-kD adipocyte-derived protein that is involved in the regulation of insulin action and glucose metabolism (Diez and Iglesias, 2003; Tschritter *et al.*, 2003). In addition, its insulin-sensitizing effects influence lipid metabolism (Baratta *et al.*, 2004; Heliovaara *et al.*, 2006; Kantartzis *et al.*, 2006). Serum adiponectin levels are inversely correlated with body mass index (BMI) and also with insulin resistance independent of BMI (Arita *et al.*, 1999; Weyer *et al.*, 2001). In non-pregnant PCOS women, adiponectin concentrations are lower compared with controls, despite them being matched by BMI (Orio *et al.*, 2003; Sieminska *et al.*, 2004). A decrease in adiponectin in the third trimester of pregnancy in comparison to the pregravid condition has been attributed to decreased insulin sensitivity (Catalano *et al.*, 2006). Decreased adiponectin concentrations during pregnancy may be associated with a higher risk of GDM (Ranheim *et al.*, 2004; Williams *et al.*, 2004; Worda *et al.*, 2004; Tsai *et al.*, 2005) and pregnancy-induced hypertension (D'Anna *et al.*, 2005; Hendler *et al.*, 2005).

In a recent study, we found that circulating androgen levels were elevated during pregnancy in PCOS women compared with control women. Moreover, pregnant PCOS women exhibited post-stimulated insulin concentrations that were significantly higher than those observed in normal pregnant (NP) women (Sir-Petermann *et al.*, 2002). However, it is not known whether the hyperandrogenaemia and hyperinsulinaemia observed during pregnancy in PCOS women may induce an abnormal lipid profile and changes in adiponectin concentrations.

The aim of this study was to evaluate serum adiponectin and lipid concentrations in normal and PCOS women during pregnancy in order to establish whether PCOS induces abnormal lipid and adiponectin concentrations that could constitute potential metabolic risk factors for pregnancy complications.

Materials and Methods

Subjects

A group of 48 pregnant women with PCOS (PPCOS) with singleton pregnancies were sequentially recruited for the study from patients attending the Unit of Endocrinology and Reproductive Medicine, University of Chile, who had desired fertility. Diagnosis of PCOS was made according to the diagnostic criteria for PCOS of the NIH consensus (Zawadzky and Dunaif, 1992) and the Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group (2004). Preconceptional inclusion criteria were chronic oligomenorrhoea or amenorrhoea, hirsutism, serum testosterone concentration >0.6 ng/ml and/or free androgen index >5.0, androstenedione concentration >3.0 ng/ml and a characteristic ovarian morphology on ultrasound, based on the criteria described by Adams *et al.* (1986). Normoglycaemic patients with and without clinical signs of hyperinsulinaemia (waist–hip ratio >0.85), and with different grades of hyperinsulinaemia evaluated by an oral glucose tolerance test (oGTT), were included.

All women had been anovulatory as indicated by progesterone measurements and ultrasound examinations. We excluded patients with hyperprolactinaemia, androgen-secreting neoplasm, Cushing's syndrome and late-onset 21-hydroxylase deficiency, as well as thyroid disease.

As part of their initial evaluation, all patients underwent a lifestyle assessment and were placed on a diet and exercise treatment programme as previously described (Sir-Petermann *et al.*, 2002). In addition, most of them (45/48) received 500–2000 mg of metformin in standard formulation on the basis of their weight, medication tolerance and insulin levels. PCOS women stopped metformin either with a positive pregnancy test or before 12 weeks of gestation.

We selected 51 NP women with singleton pregnancies and of similar age and socioeconomic level as a control group. The control women had a history of regular 28–32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, absence of galactorrhoea and thyroid dysfunction. All were healthy and were not receiving any drug therapy. These women were recruited from the antenatal care unit of our hospital from the 12th week of gestation during the same time period.

Only non-smoking and non-alcohol or drug abusing PCOS and control pregnant women were included in the study. Women of both groups with a preterm delivery in the present pregnancy were not included. All subjects had given their written consent to their participation in the study, which was approved by the local ethics committee.

Study protocol

Both groups of pregnant women were followed in the same prenatal care unit. Duration of gestation, initial BMI, BMI in the third trimester, weight gain during pregnancy and blood pressure were recorded.

During gestational weeks 10–16 (early pregnancy) and 22–28 (mid-pregnancy), the women were admitted to the Clinical Research Center in the morning (8:30–9:00 AM) after an overnight fast of between 8 and 12 h. A 2 h, 75 g oGTT was performed in accordance with published criteria (World Health Organization, 1999). Serum glucose and insulin were measured before the glucose load and 30, 60, 90 and 120 min after. Serum adiponectin and lipid concentrations were determined in the fasting sample.

Pregnant women who met the World Health Organization criteria for diabetes mellitus (fasting glucose values >126 mg/dl; 2 h glucose postload ≥ 140 mg/dl) were classified as having GDM. Pregnancy-induced hypertension was defined as gestational hypertension (blood pressure $\geq 140/90$ mmHg without proteinuria at a gestational age >20 weeks on two or more occasions) or pre-eclampsia (blood pressure $\geq 140/90$ mmHg with proteinuria >0.3 g/24 h after 20-week gestation).

Assays

Serum glucose was determined by the glucose oxidase method (Photometric Instrument 4010; Roche, Basel, Switzerland). The intra-assay coefficient of variation of this method was $<2.0\%$. The lipid profile was determined by standard colorimetric assays (Photometric Instrument 4010). Estimation of serum LDL-C concentration was calculated by Friedewald's formula [LDL-C = TC-HDL-C-(TGs/5)] (Friedewald *et al.*, 1972). The coefficient of variation of this method was $<3.0\%$. Serum insulin was assayed by RIA (Diagnostic Systems Laboratories, Inc. Texas, USA). The intra- and inter-assay coefficients of variation were 5 and 8%, respectively. Serum adiponectin was assayed by RIA (Linco-Research Inc., St Charles, MI, USA). The intra- and inter-assay coefficients of variation were 1.8 and 9.0%, respectively. Both hormones were determined in duplicate and were run in the same assay in each period.

Data analyses

The measurements derived from the oGTT included the following:

(i) Serum fasting glucose, serum fasting insulin and homeostatic model assessment (HOMA-IR) (Matthews *et al.*, 1985).
(ii) Serum 2 h glucose, 2 h insulin, ISI composite (Matsuda and DeFronzo, 1999) and area under the curve (AUC) of glucose (glucose AUC) and insulin (insulin AUC). Glucose and insulin AUCs are integrated values of the first 2 h after the glucose load, calculated by the trapezoidal method.
(iii) Serum lipid profile, TC, TGs, LDL-C and HDL-C.
(iv) Serum fasting adiponectin concentrations.

Statistical analyses

Data are expressed as median and range. Normal distribution was assessed by Kolmogorov–Smirnov test. Differences among study groups were assessed through Student's *t*-test when data were normally distributed or the Mann–Whitney test when not normally distributed. Categorical data were analysed using the χ^2 or Fisher's exact test. The effect of BMI on continuous variables was evaluated using multivariate analysis (multiple linear regression techniques). Statistical analysis was performed with STATA 7.0 package. A *P*-value of <0.05 was considered to be statistically significant.

Results

Table 1 shows the clinical characteristics of the two groups of pregnant women. By design, age was not different between both groups. No difference was found in the duration of gestation, weight gain during pregnancy or systolic and diastolic blood pressure between the groups. There were significant differences in the BMI at the initiation and in the third trimester of pregnancy between women with PCOS and normal women.

In four PPCOS (8.3%), gestational hypertension was diagnosed. In addition, the incidence of GDM was significantly higher in the PCOS group (12.2%) compared with the control group (2%) ($P < 0.05$). On the other hand, 43.8% of the PCOS patients were multiparous, whereas 52.6% of the controls were multiparous ($P = 0.539$) (data not shown).

Blood sampling was performed at similar gestational age in both groups during early pregnancy [NP: 12.0 (10–16) versus PPCOS: 12.0 (10–16) weeks] and mid-pregnancy [NP: 24.0 (22–28) versus PPCOS: 24.0 (22–28); $P = 0.734$].

Table 2 shows the metabolic characteristics during the two study periods in NP women. In NP women, fasting TC, LDL-C and TG concentrations increased significantly between the two study periods. No significant changes in fasting serum concentrations of glucose, insulin, HDL-C or adiponectin were observed. HOMA-IR was also unchanged. Two hour insulin, glucose AUC and insulin AUC increased, and ISI composite decreased, significantly during the study.

Table 3 shows the metabolic characteristics during the two study periods in PPCOS women. Serum concentrations of TC, LDL-C and TG increased significantly, whereas adiponectin concentrations decreased significantly, between the two study periods. No significant changes in fasting serum concentrations of glucose or insulin were observed. HOMA-IR, glucose AUC, insulin AUC and ISI composite were unchanged during the study.

Comparing both groups of pregnant women (Fig. 1), after the values were adjusted by BMI, TG concentrations, 2 h glucose, 2 h insulin, glucose AUC and insulin AUC were significantly different between the two groups in the two study periods. Adiponectin concentrations were not significantly different between the groups in the first study period, although they tended to be lower in the PCOS group ($P = 0.06$). This difference became significant in the second study period (gestational weeks 22–28) ($P = 0.004$).

Fasting glucose, fasting insulin, total cholesterol, HDL-C and LDL-C were not significantly different between the groups in either of the study periods.

In a simple linear regression analysis, serum adiponectin was positively correlated with ISI composite ($r = 0.346$, $P = 0.031$) and was inversely correlated with HOMA-IR ($r = -0.327$, $P = 0.042$), 2 h glucose ($r = -0.430$, $P = 0.006$) and 2 h insulin ($r = -0.444$, $P = 0.005$) in pregnant PCOS women in the second study period.

TG concentrations were positively correlated with initial BMI, HOMA-IR, 2 h glucose, 2 h insulin, glucose AUC and insulin AUC and were inversely correlated with ISI composite in pregnant PCOS women in the second study period.

There were no differences in clinical characteristics or metabolic parameters between PPCOS women with and without GDM, except for serum adiponectin concentrations which

Table 1: Clinical characteristics of NP and PPCOS women

	NP ($n = 51$)	PPCOS ($n = 48$)
Age (years)	26.0 (18.0–34.0)	29.0 (15.0–36.0)
Initial weight (kg)	58.0 (46.0 ± 78.0)	69.0 (53.0 ± 111.0)*
Height (m)	1.6 (1.5 ± 1.7)	1.6 (1.5 ± 1.7)
Initial BMI (kg/m^2)	24.2 (18.2–33.3)	28.6 (21.6–41.7)*
BMI in third trimester (kg/m^2)	28.4 (22.5–34.4)	33.4 (26.5–46.1)*
Weight gain during pregnancy (kg)	10.5 (2.0–21.5)	10.0 (−2.5–26.0)
Duration of gestation (weeks)	39.0 (37.0–41.0)	39.0 (37.0–41.0)
Systolic blood pressure (mmHg)	110.0 (100.0–120.0)	120.0 (100.0–140.0)
Diastolic blood pressure (mmHg)	70.0 (60.0–80.0)	70.0 (60.0–90.0)
Number of women with pregnancy-induced hypertension	0 (0.0%)	4 (8.3%)
Number of women with GDM	1 (2.0%)	6 (12.2%)*

Initial weight: weight at the beginning of pregnancy.
Values are median and range.
*$P < 0.05$ between NP and PPCOS.

Table 2: Metabolic characteristics of NP women during gestational weeks 10–16 and 22–28.

	Weeks 10–16 ($n = 51$)	Weeks 22–28 ($n = 51$)
Fasting		
Glucose (mg/dl)	78.0 (54.0–104.0)	74.0 (57.0–110.0)
Insulin (μIU/ml))	8.1 (3.0–59.4)	9.2 (3.9–76.8)
HOMA-IR	1.7 (0.5–11.4)	1.7 (0.5–17.2)
Cholesterol (mg/dl)	177.5 (99.0–223.0)	223.0 (155.0–447.0)*
HDL-C (mg/dl)	40.0 (19.0–59.0)	42.7 (21.1–62.7)
LDL-C (mg/dl)	119.5 (32.0–176.5)	146.6 (74.1–378.9)*
TGs (mg/dl)	94.5 (55.0–259.0)	151.0 (66.0–297.0)*
Adiponectin (μg/ml)	14.7 (6.5–29.8)	12.2 (5.8–24.5)
2 *h*		
Glucose (mg/dl)	88.5 (60.0–142.0)	98.0 (73.0–132.0)
Insulin (μIU/ml)	41.2 (4.0–194.2)	61.4 (4.0–289.3)*
ISI composite	7.0 (2.0–19.7)	6.0 (0.9–13.4)*
Glucose AUC (mg/dl/min)	89.7 (66.4–139.8)	96.0 (67.3–134.5)*
Insulin AUC (μIU/ml/min)	38.8 (7.6–167.0)	53.5 (20.5–190.0)*

Values are median and range.
*$P < 0.05$ between weeks 10–16 and 22–28.

were significantly different in the two study periods [8.9 (6.5–14.2) versus 12.3 (4.1–27.9) μg/ml; $P = 0.03$ and 6.2 (6.1–9.4) versus 10.2 (2.1–23.6) μg/ml; $P = 0.03$, respectively].

Discussion

In this study, we evaluated the adiponectin and lipid serum concentrations during early and mid-pregnancy in a group of pregnant PCOS women, compared with those in NP women. Pregnant PCOS women showed significantly lower concentrations of adiponectin and higher concentrations of TGs compared with NP women. Moreover, PPCOS women were more hyperinsulinaemic and showed a higher incidence of GDM compared with NP women. In addition, adiponectin serum concentrations were significantly lower in PPCOS women with GDM compared with PPCOS women without GDM in both study periods.

Table 3: Metabolic characteristics of PPCOS during gestational weeks 10–16 and 22–28.

	Weeks 10–16 ($n = 48$)	Weeks 22–28 ($n = 48$)
Fasting		
Glucose (mg/dl)	75.0 (50.0–106.6)	76.0 (54.0–108.0)
Insulin (μIU/ml))	13.1 (3.0–69.0)	16.8 (4.4–48.2)
HOMA-IR	2.6 (0.4–15.2)	2.8 (0.7–8.6)
Cholesterol (mg/dl)	188.0 (110.0–341.0)	219.0 (168.0–317.0)*
HDL-C (mg/dl)	39.7 (16.2–65.0)	41.6 (20.0–81.4)
LDL-C (mg/dl)	114.1 (68.4–236.0)	140.4 (94.0–220.6)*
TGs (mg/dl)	154.0 (79.0–410.0)	191.0 (81.0–353.0)*
Adiponectin (μg/ml)	12.6 (4.1–27.9)	9.4 (2.1–23.6)*
2 h		
Glucose (mg/dl)	112.7 (77.0–193.3)	108.0 (63.5–157.0)
Insulin (μIU/ml)	95.4 (7.2–317.5)	96.7 (25.0–300.0)
ISI composite	4.1 (0.9–20.8)	3.4 (1.1–11.7)
Glucose AUC (mg/dl/min)	103.1 (75.0–198.4)	108.5 (75.9–147.3)
Insulin AUC (μIU/ml/min)	79.1 (10.9–217.1)	79.7 (30.3–227.9)

Values are median and range.
*$P < 0.05$ between weeks 10–16 and 22–28.

In the present study, NP women showed an increase in TC, LDL-C and TGs between early and mid-pregnancy, which is in agreement with previous studies that demonstrate that during normal pregnancy, lipid metabolism changes significantly (Chiang *et al.*, 1995). In PCOS women, a similar dynamics in the lipid concentrations during pregnancy was observed, suggesting that the changes in lipid metabolism that occur during normal pregnancy are exacerbated in pregnant PCOS women. Moreover, TG concentrations were significantly higher in pregnant PCOS women compared with NP women in both study periods. An increase in TG occurs during late gestation due to enhanced hepatic production of VLDL TGs in a high-oestrogen milieu. There is also an increase in intestinal absorption of dietary lipid and reduced clearance of TG due to decreased extrahepatic lipoprotein lipase activity. These changes coincide with reduced insulin sensitivity, which may also contribute to the increase in TG (Chiang *et al.*, 1995; Sattar *et al.*, 1997). In our study, PCOS women showed higher concentrations of insulin compared with normal women during early and mid-pregnancy, which could explain in part the significant increase in TG concentrations observed in PCOS women in both study periods.

It has been proposed that hyperandrogenaemia plays an important role in the pathogenesis of LDL-C elevations in PCOS women (von Eckardstein *et al.*, 1996). In a previous study, we demonstrated a significant increase in androgen concentrations during pregnancy in these women (Sir-Petermann *et al.*, 2002). Therefore, a concomitant increase in serum levels of low-density lipoprotein could be expected. However, we did not observe significant differences in serum concentrations of this lipoprotein between PPCOS women and control women.

Another factor that may influence lipid metabolism during pregnancy in PCOS women is adiponectin (Catalano *et al.*, 2006). In the present study, adiponectin concentrations decreased between early and mid-gestation in pregnant PCOS women. On the other hand, in NP women, adiponectin concentrations decrease in the third trimester of pregnancy, which has been related to decreased insulin sensitivity during this period (Catalano *et al.*, 2006). In the present study, adiponectin concentrations were significantly lower in pregnant PCOS women during mid-pregnancy compared with NP women, even though the values were corrected by BMI. Therefore, according to previous reports, (Cseh *et al.*, 2004; Catalano *et al.*, 2006; Fuglsang *et al.*, 2006), a more pronounced decrease in adiponectin concentrations in PPCOS could be expected in the late third trimester. This observation is in agreement with a previous study in non-pregnant PCOS patients, who presented low adiponectin levels compared with weight-matched controls (Sieminska *et al.*, 2004). The same observation could be expected for the first study period (early pregnancy); however, adiponectin concentrations did not differ significantly between normal and pregnant PCOS women. The treatment intervention that PCOS patients received before and during the first weeks of gestation could

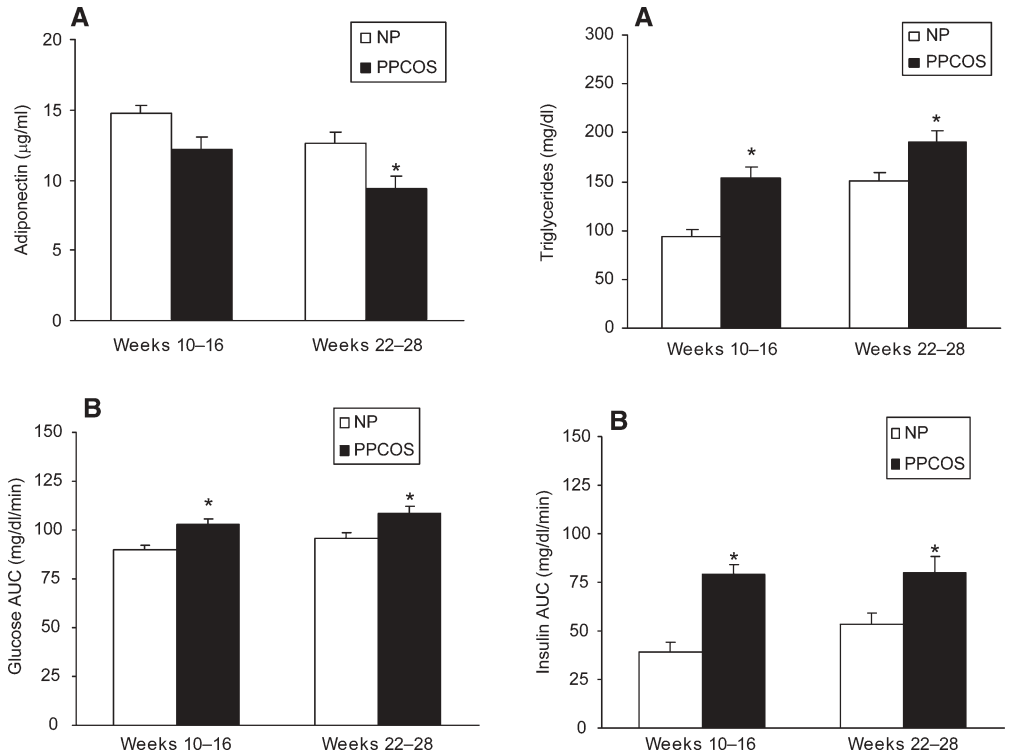

Figure 1: (**A**) Median serum concentrations of adiponectin and TGs in normal and PCOS pregnant women during gestational weeks 10–16 and 22–28. Values are medians ± SEM. *$P < 0.05$ adjusted by BMI. (**B**) AUC of glucose (glucose AUC) and of insulin (insulin AUC) in normal and PCOS pregnant women during gestational weeks 10–16 and 22–28. Values are medians ± SEM. *$P < 0.05$ adjusted by BMI

explain in part the relatively high levels of adiponectin observed in PCOS patients during early pregnancy. This assumption is based on the fact that adiponectin concentrations were lower in the same PCOS patients before they became pregnant, compared with the values observed in early pregnancy and to those obtained in a group of 20 non-pregnant normal cycling women comparable in age and BMI (data not shown). Therefore, it does not seem unreasonable to speculate that the maintenance of lifestyle modifications and metformin administration throughout pregnancy might have a beneficial effect on adiponectin concentrations, similar to that described for other endocrine and metabolic parameters (Glueck *et al.*, 2004).

In the present study, the incidence of GDM, independent of body weight, was significantly higher in pregnant PCOS women compared with NP women, which is in agreement with previous studies (Urman *et al.*, 1997; Mikola *et al.*, 2001; Bjercke *et al.*, 2002). On the other hand, adiponectin serum concentrations were significantly lower in PPCOS women with GDM compared with PPCOS women without GDM in both study periods, which is in accordance with a recent study in non-PCOS women (Tsai *et al.*, 2005). Thus, as previously proposed by Retnakaran *el al.* (2005), adiponectin may play a key role in mediating insulin resistance and beta cell dysfunction in the pathogenesis of GDM. In our study, we did not observe a relationship between TG concentrations and the risk of GDM in PPCOS as previously described (Enquobahrie, 2005).

In relation to other risk factors described for GDM such as increasing age, previous pregnancies, pre-pregnancy overweight and short stature (Di Cianni *et al.*, 2003), we did not observe differences between both groups.

Regarding other pregnancy complications, only four patients presented elevated blood pressure during pregnancy. This observation is in agreement with a previous study of our group (Sir-Petermann *et al.*, 2002) that also demonstrated that the prevalence of pregnancy-induced hypertension is lower than expected in PCOS patients. This observation is in accordance with two studies with a large series of women, which found no relationship between PCOS and pregnancy-induced hypertension compared with weight-matched controls (Haakova *et al.*, 2003; Mikola *et al.*, 2001).

In summary, the present study demonstrates a significant decrease of adiponectin and a significant increase of TG concentrations during pregnancy in PCOS women, and in comparison to NP women . We propose that in pregnant PCOS patients, low adiponectin and high insulin levels are implicated in the pathogenesis of GDM. On the other hand, high TG levels seem not to be directly involved in pregnancy complications in these patients and appear to be a reflection of the metabolic condition of pregnant PCOS women. Further studies are needed to establish if treatment with metformin throughout pregnancy is a treatment option to correct the low levels of adiponectin and counteracts the increased prevalence of GDM.

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