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Lipid profile in nonobese pregnant women with polycystic ovary syndrome: A prospective controlled clinical study

Stefano Palomba [a,*], Angela Falbo [a], Giuseppe Chiossi [a], Giovanna Muscogiuri [b], Eleonora Fornaciari [a], Francesco Orio [c], Achille Tolino [d], Annamaria Colao [b], Giovanni Battista La Sala [a,e], Fulvio Zullo [f]

[a] Obstetrics and Gynecology Unit, IRCCS – ASMN, Viale Risorgimento 80, 42123 Reggio Emilia, Italy
[b] Department of Endocrinology, University "Federico II" of Naples, Via Pansini 5, 80131 Naples, Italy
[c] Endocrinology, University "Parthenope" of Naples, Via Partenope, 80100 Naples, Italy
[d] Department of Obstetrics and Gynecology, University "Federico II" of Naples, Via Pansini 5, 80131 Naples, Italy
[e] University of Modena and Reggio Emilia, Via Università 4, 41100 Modena, Italy
[f] Department of Obstetrics and Gynecology, University "Magna Graecia" of Catanzaro, Viale Europa, 88100 Catanzaro, Italy

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ABSTRACT

Alterations in lipid pattern and increased risk for obstetric/neonatal complications have been observed in patients with polycystic ovary syndrome (PCOS). Pregnancy leads to physiologic changes in lipoprotein metabolism, and alterations in lipid profile have been related with adverse pregnancy outcomes. Based on these considerations, the aim of the present prospective controlled clinical study was to test the hypothesis that the changes in the lipid profile in patients with PCOS during pregnancy are characteristic and potentially related to the increased risk of obstetric/neonatal complications. One hundred and fifty nonobese PCOS women and 150 age- and body mass index (BMI)-matched healthy controls were enrolled. Serum lipids, glucose, insulin, and androgens levels were serially assayed in all subjects before and throughout pregnancy. Serum low-density lipoprotein (LDL) and triglyceride (TG) concentrations were significantly ($P < 0.05$) higher in PCOS group than in healthy controls at each assessment. Throughout pregnancy, serum LDL and TG levels increased significantly ($P < 0.05$) in both groups, although the change from pre-pregnancy values was significantly ($P < 0.05$) greater in PCOS patients than in healthy controls. A significant ($P < 0.05$) relationship was observed between serum LDL and TG changes and changes in both insulin sensitivity indexes and androgen levels in PCOS patients alone. After adjusting for maternal age, pre-pregnancy BMI and lipid levels, body weight gain, and insulin-resistance markers, serum TG concentrations during pregnancy were directly and independently associated with obstetric complications in both groups, whereas serum LDL levels only in PCOS patients. We can conclude that nonobese PCOS patients had specific changes in lipid profile during pregnancy, and that the lipid pattern typical of PCOS may account for the more frequent adverse pregnancy outcomes. PCOS-related hormonal and metabolic features, such as insulin resistance and high androgen levels, may mediate this phenomenon.

Abbreviations: A, androstenedione; AGA, appropriate for gestational age; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; DM, diabetes mellitus; FAI, free androgen index; GIR, glucose-to-insulin ratio; HDL, high-density lipoprotein cholesterol; HOMA, homeostasis model of assessment; HR, heart rate; IQR, interquartile range; IRMA, immunoradiometric assay; LDL, low-density lipoprotein cholesterol; LGA, large for gestational age; OGTT, oral glucose tolerance test; OR, odds ratio; PCOS, polycystic ovary syndrome; PE, preeclampsia; PIH, pregnancy-induced hypertension; RIA, radioimmunoassay; SBP, systolic blood pressure; SGA, small for gestational age; SHBG, sex-hormone binding globulin; T, testosterone; TC, total cholesterol; TG, triglycerides; VDRL, very low-density lipoprotein; WHR, waist-to-hip ratio; Δ, change from pre-study value; aΔ, absolute change from pre-study value; %Δ, percent change from pre-study value.

* Corresponding author. Address: Obstetrics and Gynecology Unit, IRCCS, Arcispedale "Santa Maria Nuova", Viale Risorgimento 80, 42123 Reggio Emilia, Italy. Tel.: +39 3475880503.
E-mail addresses: stefanopalomba@tin.it, stefano.palomba@asmn.re.it (S. Palomba).

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1. Introduction

Polycystic ovary syndrome (PCOS) may determine substantial long-term metabolic sequelae such as diabetes and dyslipidemia [1]. In fact, women with PCOS cluster risk factors for cardiovascular diseases (CVD) [2]. In particular, lower concentrations of high-density lipoprotein cholesterol (HDL) and higher levels of low-density lipoprotein cholesterol (LDL) and triglycerides (TG), regardless body weight or ethnicity, have been observed [2]. This common atherogenic pattern seems to be linked to insulin-resistance and androgen excess [1,2].

Many metabolic changes occur physiologically in normal pregnancy. Specifically, visceral fat accumulation and hyperlipidemia are the two main changes in lipid metabolism associated with gestation, reflecting a response of maternal metabolic adaptation to support fetal growth [3]. However, lipid dysregulation in pregnancy seems to be associated with pregnancy complications and adverse neonatal outcomes [4–9]. Similarly, hyperinsulinemia and insulin resistance ensure constant metabolic supply to the growing fetus, although the switch to maternal hyperglycemia, sometimes observed in late pregnancy, is associated with increased risks of adverse pregnancy outcomes [10].

Several and consolidated data [11–14] have designated PCOS as a risk factor for increased incidence of adverse obstetric/neonatal outcomes. The risks for gestational diabetes mellitus (DM), pre-eclampsia (PE), pregnancy-induced hypertension (PIH), admission to neonatal intensive care units, and perinatal mortality are higher in the PCOS population [11–14].

On the basis of these considerations, we conducted a prospective controlled clinical study to test the hypothesis that the changes in the lipid profile in patients with PCOS during pregnancy are characteristic and potentially related to an increased risk of pregnancy complications.

2. Experimental

The study was approved by the Institutional Review Board of the Academic Department of Obstetrics and Gynecology of the Pugliese-Ciaccio Hospital, Catanzaro, Italy. Between February 2003 and April 2012, primigravidas with PCOS and healthy controls at less than 7 weeks' gestation were approached for informed consent.

PCOS was diagnosed before pregnancy and confirmed at study entry according to the Rotterdam criteria [15] in a pre-study phase. Similarly, controls were also screened before pregnancy for all PCOS features, i.e. irregular menstrual cycles, clinical hyperandrogenism, abnormal serum androgen levels, and polycystic ovary morphology (PCO) on transvaginal ultrasound, and were matched one-to-one with PCOS subjects according to age and body mass index (BMI). During this pre-study phase, complete hormonal and metabolic patterns, such as inflammatory markers, were assayed in each subject.

Exclusion criteria were: age over 35 years, BMI higher than 30 kg/m^2 [16], pre-malignancies or malignancies, major medical illnesses (including cardiovascular disease, preexistent diabetes, and so on), hematological disease (including anemia, thalassemia, and so on), cigarette smoking, drug or alcohol use, use of any metabolic and/or hormonal and/or other lipid altering drugs at the time of enrollment and/or in the preceding three months (only gonadotropins or clomiphene citrate treatments for ovulation induction were permitted), multiple pregnancy, and non compliance to the study protocol.

At study entry, all women received 0.4 mg daily folic acid and were counseled about diet and physical activity. Oral iron supplements were given in case of anemia.

Serial clinical, biochemical, and ultrasonographic assessments for mother and/or fetal wellbeing monitoring were performed during the pregnancy as previously described [17].

Clinical visits were performed at the pre-study evaluation, at study entry (within the 7th week of gestation), every two weeks in the first trimester, and then every four weeks until delivery. They consisted of pelvic examination, vital signs assessment (systolic [SBP] and diastolic [DBP] blood pressure, and heart rate [HR]), and anthropometric measurements (height, weight, BMI, and waist-to-hip ratio [WHR]) recording.

Each subject underwent serial drawn blood samples at the pre-study visit, at study entry, and at the 12th, 20th, and 32nd week of gestation [18]. All blood samples were obtained between 08:00 h and 09:00 h a.m. after at least an 8-h overnight fasting and bed rest, assayed in duplicate and immediately centrifuged; the serum was then store at −80 °C until analysis.

A complete hormonal and metabolic pattern was only determined at the pre-study assessment and at study entry, whereas androgens (total serum testosterone [T], androstenedione [A], dehydroepiandrosterone sulfate [DHEAS], and sex-hormone binding globulin [SHBG]), insulin-sensitivity markers (homeostasis model of assessment [HOMA] and fasting glucose-to-insulin ratio [GIR]), and lipids (serum total cholesterol [TC], HDL, and TG) were serially assayed [18,19].

Glucose and insulin concentrations were assessed fasting (at the pre-study evaluation, at study entry, and serially during gestation) and after a 75 g oral glucose tolerance test (OGTT, at the pre-study evaluation and at 26th week of gestation to screen for gestational DM). According to the trapezoidal method, glucose and insulin responses were calculated as area under the curve (AUCglucose and AUCinsulin, respectively); the AUCglucose/AUCinsulin ratio was also obtained for each subject.

All plasma hormone concentrations were measured by specific radioimmunoassay (RIA), whereas SHBG levels were determined using an immunoradiometric assay (IRMA) [19]. Serum glucose was measured by the glucose oxidase method, whereas insulin was measured by a solid-phase chemiluminescent enzyme immunoassay using commercially available kits [19]. Overall, intra- and inter-assay coefficients of variation (CV) were less than 10% [19].

HOMA (fasting glucose [mmol/L] × fasting insulin [μU/mL]/22.5) [20], GIR (mg/10–4U) [21], and FAI (T [nmol/l]/SHBG × 100) [22] were also calculated in each subject.

Serum TC, HDL, and TG levels were measured with an auto-analyzer using commercially available kits. Intra-assay CV for TC, HDL, and TG were 1.1%, 1.9%, and 1.7%, respectively. Inter-assay for TC, HDL, and TG were 1.4%, 4.0%, and 2.2%, respectively. Serum LDL was calculated using Friedewald's formula [23].

Obstetric/neonatal outcomes were recorded for each participant. In particular, miscarriage, gestational DM [24], PIH [25], PE [26], antepartum hemorrhage [26], gestational age at delivery (including pre-term, at term, and post-term delivery), type of delivery (instrumental, including forceps and/or vacuum extraction, or Caesarean section), fetal growth (evaluated by serial ultrasonographic assessments and classifying the fetus as appropriate for gestational age [AGA], small for gestational age [SGA], and large for gestational age [LGA], according to reference standards), birth weight, Apgar score, fetal malformations, and intrauterine deaths were recorded.

2.1. Statistical analysis

Data were analyzed according to the intention-to-treat principle, i.e., data of all subjects seen at least once were included in the final analysis. In patients lost to follow-up, the last biochemical assay and obstetric evaluation were considered for analysis.