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ARTICLE

Early trophoblast invasion and placentation in women with different PCOS phenotypes

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Abstract This study evaluated the impact of different phenotypes of polycystic ovary syndrome (PCOS) on early trophoblast invasion and placentation. Pregnant patients with different PCOS phenotypes and healthy pregnant women, matched for age and body mass index, were enrolled. Histological analysis of trophoblastic and decidual tissue and macroscopic and microscopic assessment of the placentas were performed. Implantation-site vessels with endovascular trophoblast differed significantly among PCOS phenotypes. Placental weight, thickness, density and fetal–placental weight ratio were significantly different in the full-blown and non-polycystic ovary (PCO) phenotypes versus the ovulatory and non-hyperandrogenic phenotypes. The incidence of macroscopic placental lesions was only significantly different between controls and the full-blown and non-PCO phenotypes. The overall incidence of microscopic placental lesions was significantly different among PCOS phenotypes and was significantly higher in the full-blown and non-PCO phenotypes than in the ovulatory and non-hyperandrogenic phenotypes. The rates of chorionic villitis and intervillositis were significantly higher in full-blown and non-PCO phenotypes than in ovulatory and non-hyperandrogenic phenotypes. In conclusion, alterations in early trophoblast invasion and placentation observed in PCOS vary widely according to phenotype.

KEYWORDS: insulin resistance, PCOS, phenotypes, placentation, pregnancy, trophoblast invasion

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Introduction

The Rotterdam criteria for diagnosing polycystic ovary syndrome (PCOS), which was proposed to standardize the working definition of the syndrome, introduced four main phenotypes of the disease (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). In addition, new research seems to clarify that insulin-resistance and metabolic aberrations are not absolute prerequisites of the syndrome and vary significantly among phenotypes and among subjects with the same phenotype (Diamanti-Kandarakis and Dunaif, 2012).

A recent meta-analysis (Kjerulff et al., 2011) demonstrated that the syndrome is also related to a high incidence of obstetric and neonatal complications, which is significantly greater when compared with non-PCOS controls. Moreover, several biases due to the heterogeneity of studied populations were described (Kjerulff et al., 2011). Therefore, in a well-defined population of pregnant patients with PCOS, the risk for adverse obstetric/neonatal outcomes varies according to phenotype and features. Specifically, patients with full-blown and non-polycystic ovary (PCO) phenotypes are at higher risk for adverse outcomes than those with the non-hyperandrogenic and ovulatory phenotypes (Palomba et al., 2010a).

The spectrum of pregnancy complications associated with PCOS has been related to impaired decidual trophoblast invasion and defects in placentation (Palomba et al., 2012, 2013). In fact, these studies demonstrated alterations in the endovascular trophoblast invasion (Palomba et al., 2012) and in the macroscopic and microscopic structure of the placenta (Palomba et al., 2013) in women with PCOS who were studied at 12 weeks' gestation and at term, respectively.

Based on these data, the aim of the present study was to test the hypothesis that the alterations in early trophoblast invasion and placentation detected in PCOS patients vary according to PCOS phenotype.

Materials and methods

The procedures used in this study were carried out in accordance with the Declaration of Helsinki's principles for conducting experiments on human subjects. The study was approved by the Institutional Review Board of the Department of Obstetrics and Gynecology, University 'Magna Graecia' of Catanzaro, Italy (reference no. UMG 10/2008, approved 10 October 2008).

The experimental study protocol followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (http://www.strobe-statement.org/).

Subjects

Subjects were enrolled between September 2008 and May 2012. Some of the included participants had already been enrolled in two previous experimental protocols (Palomba et al., 2012, 2013). The sample size was significantly increased by approximately 50% in about a year and a half extension of the period of enrolment, in order to obtain a population homogeneous for all phenotypes, including the rarest.

Pregnant patients with PCOS, who were diagnosed before pregnancy according to the criteria specified by the European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), were consecutively screened and enrolled as cases. In summary, outpatients who were on a waiting list for infertility treatment and who were treated with behavioural therapies (diet and physical activity) and with periodic induction of progesterone withdrawal bleeding were examined. Those who met the inclusion/exclusion criteria were enrolled.

PCOS patients were enrolled according to phenotype to obtain groups of 15 subjects for each phenotype in both study protocols: (i) patients with hyperandrogenism, oligoanovulation and PCO (full-blown PCOS); (ii) patients with hyperandrogenism and oligoanovulation but without the appearances of PCO on ultrasound (non-PCO PCOS); (iii) patients with hyperandrogenism and PCO (ovulatory PCOS); and (iv) patients with oligoanovulation and PCO (non-hyperandrogenic PCOS).

Healthy pregnant women without PCOS, matched with the cases for age and body mass index (BMI), were enrolled as controls. The matching procedure was one-to-one for each phenotype, and patients were defined as age- and BMI-matched when the differences between them were less than 2 years and 1 kg/m^2 for age and BMI, respectively. At study entry, all controls had had regular menstrual cycles before pregnancy, had no signs of clinical hyperandrogenism, had normal range of serum androgen concentration and had no PCO morphology on transvaginal ultrasound.

For cases and controls, the baseline clinical and biochemical data for the screening process and for inclusion/exclusion in the study protocol were obtained before week 7 of gestation. Gestational age was calculated from the last menstrual period and confirmed by measurement of the fetal crown–rump length using first-trimester ultrasound.

The exclusion criteria for all subjects were as follows: age <18 years or >35 years, BMI higher than 30 kg/m^2, multiple pregnancies, premalignancies or malignancies, any major medical condition or other concurrent major medical illnesses, cigarette smoking, drug/alcohol abuse, uterine malformations, high altitude residents, women noncompliant with the study protocol, current or previous use of any hormonal and/or antidiabetic drugs, pregnancy achieved with the use of assisted reproduction techniques, including natural cycle and with in-vitro matured oocytes and/or any genetic/familial relationship among enrolled subjects.

Protocols

At study entry, each subject underwent a clinical evaluation and an ultrasonographic assessment. In addition, a venous blood sample was taken for biochemical analysis (Palomba et al., 2012, 2013). Clinical assessments consisted of anthropometric measurements, Ferriman-Gallwey score calculation and heart rate and blood pressure assessments. A venous blood sample was drawn to assess hormonal and glucose metabolism patterns, blood count and liver and renal