Cytokine 91 (2017) 180–186

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

# Follicular fluid cytokine composition and oocyte quality of polycystic ovary syndrome patients with metabolic syndrome undergoing in vitro fertilization

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ARTICLE INFO

*Article history:*
Received 20 July 2016
Received in revised form 22 December 2016
Accepted 22 December 2016

*Keywords:*
Follicular fluid
Oocyte
Cytokine
PCOS
Metabolic syndrome

ABSTRACT

*Purpose:* To provide insights into the correlation among lipid metabolism, cytokine profiles in the follicular fluid (FF) and embryo quality of women with Polycystic Ovary Syndrome (PCOS) with metabolic syndrome (MS).

*Methods:* Ninety women undergoing in vitro fertilization (IVF) treatment were recruited, including 60 PCOS patients (PCOS non MS and PCOS MS) and 30 age-matched controls. Individual FF samples were analyzed using the cytometric multiplex immunoassay.

*Results:* In the FF, the PCOS MS group was associated with higher, total cholesterol (TC), triglyceride (TG) and lower high-density lipoprotein (HDL) concentrations compared with that in the control group ($P < 0.05$). The FF tumor necrosis factor-α (TNF-α) level in the PCOS MS group was 3.89 ± 1.18 ng/mL, which was significantly higher compared with the control (2.94 ± 1.02 ng/mL) and PCOS non-MS groups (3.05 ± 1.21 ng/mL) ($P = 0.002$), while the granulocyte colony-stimulating factor (G-CSF) level in the PCOS MS group (4.18 ± 1.33 ng/mL) was lower compared with the control (5.61 ± 1.82 ng/mL) and PCOS non-MS groups (5.32 ± 1.91 ng/mL) ($P = 0.004$). The FF G-CSF showed a trend toward negative relationship with TG and TC; TNF-α concentration was positively associated with TG. The percentage of top-quality embryo decreased in the PCOS MS group than in the other two groups (20% vs. 38.4% and 34.6%).

*Conclusions:* In conclusion, there was an elevated lipolysis condition within the FF of PCOS MS patients and the TNF-α and G-CSF levels in FF were associated with top-quality embryo percentage. TNF-α and G-CSF may be the key cytokines involved in the mechanism of decreased embryo development potential in PCOS MS patients.

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## 1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, with a prevalence of 5–10% [1]. Its common clinical manifestations include hyperandrogenism, oligomenorrhea, chronic anovulation, and hyperinsulinemia. As insulin resistance is one of the pathophysiological bases of metabolic syndrome (MS), patients with PCOS and high levels of plasmatic insulin have a substantial risk of developing metabolic and cardiovascular complications such as obesity, glucose intolerance and type 2 diabetes, dyslipidemia, and coronary heart disease. A higher frequency of MS has been reported in women with PCOS compared with that in the normal women [1,2].

The quality of oocyte and embryo tend to be lower and pregnancy outcomes inclined to be poorer in PCOS patients during assisted conception, which may be linked to metabolism-induced changes in the oocyte through the microenvironment of follicular fluid (FF). Actually, metabolic disorders, such as obesity and type II diabetes, as well as a negative energy balance, are associated with upregulated lipolysis, leading to abnormal metabolic indications in the serum [3]. These changes are reflected in the FF of the dominant follicle [4,5] and could, therefore, directly affect the oocyte quality and metabolism. Oocytes from diabetic, insulin-resistant, and obese mice show delayed maturation, smaller size, and increased granulosa cell apoptosis [6,7]. These findings are linked to adverse embryonic and fetal outcomes, including delayed embryonic development, growth restriction, anatomical defects, and smaller fetuses [8,9].

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http://dx.doi.org/10.1016/j.cyto.2016.12.020
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However, evidence suggests that PCOS is associated with a proinflammatory state or a state of elevated sensitivity of inflammatory cells to cytokines and chemokine, with obesity and especially central adiposity being the most aggravating factors. Cytokines are essential for ovarian function modulating the secretion of ovarian steroid hormones, having an essential function in embryonic development and implantation, and promoting cellular differentiation, vascularization, and finally trophoblast invasion of the endometrium [10,11]. Cytokine profiles within the FF also vary depending on the reproductive pathology or the cause of infertility [12]. Leukocytes, together with granulosa cells, may contribute to the pathogenesis of PCOS through their ability to secrete an array of cytokines implicated in the follicle growth. Recent studies have indicated the presence of cytokines in the FF and have correlated these with oocyte quality, embryo development potential, and outcomes of assisted reproduction technology. Gallinelli et al. [13] reported that FF from PCOS patients undergoing in vitro fertilization (IVF) has elevated interleukin-6 (IL-6), interleukin-13 (IL-13), tumor necrosis factor-$\alpha$ (TNF-$\alpha$); activated T-lymphocyte numbers; and reduced interleukin-12 (IL-12) concentrations compared with non-PCOS patients. No previous study has correlated the presence of cytokine profile and lipid metabolism within the FF of PCOS with MS patients.

This study hypothesized that abnormal lipid metabolism in PCOS patients may be related to low-grade chronic inflammation condition within the FF, which is reflected by cytokine profile characteristics in the FF. Therefore, this study aimed (1) to provide insights into the correlation between lipid metabolism and cytokine profile characteristics in the FF of women with PCOS complicated with MS undergoing in vitro fertilization (IVF) and (2) to examine the relationship between cytokine concentration in the FF and embryo quality of PCOS patients. This study provided a novel detailed description of lipid metabolism and cytokine profiles in the FF of PCOS patients with and without MS.

## 2. Material and methods

### 2.1. Patients

This study included 90 women who were undergoing their first cycle of IVF or intracytoplasmic sperm injection (ICSI) during May 2014 to March 2015 in the Reproductive Medical Center of Ruijin Hospital affiliated with the Shanghai Jiaotong University, Shanghai, People's Republic of China. Written informed consent was obtained from all subjects before participation, and the human ethics committee of the Ruijin Hospital approved the protocol. All patients received the regular gonadotropin-releasing hormone antagonist protocol for ovarian stimulation to obtain multiple oocytes as described by Niu et al. [14]. Patients were divided into three groups: control group, PCOS without MS (PCOS non-MS) group, and PCOS with MS (PCOS MS) group. The height (m) and weight (kg) of the patients were used to calculate the body mass index (BMI) score (kg/m$^2$). Control patients were women seeking treatment for male factor or tubal infertility but who had normal BMI and endocrine profiles. Patients who fulfilled two of the three criteria defined in the 2003 Rotterdam consensus definition for PCOS [15,16] were categorized as PCOS. For diagnosing MS, the criteria proposed by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) and adapted for PCOS patients by the Rotterdam ESHRE/ASRM–Sponsored PCOS Consensus Workshop [17] were used. The criteria used are listed as follows:

– Waist circumference >88 cm
– Fasting glucose $\geqslant$110 mg/dL
– Glucose 2 h after overload $\geqslant$140 mg/dL (oral glucose tolerance test)
– Fasting triglyceride (TG) $\geqslant$150 mg/dL
– High-density lipoprotein (HDL) cholesterol <50 mg/dL
– Blood pressure $\geqslant$130/85 mmHg

Patients in the PCOS MS group were required to fulfill at least three of the mentioned criteria.

### 2.2. Blood and FF sample collection

Baseline blood samples were collected on day 3 of the menstrual cycle in the control group and 3 days after a spontaneous bleeding episode in patients with PCOS. In women with PCOS who did not have a spontaneous bleeding episode for 90 days, 60 mg progesterone was administered to induce a bleeding episode, and blood samples were collected afterward. On the day of human chorionic gonadotropin (HCG) trigger and oocyte retrieval, blood samples were collected at 8 am.

For each patient, the FF of the largest and first-punctured follicle was recovered during the oocyte retrieval procedure by means of a transvaginal follicular aspiration. Patients with only a blood-free aspirate of a follicle with diameter $\geqslant$18 mm were considered for inclusion into the study. The FF samples were cooled immediately after aspiration and were transported on ice within 2 h of collection. At the laboratory, whole blood and FF samples were centrifuged at 2000 rpm at 4 °C for 10 min to isolate plasma from whole blood and remove cell debris from the FF samples. All samples were frozen at −80 °C within 1 h of retrieval until further analysis.

### 2.3. Laboratory analysis

Serum sex hormones including follicle stimulation hormone (FSH), luteinizing hormone (LH), estradiol (E2), and progesterone (P) were analyzed using commercially available kits from the Unicel DXI 800 Access Immunoassay System (Beckman Coulter, USA). The inter- and intra-assay coefficients of variation were all <10%. The concentrations of lipoproteins in serum and FF, including total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL), were measured using the Unicel DXC 800 Synchron (Beckman Coulter).

### 2.4. Multiplex immunoassay

Individual FF samples were analyzed using the cytometric multiplex immunoassay (Bio-Rad Laboratories) run on a Luminex 100 cytometer equipped with the Bio-Plex Manager Software 4.0 (Bio-Rad Laboratories). Key soluble cytokines in the follicle growth were identified as candidate mediators for inclusion in the assay. The panel included interleukin-1b (IL-1b), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-17 (IL-17), interleukin-18 (IL-18), tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interferon-$\gamma$ (IFN-$\gamma$), granulocyte colony-stimulating factor (G-CSF), monocyte chemotactic protein-1 (MCP-1), and regulated on activation normal T-cell expressed and secreted (RANTES). Assays were performed as described in a previous study [18]. Samples were diluted 1:10 with sample diluent supplied in the Bio-Plex kit prior to analysis. Follicular aspiration frequently results in blood contamination because of the intraovarian vasculature disruption in the retrieved FF. Furthermore, the priming of needle and tubing with normal saline solution at the commencement of aspiration remained a potential for FF dilution. Blood contamination was corrected by measuring the von Willebrand factor (vWF; an enzyme-linked immunosorbent assay, ELISA; R&D Systems) in FF samples. Because vWF is a large plasma multimeric

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