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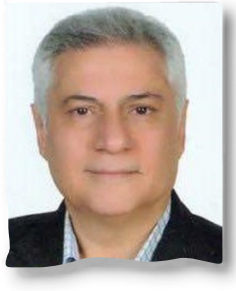
Distinct changes in the proteome profile of endometrial tissues in polycystic ovary syndrome compared with healthy fertile women

Fatemehsadat Amjadi [a], ***Mehdi Mehdizadeh*** [b,*,1], ***Mahnaz Ashrafi*** [c], ***Davood Nasrabadi*** [d], ***Sara Taleahmad*** [d], ***Mehdi Mirzaei*** [e], ***Vivek Gupta*** [f], ***Ghasem Hosseini Salekdeh*** [d,g], ***Reza Aflatoonian*** [h,*,1]

[a] *Department of Anatomy, School of Medicine, Iran University of Medical Science, Tehran, Iran*
[b] *Cellular and Molecular Research Center, Faculty of Advanced Technologies, Department of Anatomical Sciences , Iran University of Medical Sciences, Tehran, Iran*
[c] *Obstetrics and Gynecology Department, School of Medicine, Iran University of Medical Science, Tehran, Iran*
[d] *Department of Molecular Systems Biology, Cell Science Research Centre, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran*
[e] *Department of Chemistry and Biomolecular Sciences, Macquarie University, North Ryde, NSW, Australia*
[f] *Faculty of Medicine and Health Sciences, Macquarie University, North Ryde, NSW, Australia*
[g] *Department of Systems Biology, Agricultural Biotechnology Research Institute of Iran, Karaj, Iran*
[h] *Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Centre, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran*



Mehdi Mehdizadeh has a PhD in anatomy from Iran University of Medical Sciences and is a member of the Cellular and Molecular Research Center. He has worked as a Fellow at the German Research Center for Biotechnology in Transgenic Animals.

KEY MESSAGE

Differences were found between the proteomic profiles of endometria obtained from PCOS and healthy fertile women. The identified proteins were mostly involved in apoptosis, oxidative stress, the cytoskeleton and inflammation. They could be potential targets for drug discovery, to enhance the probability of implantation in this common disorder.

A B S T R A C T

Research question: What is the molecular basis of infertility related to uterine dysfunction in women with polycystic ovary syndrome (PCOS)?
Design: In this study, differences in protein expression between PCOS and normal endometrium were identified using a proteomic approach based on two-dimensional electrophoresis (2-DE) coupled with mass spectrometry (MS). The proteome of endometrium were analysed during the proliferative

* Corresponding authors.
E-mail address: mehdizadeh.m@iums.ac.ir (M Mehdizadeh); r.aflatoonian@gmail.com (R Aflatoonian).
[1] These authors contributed equally to this work.
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(on day 2 or 3 before ovulation, *n* = 6) and luteal phases (on day 3–5 after ovulation, *n* = 6) from healthy women and PCOS patients (12–14 days after spontaneous bleeding, *n* = 12). The differentially expressed proteins were categorized based on the biological process using the DAVID bioinformatics resources.

Results: Over 803 reproducible protein spots were detected on gels, and 150 protein spots showed different intensities between PCOS and normal women during the proliferative and luteal phases. MS analysis detected 70 proteins out of 150 spots. For four of the 70 proteins, 14-3-3 protein, annexin A5, SERPINA1 and cathepsin D, 2-DE results were validated and localized by Western blot and immunohistochemistry, respectively, and their gene expression profiles were confirmed by real-time quantitative PCR. The obtained results corresponded to the proteomic analysis. The differentially expressed proteins identified are known to be involved in apoptosis, oxidative stress, inflammation and the cytoskeleton.

Conclusions: The processes related to the differentially expressed proteins play important roles in fecundity and fecundability. The present study may reveal the cause of various endometrial aberrations as a limiting factor for achieving pregnancy in PCOS women.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a prevalence of 6–15% worldwide (Gao et al., 2013; Yildiz et al., 2012). The pathogenesis of PCOS is complex and its aetiology remains unknown. Patients with PCOS are often infertile, mainly due to ovulation failure (Matsuzaki et al., 2017). Although anovulation can be treated, pregnancy rates are still low and spontaneous miscarriages occur at a higher rate in affected women (Chakraborty et al., 2013; Yan et al., 2012). Growing evidence suggests that a disorder of endometrial receptivity may contribute to the adverse reproductive outcomes in PCOS (Lopes et al., 2011; Yan et al., 2012). Endometrial receptivity is dependent on regulation of protein networks which are essential for coordinated cross-talk with the implanting embryo. Any alteration in these networks causes implantation failure and infertility (Singh et al., 2011). The main interest in identifying any possible endometrial defect has stemmed from poor pregnancy outcomes and implantation failures despite the transfer of top-quality embryos in a significant percentage of PCOS cases who opt for assisted reproductive technologies (Lopes et al., 2011). The exact mechanism underlying implantation failure is still poorly understood, particularly among patients suffering from PCOS.

A genomic study has reported differential gene expression in the endometrium of PCOS patients compared with normal women during the implantation window (Qiao et al., 2008). Considering the hypothesis that genetic changes do not always mirror translated proteins and biological function due to post-translational events or protein–protein interactions, ongoing research has increasingly focused on proteomic analyses (Salamonsen et al., 2013).

In recent years, proteomics approaches have been applied to identify potential molecules involved in the pathophysiology of PCOS (Insenser et al., 2013). To date, there have not been any studies carried out on the endometrial proteome in PCOS patients.

With the aim of exploring the molecular basis of infertility related to uterine dysfunction in PCOS, this study compared the endometrial proteomic profile of PCOS patients with that of healthy fertile women using 2-DE followed by matrix-assisted laser desorption/ionization tandem time-of-flight (MALDI-TOF/TOF) mass spectrometry. The proteome of the proliferative versus the luteal endometrial tissue in healthy fertile women was also compared.

Materials and methods

Patient selection and sample collection

This project was approved by the Local Ethics Committee (reference number: 19950, approval date: 7 July, 2012), and has been conducted according to the principles expressed in the Declaration of Helsinki. Written informed consents were obtained prior to the collection of tissue samples from the participants. Human endometrial samples were obtained from 12 PCOS patients with irregular menstruation in the proliferative phase (12–14 days after spontaneous bleeding), 12 healthy fertile women in the proliferative phase (on days 2 or 3 before ovulation, *n* = 6) and the luteal phase (on days 3–5 after ovulation, *n* = 6). Healthy fertile women had at least one child and regular menstrual cycles. They were also screened for endocrine normality with serum determinations of FSH, LH and oestradiol on day 3 of the menstrual cycle. Histological examination, timing of the LH surge and ultrasonography ensured that samples were taken during the proliferative and luteal phases. Daily urinary LH levels were monitored using an ovulation prediction kit (Assure Ovulation Predictor; Conception Technologies, San Diego, CA, USA). The mean age of the women taking part in this study was 26 ± 3.87 years (range 18–35). No participants showed any evidence of pathological uterine disorder or endometrial hyperplasia. None had used oral contraception, an intrauterine device or hormonal therapy during the previous 3 months. Patients with chronic oligo/anovulation (cycle length >35 days and <6 months), clinical and biochemical signs of hyperandrogenism, or polycystic ovaries were diagnosed as PCOS in the current investigation (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The main demographic characteristics (age and body mass index [BMI]) of the patient and control groups are summarized in **Table 1**; the PCOS and control groups did not differ regarding age and BMI but did differ regarding LH/FSH ratio and testosterone. Endometrial biopsies were taken at 12–14 days after spontaneous bleeding using pipelle catheters (Pipelle®; Laboratoire CCD, France). Each biopsy was divided into two pieces; one portion was dry frozen at –80°C for RNA and protein extraction, another portion was fixed in formalin to perform histological dating.

Protein extraction

Briefly, endometrial tissue samples were homogenized in 1 ml of TRIzol (Sigma-Aldrich, Poole, UK) using an ULTRA-TURRAX® homogenizer

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