CellPress

Review

Oocyte Competence in Women with Polycystic Ovary Syndrome

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age and affects fertility and pregnancy in cases of oligoanovulation. Ovulation induction is often used to treat anovulatory patients with PCOS, but many of these women fail to conceive and resort to assisted reproductive technologies. Alterations in oocyte competence (OC) are considered potential causative factors for subfertility in women with PCOS. In this review we present and critically assess all recent clinical and experimental data regarding OC in women with PCOS. Our analysis demonstrates that the contribution of OC to reproductive potential in women with PCOS varies and largely depends on the PCOS phenotype and comorbidities associated with PCOS.

Introduction

PCOS is a common endocrine disorder in women of reproductive age, with a prevalence of 6–25% according to different diagnostic criteria [1]. Currently, the diagnostic criteria established by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) Consensus Workshop Group are widely accepted and used to diagnose PCOS [2]. After excluding disorders that mimic the PCOS phenotype (Table 1), the presence of two of the following three features is required for PCOS diagnosis: **oligoanovulatory ovarian dysfunction (OAD)** (see Glossary), **polycystic ovarian morphology (PCOM)**, and/or clinical or biochemical **hyperandrogenism (HA)** [2]. Given the possible combinations, four different PCOS phenotypes have been identified (Table 1).

Although international guidelines suggest that PCOS is a risk factor for infertility only in the presence of OAD [3] and recommend *in vitro* fertilization (IVF) as a last resort [4], a high proportion of women with PCOS fail to conceive after ovulation induction and require hospitalization for infertility and IVF treatments eight and ten times more frequently than women without PCOS, respectively [5]. Thus, other factors such as endometrial competence [6] and **OC** [7] may play a role in reducing the reproductive potential of PCOS women independently of OAD.

In reproductive medicine the terms OC and **oocyte quality (OQ)** are often used interchangeably. Moreover, while the concept of competence is associated with the ability of oocytes to perform reproductive functions, OQ is defined based on the morphology of the oocyte and its annexed structures [8] and is considered a proxy for OC [9]. Thus, a good-quality oocyte may be competent in the absence of morphological abnormalities [8]. In this regard, OC/OQ could be supported or hampered by molecular changes governing the extra- and/or intraovarian environments affecting cumulus/corona mass–oocyte interaction, oocyte maturation, and embryonic development [7,8].

Trends

No clear evidence is available regarding the impact of polycystic ovary syndrome (PCOS) and PCOS phenotypes on oocyte competence (OC).

Although oligoanovulatory ovarian dysfunction (OAD) is generally considered the only feature associated with subfertility in PCOS, many women with the syndrome are infertile, notwithstanding spontaneous or induced ovulations, and require screening for infertility and *in vitro* fertilization (IVF) treatments.

An altered OC could be a subclinical factor in infertility in PCOS, although at present no morphological, biochemical, or omics tool can be considered the gold standard for the assessment of OC and/or oocyte quality (OQ).

Specific features of PCOS [OAD, polycystic ovarian morphology (PCOM), and/or hyperandrogenism (HA)] and/or associated morbidities [obesity, hyperinsulinemic insulin resistance (HIR), low-grade chronic inflammation, etc.] vary widely among women with PCOS and can influence OC independently or in combination.

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 http://dx.doi.org/10.1016/j.tem.2016.11.008

Table 1. Criteria for Diagnosis of PCOS and Resulting PCOS Phenotypes [2]

PCOS features	PCOS phenotype
HA, OAD, and PCOM	Phenotype A or complete phenotype
HA and OAD without PCOM	Phenotype B or non-PCOM phenotype
HA and PCOM with ovulatory cycles	Phenotype C or ovulatory PCOS phenotype
OAD and PCOM without HA	Phenotype D or normoandrogenic PCOS
Pathologies to be excluded for PCOS diagnosis	
Nonclassical adrenal hyperplasia	
Cushing's syndrome	
HA due to androgen-producing tumors or drug-induced androgen excess	
OAD due to thyroid dysfunction and/or hyperprolactinemia	

Although the oocyte might be considered a biological system on which the effects of clinical and metabolic alterations characterizing women with PCOS converge, the study of OQ/OC in PCOS is extremely difficult due to the syndrome's heterogeneous presentation. This heterogeneity is related to the different features of each specific phenotype (Table 1) and the various metabolic conditions (hereafter called 'associated morbidities') such as **obesity**, **hyperinsulinemic insulin resistance (HIR)**, and low-grade chronic inflammation that are frequently present in women with PCOS. These comorbidities, alone or combined, vary in incidence and severity across PCOS phenotypes, increasing not only PCOS severity [1] but also the reproductive potential of women with PCOS [10].

To date, the causative role of OC/OQ in women with PCOS remains controversial and the literature provides only limited studies without precise conclusions [7,11]. Based on these issues, this review examines the clinical and experimental data regarding the relationship between OC/OQ and PCOS in humans, with specific consideration of PCOS phenotypes, individual features, and PCOS-associated morbidities to clarify the reproductive potential of oocytes in women with PCOS and to determine whether oocyte abnormalities contribute to PCOS-related subfertility.

Pathophysiology of PCOS as a Rationale for Impaired OC

Neuroendocrine Alterations

In PCOS alterations in luteinizing hormone (LH), follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), insulin-like growth factor (IGF), and androgen conversion enzymes are well documented pathogenic mechanisms [12,13]. They can result in the failure of selection of the dominant follicle and ovulation as well as in an abnormal ovarian microenvironment that may alter OC. Specifically, HA impairs the feedback of ovarian steroids to the hypothalamic–pituitary–ovarian (HPO) axis [14], causing persistent increases in gonadotropin-releasing hormone (GnRH) pulse frequency, hypersecretion of LH over FSH and an increased LH/FSH ratio [15], and premature granulosa cell (GC) luteinization and abnormal oocyte maturation [16]. Consequently, these events lead to abnormal folliculogenesis and premature arrest of activated primary follicles [17]. In the latter, premature luteinization of surrounding GCs hampers them from undergoing physiological atresia. HA mediates these LH hypersecretion-induced events [18], which may impair OC indirectly, causing premature oocyte maturation, or directly, activating proapoptotic signaling pathways in oocytes [7].

Follicular FSH resistance is exacerbated by high levels of AMH secreted by GCs from the growing FSH-dependent follicles irrespective of the androgen and/or metabolic status of women with PCOS [13,19]. Specifically, a high level of AMH inhibits FSH-dependent aromatase activity

Glossary

Body mass index (BMI): calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).
Hyperandrogenism (HA): a condition characterized by excessive secretion of androgens by the adrenal cortex, ovaries, or testes (hyperandrogenemia). Symptoms can include severe acne, alopecia, and hirsutism. In PCOS serum concentrations of total and/or free testosterone >0.5 ng/ml and >3.5 pg/ml, respectively, are diagnostic for hyperandrogenemia. Clinical hyperandrogenism is diagnosed primarily by assessing hirsutism using the classical or modified/simplified Ferriman–Gallwey scores.
Hyperinsulinemic insulin resistance (HIR): a condition characterized by reduced sensitivity and responsiveness to insulin-stimulated glucose uptake, primarily in skeletal muscle and adipose tissue. Insulin resistance stimulates excessive release of insulin (hyperinsulinemia) and IGFs.
Obesity: a medical condition with increased risk for mortality and morbidity characterized by BMI higher than 30 kg/m^2.
Oligoanovulatory ovarian dysfunction (OAD): a condition characterized by reduced frequency of menstrual cycles with no less than 35-day intervals or no fewer than ten bleeds per year due to irregular ovulatory activity.
Omics: high-throughput measurements that profile genes (genomics), transcripts (transcriptomics), proteins (proteomics), metabolites (metabolomics), epigenetic modifications (epigenomics), or other biological constituents in a cell, tissue, or system.
Oocyte competence (OC): the ability of the oocyte to resume meiosis, undergo fertilization, and reach the blastocyst stage for further embryonic development. These features are influenced by the nuclear and mitochondria genomes as well as the microenvironment provided by the ovary and the preovulatory follicle influencing transcription and translation and, consequently, cytoplasmic maturity.
Oocyte quality (OQ): a characteristic of the oocyte following morphological assessment of the